

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Otel 100 (Paclitaxel Injection 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains;

Paclitaxel USP100 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic Breast Cancer

Paclitaxel Injection is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

Non-Small Cell Lung Cancer

Paclitaxel Injection is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

Adenocarcinoma of the Pancreas

Paclitaxel Injection is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

4.2 Posology and Method of Administration

Important Administration Instructions

DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

Paclitaxel Injection has different dosage and administration instructions from other paclitaxel products.

Closely monitor the infusion site for extravasation or drug infiltration during administration. Limiting the infusion of paclitaxel to 30 minutes may reduce the risk of infusion-related reactions.

Consider premedication in patients who have had prior hypersensitivity reactions to paclitaxel. Do not re-challenge patients who experience a severe hypersensitivity reaction to paclitaxel.

Recommended Dosage for Metastatic Breast Cancer

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for paclitaxel is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

Recommended Dosage for Non-Small Cell Lung Cancer

The recommended dose of paclitaxel is 100 mg/m² administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. Administer carboplatin on Day 1 of each 21-day cycle immediately after paclitaxel.

Recommended Dosage for Adenocarcinoma of the Pancreas

The recommended dose of paclitaxel is 125 mg/m² administered as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Administer gemcitabine immediately after paclitaxel on Days 1, 8, and 15 of each 28-day cycle.

Dosage Modifications for Hepatic Impairment

For patients with moderate or severe hepatic impairment, reduce the starting dose of paclitaxel as shown in [Table 1](#).

Table 1: Recommendations for Starting Dose in Patients with Moderate and Severe Hepatic Impairment

	AST Levels		Bilirubin Levels	Paclitaxel Dose ^a		
				MBC	NSCLC ^c	Adenocarcinoma of Pancreas ^c
Moderate	< 10 x ULN	AND	> 1.5 to ≤ 3 x ULN	200 mg/m ² _b	80 mg/m ² _b	not recommended
Severe	< 10 x ULN	AND	> 3 to ≤ 5 x ULN	200 mg/m ² _b	80 mg/m ² _b	not recommended
	> 10 x ULN	OR	> 5 x ULN	not recommended	not recommended	not recommended

AST = Aspartate Aminotransferase; MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer; ULN = Upper limit of normal.

^a Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.

^b A dose increase to 260 mg/m² for patients with metastatic breast

cancer or 100 mg/m² for patients with non-small cell lung cancer in subsequent courses should be considered if the patient tolerates the reduced dose for two cycles.

^C Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

No adjustment of the starting paclitaxel dose is required for patients with mild hepatic impairment (total bilirubin > ULN and ≤ 1.5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN). Reduce paclitaxel starting dose in patients with moderate to severe hepatic impairment. Paclitaxel is not recommended for use in patients with total bilirubin > 5 x ULN or AST > 10 x ULN. paclitaxel is not recommended for use in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment.

Renal Impairment

No adjustment of the starting paclitaxel dose is required for patients with mild to moderate renal impairment (estimated creatinine clearance 30 to <90 mL/min). There are insufficient data to permit dosage recommendations in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 mL/min).

Dosage Modifications for Adverse Reactions

Metastatic Breast Cancer

Patients who experience severe neutropenia (neutrophils less than 500 cells/mm³ for a week or longer) or severe sensory neuropathy during paclitaxel therapy should have dosage reduced to 220 mg/m² for subsequent courses of paclitaxel. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m². For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of paclitaxel.

Non-Small Cell Lung Cancer

- Do not administer paclitaxel on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm³ and platelet count is at least 100,000 cells/mm³.
- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm³ and platelet count of at least 100,000 cells/mm³ on Day 1 or to an absolute neutrophil count of at least 500 cells/mm³ and platelet count of at least 50,000 cells/mm³ on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce paclitaxel and carboplatin doses as outlined in [Table 2](#).

- Withhold paclitaxel for Grade 3-4 peripheral neuropathy. Resume paclitaxel and carboplatin at reduced doses (see [Table 2](#)) when peripheral neuropathy improves to Grade 1 or completely resolves.

Table 2: Permanent Dose Reductions for Hematologic and Neurologic Adverse Reactions in NSCLC

Adverse Reaction	Occurrence	Weekly paclitaxel Dose (mg/m²)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm ³ with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm ³ OR ANC less than 500/mm ³ for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm ³	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Adenocarcinoma of the Pancreas

Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in [Table 4](#) and [Table 5](#), are provided in [Table 3](#).

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	Paclitaxel (mg/m ²)	Gemcitabine (mg/m ²)
Full dose	125	1000
1 st dose reduction	100	800
2 nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in [Table 4](#).

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm ³)		Platelet count (cells/mm ³)	Paclitaxel / Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

ANC = Absolute Neutrophil Count

Recommended dose modifications for other adverse reactions in patients with adenocarcinoma of the pancreas are provided in [Table 5](#).

Table 5: Dose Modifications for Other Adverse Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Reaction	Paclitaxel	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction

Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to $\leq$ Grade 1; resume at next lower dose level

Administration

Preparing of the patient

All patients who must be treated with Paclitaxel Injection must be previously medicated to avoid severe hypersensitivity reactions. Pre-medication may consist in 20 mg Dexamethasone orally taken between 12 and 6 hours previous to receiving the drug, 50 mg Diphenhydramine intravenously administered 30 to 60 minutes before receiving the drug and 50 mg Ranitidine or 300 mg Cimetidine via intravenously 30 to 60 minutes before receiving the drug.

Preparing for the administration

Paclitaxel concentrated solution contained in each flask shall be diluted before the infusion. The following solutions may be used for dilution: Sodium chloride solution at 0.9%, dextrose solution at 5% and sodium chloride at 0.9% , dextrose solution at 5% in Ringer solution. In all cases, final Paclitaxel solutions of 0.3 to 1.2 mg/ml (30 mg Paclitaxel in 100 to 25 ml solution respectively) must be obtained. Before being administered, the obtained solutions must be visually checked for particles or color changes. After being prepared, the solution might present a certain turbidity possibly due to the formation of vehicles.

Precautions during preparing

Paclitaxel Injection is a cytotoxic anti-blastic product and as such, must be handled with care. the use of rubber gloves is recommended during all the handling process. If the Paclitaxel solution accidentally be in touch with the skin, it must be immediately washed with water and soap. Should the accidental contact be with mucous membranes, they must be washed with abundant water. The contact of Paclitaxel Injection with polyvinyl chloride (PVC) equipment must be avoided, in order to prevent phthalate DEHP (di-[2-ethylhexil]plasticizer of PVC from releasing and becoming in contact with the patient). To prevent patient contact with said plasticizer, said Paclitaxel solution, once diluted, must be kept in glass or polypropylene containers. For infusion administration, the line used must be polyethylene provided with a

filter with lower than 0.22% microns membrane.

Stability

The concentrated solution of Paclitaxel Injection is stable in its original package (unopened) until its expiration date when stored between 2°C and 8°C and protected from light.

Neither freezing nor refrigeration affects the stability of product. Precipitation of some crystal of the product may be observed when it is stored at the indicated temperatures giving an opalescence effect in the solution. This condition is reversible with little agitation and upon reaching the product room temperature. If the solution remains opalescent at room temperature the vial should be discarded. Paclitaxel Injection should be diluted before its infusion. The prepared solutions for infusion are stable at room temperature (<25°C) for no more than 24 hours.

Discard any unused portion.

4.3 Contraindications

Paclitaxel is contraindicated in patients with:

- Baseline neutrophil counts of < 1,500 cells/mm³
- A history of severe hypersensitivity reactions to paclitaxel

4.4 Special warnings and precautions for use

WARNING: SEVERE MYELOSUPPRESSION

- Do not administer paclitaxel therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm³.
- Monitor for neutropenia, which may be severe and result in infection or sepsis, it is recommended that frequent.
- Perform frequent complete blood cell counts on all patients receiving paclitaxel.

Severe Myelosuppression

Severe myelosuppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of paclitaxel. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non-small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.

Monitor for severe neutropenia and thrombocytopenia by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer). Do not administer

paclitaxel to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm³.

In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of paclitaxel therapy, reduce the dose of paclitaxel in subsequent courses in patients with either MBC or NSCLC.

In patients with MBC, resume treatment with every-3-week cycles of paclitaxel after ANC recovers to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. In patients with NSCLC, resume treatment if recommended at permanently reduced doses for both weekly paclitaxel and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm³ and platelet count of at least 100,000 cells/mm³ on Day 1 or to an ANC of at least 500 cells/mm³ and platelet count of at least 50,000 cells/mm³ on Days 8 or 15 of the cycle.

In patients with adenocarcinoma of the pancreas, withhold paclitaxel and gemcitabine if the ANC is less than 500 cells/mm³ or platelets are less than 50,000 cells/mm³ and delay initiation of the next cycle if the ANC is less than 1500 cells/mm³ or platelet count is less than 100,000 cells/mm³ on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended.

Severe Neuropathy

Sensory neuropathy is dose- and schedule-dependent. If ≥ Grade 3 sensory neuropathy develops, withhold paclitaxel treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of paclitaxel.

Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received paclitaxel in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis.

If a patient becomes febrile (regardless of ANC) initiate treatment with broad spectrum antibiotics. For febrile neutropenia, interrupt paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels.

Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of

patients receiving paclitaxel in combination with gemcitabine.

Monitor patients for signs and symptoms of pneumonitis and interrupt paclitaxel and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with paclitaxel and gemcitabine.

Severe Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Do not rechallenge patients who experience a severe hypersensitivity reaction to paclitaxel with this drug.

Cross-hypersensitivity between paclitaxel and other taxane products has been reported and may include severe reactions such as anaphylaxis. Closely monitor patients with a previous history of hypersensitivity to other taxanes during initiation of paclitaxel therapy.

Use in Patients with Hepatic Impairment

The exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment. Closely monitor patients with hepatic impairment for severe myelosuppression.

Paclitaxel is not recommended in patients who have total bilirubin $>5 \times$ ULN or AST $>10 \times$ ULN. In addition, paclitaxel is not recommended in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment (total bilirubin $>1.5 \times$ ULN and AST $\leq 10 \times$ ULN). Reduce the starting dose for patients with moderate or severe hepatic impairment.

Albumin (Human)

Paclitaxel contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Embryo-Fetal Toxicity

Based on mechanism of action and findings in animals, paclitaxel can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy at doses lower than the maximum recommended

human dose, based on body surface area, caused embryo-fetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with paclitaxel and for at least six months after the last dose of paclitaxel.

Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with paclitaxel and for at least three months after the last dose of paclitaxel.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pharmacokinetics, safety, and antitumor activity of paclitaxel were assessed in an open-label, dose escalation, dose expansion study (NCT01962103) in 96 pediatric patients aged 1.4 to < 17 years with recurrent or refractory pediatric solid tumors. The maximum tolerated dose (MTD) normalized for body surface area (BSA) was lower in pediatric patients compared to adults. No new safety signals were observed in pediatric patients across these studies.

Paclitaxel protein-bound exposures normalized by dose were higher in 96 pediatric patients (aged 1.4 to < 17 years) as compared to those in adults.

Geriatric Use

Of the 229 patients in the randomized study who received paclitaxel for the treatment of metastatic breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. This study of paclitaxel did not include a sufficient number of patients with metastatic breast cancer who were 65 years and older to determine whether they respond differently from younger patients.

A subsequent pooled analysis was conducted in 981 patients receiving paclitaxel monotherapy for metastatic breast cancer, of which 15% were 65 years of age or older and 2% were 75 years of age or older. A higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found in patients 65 years of age or older.

Of the 514 patients in the randomized study who received paclitaxel and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were

65 years or older and 3.5% were 75 years or older. Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No overall difference in effectiveness, as measured by response rates, was observed between patients 65 years or older compared to patients younger than 65 years old.

Of the 431 patients in the randomized study who received paclitaxel and gemcitabine for the first-line treatment of pancreatic adenocarcinoma, 41% were 65 years or older and 10% were 75 years or older. No overall differences in effectiveness were observed between patients who were 65 years of age or older and younger patients. Diarrhea, decreased appetite, dehydration, and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. Clinical studies of paclitaxel did not include sufficient number of patients with pancreatic cancer who were 75 years and older to determine whether they respond differently from younger patients.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

4.6 Pregnancy and lactation

Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, paclitaxel can cause fetal harm when administered to a pregnant woman. There are no available human data on paclitaxel use in pregnant women to inform the drug-associated risk.

In animal reproduction studies, administration of paclitaxel formulated as albumin-bound particles to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicity at doses approximately 2% of the daily maximum recommended human dose on a mg/m² basis (see Data). Advise females of reproductive potential of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In embryo-fetal development studies, intravenous administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m² (approximately 2% of the daily maximum recommended human dose on a mg/m² basis) caused embryo-fetal toxicities, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight, and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles.

Lactation

Risk Summary

There are no data on the presence of paclitaxel in human milk, or its effect on the breastfed child or on milk production. In animal studies, paclitaxel and/or its metabolites were excreted into the milk of lactating rats (see Data). Because of the potential for serious adverse reactions in a breastfed child from paclitaxel, advise lactating women not to breastfeed during treatment with paclitaxel and for two weeks after the last dose.

Data

Animal Data

Following intravenous administration of radiolabeled 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.

Females and Males of Reproductive Potential

Based on animal studies and mechanism of action, paclitaxel can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with paclitaxel.

Contraception

Females

Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with paclitaxel and for at least six months after the last dose of paclitaxel.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with paclitaxel and for at least three months after the last dose of paclitaxel.

Infertility

Females and Males

Based on findings in animals, paclitaxel may impair fertility in females and males of reproductive potential.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions ($\geq 20\%$) with single-agent use of paclitaxel in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthritis, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea.

The most common adverse reactions ($\geq 20\%$) of paclitaxel in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. The most common serious adverse reactions of paclitaxel in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of paclitaxel are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of paclitaxel are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in paclitaxel dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

In a randomized open-label trial of paclitaxel in combination with gemcitabine for pancreatic adenocarcinoma, the most common ($\geq 20\%$) selected (with a $\geq 5\%$ higher incidence) adverse reactions of paclitaxel are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common

serious adverse reactions of paclitaxel (with a $\geq 1\%$ higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of paclitaxel are peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of paclitaxel are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in paclitaxel dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%).

Clinical Trials Experience

Metastatic Breast Cancer

Table 6 shows the frequency of important adverse reactions in the randomized comparative trial for the patients who received either single-agent paclitaxel or paclitaxel injection for the treatment of metastatic breast cancer.

Table 6: Adverse Reactions in the Randomized Metastatic Breast Cancer Study on an Every-3-Weeks Schedule

	Percent of Patients	
	Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) 260 mg/m² over 30 min (n=229)	Paclitaxel Injection 175 mg/m² over 3 h^a (n=225)
Bone Marrow		
Neutropenia		
< 2.0 x 10 ⁹ /L	80	82
< 0.5 x 10 ⁹ /L	9	22
Thrombocytopenia		
< 100 x 10 ⁹ /L	2	3
< 50 x 10 ⁹ /L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Neutropenic Sepsis	<1	<1
Bleeding	2	2
Hypersensitivity Reaction^b		
All	4	12
Severe ^c	0	2
Cardiovascular		
Vital Sign Changes During Administration		

Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events ^c	3	4
Abnormal ECG		
All Patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms ^c	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms ^c	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms ^c	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms ^c	0	<1
Gastrointestinal		
Nausea		
Any Symptoms	30	22

	Percent of Patients	
	Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) 260 mg/m ² over 30 min (n=229)	Paclitaxel Injection 175 mg/m ² over 3 h ^a (n=225)
Severe Symptoms ^c	3	<1
Vomiting		
Any Symptoms	18	10
Severe Symptoms ^c	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms ^c	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms ^c	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7

Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

^a Paclitaxel injection patients received premedication.

^b Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.

^c Severe events are defined as at least Grade 3 toxicity.

Other Adverse

Reactions

Hematologic

Disorders

Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm³ (Grade 4) in 9% of the patients treated with a dose of 260 mg/m² compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m². Pancytopenia has been observed in clinical trials.

Infections

Infectious episodes were reported in 24% of the patients treated with paclitaxel. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

Hypersensitivity Reactions (HSRs)

Grade 1 or 2 HSRs occurred on the day of paclitaxel administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of paclitaxel in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular

Hypotension, during the 30-minute infusion, occurred in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory

Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with paclitaxel.

Neurologic

The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of paclitaxel discontinuation in 7/229 (3%) patients. Twenty-four patients (10%) treated with paclitaxel developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of paclitaxel and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

Vision Disorders

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with paclitaxel and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m²).

These effects generally have been reversible.

Arthralgia/Myalgia

The symptoms were usually transient, occurred two or three days after paclitaxel administration, and resolved within a few days.

Hepatic

Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with paclitaxel and 10% of patients treated with paclitaxel injection in the randomized trial.

Renal

Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Other Clinical Events

Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

Non-Small Cell Lung Cancer

Adverse reactions were assessed in 514 paclitaxel /carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients receiving first-line systemic treatment for locally advanced (stage IIIB) or metastatic (IV) non-small cell lung cancer (NSCLC) in a multicenter, randomized, open-label trial. paclitaxel was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m² on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m², following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of paclitaxel /paclitaxel infusion.

The differences in paclitaxel dose and schedule between the two arms limit direct comparison of dose- and schedule-dependent adverse reactions. Among patients evaluable for adverse reactions, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous

cell lung cancer, 76% were ECOG PS 1. Patients in both treatment arms received a median of 6 cycles of treatment.

The following common ($\geq 10\%$ incidence) adverse reactions were observed at a similar incidence in paclitaxel plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the paclitaxel plus carboplatin treatment group).

Table 7 provides the frequency and severity of laboratory-detected abnormalities which occurred with a difference of $\geq 5\%$ for all grades (1-4) or $\geq 2\%$ for Grade 3-4 toxicity between paclitaxel plus carboplatin-treated patients or paclitaxel injection plus carboplatin-treated patients.

Table 7: Selected Hematologic Laboratory-Detected Abnormalities with a Difference of $\geq 5\%$ for grades (1-4) or $\geq 2\%$ for Grade 3-4 Toxicity Between Treatment Groups

	Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (100 mg/m ² weekly) plus carboplatin		Paclitaxel Injection (200 mg/m ² every 3 weeks) plus carboplatin	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Anemia ^{1,2}	98	28	91	7
Neutropenia ^{1,3}	85	47	83	58
Thrombocytopenia ^{1,3}	68	18	55	9

¹ 508 patients assessed in paclitaxel /carboplatin-treated group.

² 514 patients assessed in paclitaxel injection/carboplatin-treated group.

³ 513 patients assessed in paclitaxel injection/carboplatin-treated group.

Table 8 provides the frequency and severity of adverse reactions, which occurred with a difference of $\geq 5\%$ for all grades (1-4) or $\geq 2\%$ for Grade 3-4 between either treatment group for the 514 paclitaxel plus carboplatin-treated patients compared with the 524 patients who received paclitaxel injection plus carboplatin.

Table 8: Selected Adverse Reactions with a Difference of $\geq 5\%$ for All Grade Toxicity or $\geq 2\%$ for Grade 3-4 Toxicity Between Treatment Groups

System Organ Class	Adverse Reaction	Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (100 mg/m ² weekly) + carboplatin (N=514)		Paclitaxel Injection (200 mg/m ² every 3 weeks) + carboplatin (N=524)	
		Grade 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)	Grades 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)
<i>Nervous system disorders</i>	Peripheral neuropathy ^a	48	3	64	12
<i>General disorders and administration site conditions</i>	Edema peripheral	10	0	4	<1
<i>Respiratory thoracic and mediastinal disorders</i>	Epistaxis	7	0	2	0
<i>Musculoskeletal and connective tissue disorders</i>	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2

^a Peripheral neuropathy is defined by the MedDRA Version 14.0 SMQ neuropathy (broad scope).

For the paclitaxel plus carboplatin treated group, 17/514 (3%) patients developed Grade 3 peripheral neuropathy and no patients developed Grade 4 peripheral neuropathy. Grade 3 neuropathy improved to Grade 1 or resolved in 10/17 patients (59%) following interruption or discontinuation of paclitaxel.

Adenocarcinoma of the Pancreas

Adverse reactions were assessed in 421 patients who received paclitaxel plus gemcitabine and

402 patients who received gemcitabine for the first-line systemic treatment of

metastatic adenocarcinoma of the pancreas in a multicenter, multinational, randomized, controlled, open-label trial. Patients received a median treatment duration of 3.9 months in the paclitaxel /gemcitabine group and 2.8 months in the gemcitabine group. For the treated population, the median relative dose intensity for gemcitabine was 75% in the paclitaxel/gemcitabine group and 85% in the gemcitabine group. The median relative dose intensity of paclitaxel was 81%.

Table 9 provides the frequency and severity of laboratory-detected abnormalities which occurred at a higher incidence for Grades 1- 4 ($\geq 5\%$) or for Grade 3-4 ($\geq 2\%$) toxicity in paclitaxel plus gemcitabine-treated patients.

Table 9: Selected Hematologic Laboratory-Detected Abnormalities with a Higher Incidence ($\geq 5\%$ for Grades 1-4 or $\geq 2\%$ for Grades 3-4 Events) in the paclitaxel injection /Gemcitabine Arm

	Paclitaxel Injectable (125 mg/m ²)/ Gemcitabine ^d		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Neutropenia ^{a,b}	73	38	58	27
Thrombocytopenia ^{b,c}	74	13	70	9

^a 405 patients assessed in paclitaxel /gemcitabine-treated group.

^b 388 patients assessed in gemcitabine-treated group.

^c 404 patients assessed in paclitaxel /gemcitabine-treated group.

^d Neutrophil growth factors were administered to 26% of patients in the paclitaxel /gemcitabine group.

Table 10 provides the frequency and severity of adverse reactions which occurred with a difference of $\geq 5\%$ for all grades or $\geq 2\%$ for Grade 3 or higher in the paclitaxel plus gemcitabine-treated group compared to the gemcitabine group.

Table 10: Selected Adverse Reactions with a Higher Incidence ($\geq 5\%$ for All Grade Toxicity or $\geq 2\%$ for Grade 3 or Higher Toxicity) in the paclitaxel injection/Gemcitabine Arm

System Organ Class	Adverse Reaction	Paclitaxel injection(125 mg/m ²) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
General	Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)

disorders and administration site conditions	Peripheral edema	194 (46%)	13 (3%)	122 (30%)	12 (3%)
	Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
	Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
	Mucositis	42 (10%)	6 (1%)	16 (4%)	1 (<1%)
Gastrointestinal disorders	Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
	Diarrhea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
	Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
Skin and subcutaneous tissue disorders	Alopecia	212 (50%)	6 (1%)	21 (5%)	0
	Rash	128 (30%)	8 (2%)	45 (11%)	2 (<1%)
Nervous system disorders	Peripheral neuropathy ^a	227 (54%)	70 (17%)	51 (13%)	3 (1%)

System Organ Class	Adverse Reaction	Paclitaxel injection(125 mg/m ²) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	Dysgeusia	68 (16%)	0	33 (8%)	0
	Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Metabolism and nutrition disorders	Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
	Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
	Hypokalemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	Cough	72 (17%)	0	30 (7%)	0
	Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Infections and infestations	Urinary tract infections ^b	47 (11%)	10 (2%)	20 (5%)	1 (<1%)
Musculoskeletal and connective tissue disorders	Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
	Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
	Myalgia	44 (10%)	4 (1%)	15 (4%)	0
Psychiatric disorders	Depression	51 (12%)	1 (<1%)	24 (6%)	0

^a Peripheral neuropathy is defined by the MedDRA Version 15.0 Standard MedDRA Query neuropathy (broad scope).

^b Urinary tract infections includes the preferred terms of: urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, and urinary tract infection enterococcal.

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received paclitaxel/gemcitabine included:

Infections & infestations: oral candidiasis, pneumonia Vascular disorders: hypertension

Cardiac disorders: tachycardia, congestive cardiac failure Eye disorders: cystoid macular edema

Peripheral Neuropathy

Grade 3 peripheral neuropathy occurred in 17% of patients who received

paclitaxel/gemcitabine compared to 1% of patients who received gemcitabine only; no patients developed Grade 4 peripheral neuropathy. The median time to first occurrence of Grade 3 peripheral neuropathy in the paclitaxel arm was 140 days. Upon suspension of paclitaxel dosing, the median time to improvement from Grade 3 peripheral neuropathy to $\leq$ Grade 1 was 29 days. Of paclitaxel - treated patients with Grade 3 peripheral neuropathy, 44% resumed paclitaxel at a reduced dose.

Sepsis

Sepsis occurred in 5% of patients who received paclitaxel/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred both in patients with and without neutropenia. Risk factors for sepsis included biliary obstruction or presence of biliary stent.

Pneumonitis

Pneumonitis occurred in 4% of patients who received paclitaxel/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 patients in the paclitaxel arm with pneumonitis died.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of paclitaxel or with paclitaxel injection and may be expected to occur with paclitaxel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity Reactions

Severe and sometimes fatal hypersensitivity reactions. Cross-hypersensitivity between paclitaxel and other taxanes has been reported.

Cardiovascular

Congestive heart failure, left ventricular dysfunction, and atrioventricular block. Most patients were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory

Pneumonitis, interstitial pneumonia, and pulmonary embolism Radiation pneumonitis in patients receiving concurrent radiotherapy. Lung fibrosis has been reported with paclitaxel injection.

Neurologic

Cranial nerve palsies and vocal cord paresis, as well as autonomic neuropathy resulting in paralytic ileus.

Vision Disorders

Reduced visual acuity due to cystoid macular edema (CME). After cessation of treatment, CME may improve, and visual acuity may return to baseline. Abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage.

Hepatic

Hepatic necrosis and hepatic encephalopathy leading to death in patients treated with paclitaxel injection.

Gastrointestinal (GI)

Intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis. In patients treated with paclitaxel injection, neutropenic enterocolitis (typhlitis) despite the coadministration of G-CSF, alone and in combination with other chemotherapeutic agents.

Injection Site Reaction

Extravasation. Closely monitor the paclitaxel infusion site for possible infiltration during drug administration. Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported with paclitaxel injection. In some cases, the onset of the injection site reaction occurred during a prolonged infusion or was delayed up to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site has been reported.

Metabolic and Nutritional Disorders

Tumor lysis syndrome

Other Clinical Events

Skin reactions including generalized or maculopapular rash, erythema, and pruritus

Photosensitivity reactions, radiation recall phenomenon, scleroderma, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Conjunctivitis, cellulitis, and increased lacrimation have been reported with paclitaxel injection.

Accidental Exposure

Upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, tingling, burning, and redness have been reported.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)
<https://pv.pharmacyboardkenya.org>

4.9 Overdose

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

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 a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

CLINICAL STUDIES

Metastatic Breast Cancer

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of paclitaxel in metastatic breast cancer.

Single Arm Open Label Studies

In one study, paclitaxel was administered as a 30-minute infusion at a dose of 175 mg/m² to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m² as a 30-minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3-week intervals. Objective responses were observed in both studies.

Randomized Comparative Study

This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive paclitaxel at a dose of 260 mg/m² given as a 30-minute infusion, or paclitaxel injection at 175 mg/m² given as a 3-hour infusion. 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, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the paclitaxel treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See [Table 11](#). There was no statistically significant difference in overall survival between the two study arms.

Table 11: Efficacy Results from Randomized Metastatic Breast Cancer Trial

		Paclitaxel for Injectable Suspension paclitaxel protein-bound articles for injectable suspension) 260 mg/m²	Paclitaxel Injection 175 mg/m²
Reconciled Target Lesion Response Rate (primary endpoint)^a			
All randomized patients	Response Rate	50/233 (21.5%)	25/227 (11.1%)
	[95% CI]	[16.19% – 26.73%]	[6.94% – 15.09%]
	p-value ^b	0.003	

Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy ^c	Response Rate [95% CI]	20/129 (15.5%) [9.26% – 21.75%]	12/143 (8.4%) [3.85% – 12.94%]
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^a Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.

^b From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.

^c Prior therapy included an anthracycline unless clinically contraindicated.

Non-Small Cell Lung Cancer

A multicenter, randomized, open-label study was conducted in 1052 chemotherapy naive patients with Stage IIb/IV non-small cell lung cancer to compare paclitaxel in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. Paclitaxel was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m² on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m², following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of paclitaxel/paclitaxel infusion. Treatment was administered until disease progression or development of an unacceptable toxicity. The major efficacy outcome measure was overall response rate as determined by a central independent review committee using RECIST guidelines (Version 1.0).

In the intent-to-treat (all-randomized) population, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1, and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms.

Patients in the paclitaxel/carboplatin arm had a statistically significantly higher overall response rate compared to patients in the paclitaxel injection/carboplatin arm [(33% versus 25%) see [Table 12](#)]. There was no statistically significant difference in overall survival between the two study arms.

Table 12: Efficacy Results from Randomized Non-Small Cell Lung Cancer Trial (Intent-to-Treat)

Population)		
	Paclitaxel injection (100 mg/m² weekly) + carboplatin (N=521)	Paclitaxel Injection (200 mg/m² every 3 weeks) + carboplatin (N=531)
Overall Response Rate (ORR)		
Confirmed complete or partial overall response, n (%)	170 (33%)	132 (25%)
95% CI	28.6, 36.7	21.2, 28.5
P-value (Chi-Square test)	0.005	
Median DoR in months (95% CI)	6.9 (5.6, 8.0)	6.0 (5.6, 7.1)
Overall Response Rate by Histology		
Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)
Other	7/29 (24%)	5/33 (15%)

CI = confidence interval; DoR= Duration of response.

Adenocarcinoma of the Pancreas

A multicenter, multinational, randomized, open-label study was conducted in 861 patients comparing paclitaxel plus gemcitabine versus gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas. Key eligibility criteria were Karnofsky Performance Status (KPS) ≥ 70 , normal bilirubin level, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for patients with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. Patients with rapid decline in KPS ($\geq 10\%$) or serum albumin ($\geq 20\%$) during the 14-day screening period prior to study randomization were ineligible.

A total of 861 patients were randomized (1:1) to the paclitaxel/gemcitabine arm (N=431) or to the gemcitabine arm (N=430).

Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no). Patients randomized to paclitaxel/gemcitabine received paclitaxel 125 mg/m² as an intravenous infusion over 30-40 minutes followed by gemcitabine 1000 mg/m² as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Patients randomized to gemcitabine received 1000 mg/m² as an

intravenous infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1 then as 1000 mg/m² on Days 1, 8, and 15 of each subsequent 28-day cycle. Patients in both arms received treatment until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using RECIST (version 1.0).

In the intent-to-treat (all randomized) population, the median age was 63 years (range 27-88 years) with 42% ≥ 65 years of age; 58% were men; 93% were White and KPS was 90-100 in 60%. Disease characteristics included 46% of patients with 3 or more metastatic sites; 84% of patients had liver metastasis; and the location of the primary pancreatic lesion was in the head of pancreas (43%), body (31%), or tail (25%).

Results for overall survival, progression-free survival, and overall response rate are shown in [Table 13](#).

Table 13: Efficacy Results from Randomized Study in Patients with Adenocarcinoma of the Pancreas (ITT Population)

	Paclitaxel injection (125 mg/m ²) and gemcita bine	Gemcitabi ne (N = 430)
	(N = 431)	
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (months)	8.5	6.7
95% CI	7.9, 9.5	6.0, 7.2
HR (95% CI) ^a	0.72 (0.62, 0.83)	
P-value ^b	<0.0001	
Progression-free Survival ^c		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	5.5	3.7
95% CI	4.5, 5.9	3.6, 4.0
HR (95% CI) ^a	0.69 (0.58, 0.82)	
P-value ^b	<0.0001	
Overall Response Rate ^c		
Confirmed complete or partial overall response, n (%)	99 (23)	31 (7)
95% CI	19.1, 27.2	5.0, 10.1

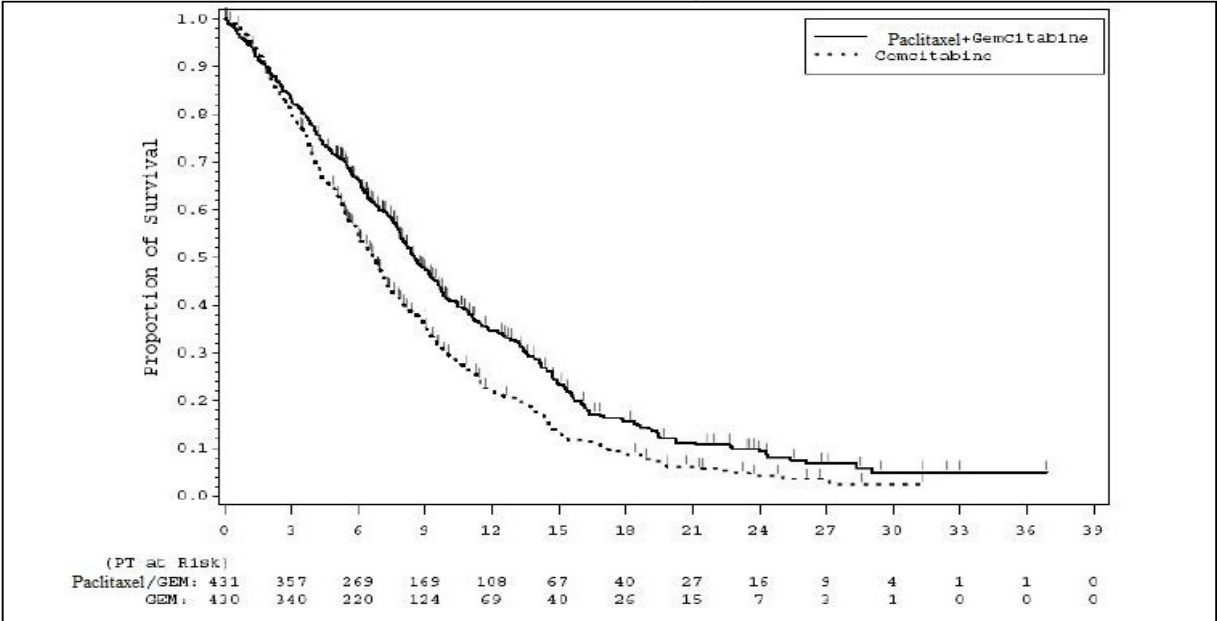
P-value ^d	<0.0001
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CI = confidence interval, HR = hazard ratio of paclitaxel plus gemcitabine / gemcitabine, ITT = intent-to-treat population.

- a Stratified Cox proportional hazard model.
- b Stratified log-rank test stratified by geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).
- c Based on Independent Radiological Reviewer Assessment.
- d Chi-square test.

In exploratory analyses conducted in clinically relevant subgroups with a sufficient number of subjects, the treatment effects on overall survival were similar to that observed in the overall study population.

Figure 1: Kaplan-Meier Curve of Overall Survival (Intent-to-Treat Population)



5.2 Pharmacokinetic properties

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of paclitaxel at dose levels of 80 to 375 mg/m² (0.31 to 1.15 times the maximum approved recommended dosage) were determined in clinical studies. Dose levels of mg/m² refer to mg of paclitaxel in paclitaxel. Following intravenous administration of paclitaxel to patients with solid tumors, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination.

Following paclitaxel infusion, paclitaxel exhibited linear drug exposure (AUC) across clinical doses ranging from 80 to 300 mg/m² (0.31 to 1.15 times the maximum approved recommended dosage). The pharmacokinetics of paclitaxel in paclitaxel were independent of the duration of intravenous administration.

The pharmacokinetic data of 260 mg/m² paclitaxel administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m² paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for paclitaxel than for paclitaxel injection. There were no differences in terminal half-lives.

Distribution

Following paclitaxel administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with paclitaxel (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with paclitaxel compared with solvent-based paclitaxel, when the total exposure is comparable. *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Elimination

At the clinical dose range of 80 to 300 mg/m² (0.31 to 1.15 times the maximum approved recommended dosage), the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m² and the mean terminal half-life ranges from 13 to 27 hours.

Metabolism

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel in paclitaxel was metabolized primarily to 6 α -hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6 α , 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 α -hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17 α -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 α -hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

Excretion

After a 30-minute infusion of 260 mg/m² doses of paclitaxel, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6 α -hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of paclitaxel in paclitaxel were observed based on body weight (40 to 143 kg), body surface area (1.3 to 2.4 m²), sex, race (Asian vs. White), age (24 to 85 years), type of solid tumors, mild to moderate renal impairment (creatinine clearance 30 to <90 mL/min), and mild hepatic impairment (total bilirubin >1 to $\leq$ 1.5 x ULN and AST $\leq$ 10 x ULN).

Patients with moderate (total bilirubin >1.5 to 3 x ULN and AST $\leq$ 10 x ULN) or severe (total bilirubin >3 to 5 x ULN) hepatic impairment had 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 (total bilirubin $\leq$ ULN and AST $\leq$ ULN).

The effect of severe renal impairment or end stage renal disease (creatinine clearance < 30 mL/min) on the pharmacokinetics of paclitaxel in paclitaxel is unknown.

Drug Interaction Studies

Carboplatin: Administration of carboplatin immediately after the completion of the paclitaxel infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure. The observed mean AUC_{inf} of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with

those reported in the absence of paclitaxel.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of paclitaxel has not been studied.

Paclitaxel was clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel formulated as albumin-bound particles to male rats at 42 mg/m² on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a body surface area basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A dose of 42 mg/m² also reduced male reproductive organ weights, mating performance, and sperm production.

Testicular atrophy/degeneration was observed in single-dose toxicology studies in animals administered paclitaxel formulated as albumin-bound particles at doses lower than the recommended human dose; doses were 54 mg/m² in rodents and 175 mg/m² in dogs. Similar testicular degeneration was seen in monkeys administered three weekly doses of 108 mg/m² paclitaxel formulated as albumin bound particles.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats. Paclitaxel caused reduced fertility and reproductive indices, and increased embryo-fetal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cremophor, Ethanol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store between 2°C and 8°C (refrigeration temperature) and protect from light. Neither freezing nor refrigeration adversely affects the stability of the product.

6.5 Nature and contents of container

Clear, colourless to slightly yellowish solution, viscose and free of suspended foreign particles in Glass amber vial with rubber stopper and aluminium crimp cap with plastic white flip-off

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals
Limited B/2, Mahalaxmi
Chambers,
22, Bhulabhai Desai road, Mumbai – 400 026. Maharashtra. India.
Manufactured at:
Glenmark Generics
S.A. Calle 9 N 593
(B1629MAX)
Parque Industrial Pilar Buenos Argentina

8. MARKETING AUTHORISATION NUMBER(S)

18106

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05-06-2008

10. DATE OF REVISION OF THE TEXT

January 2026, 12th August 2026