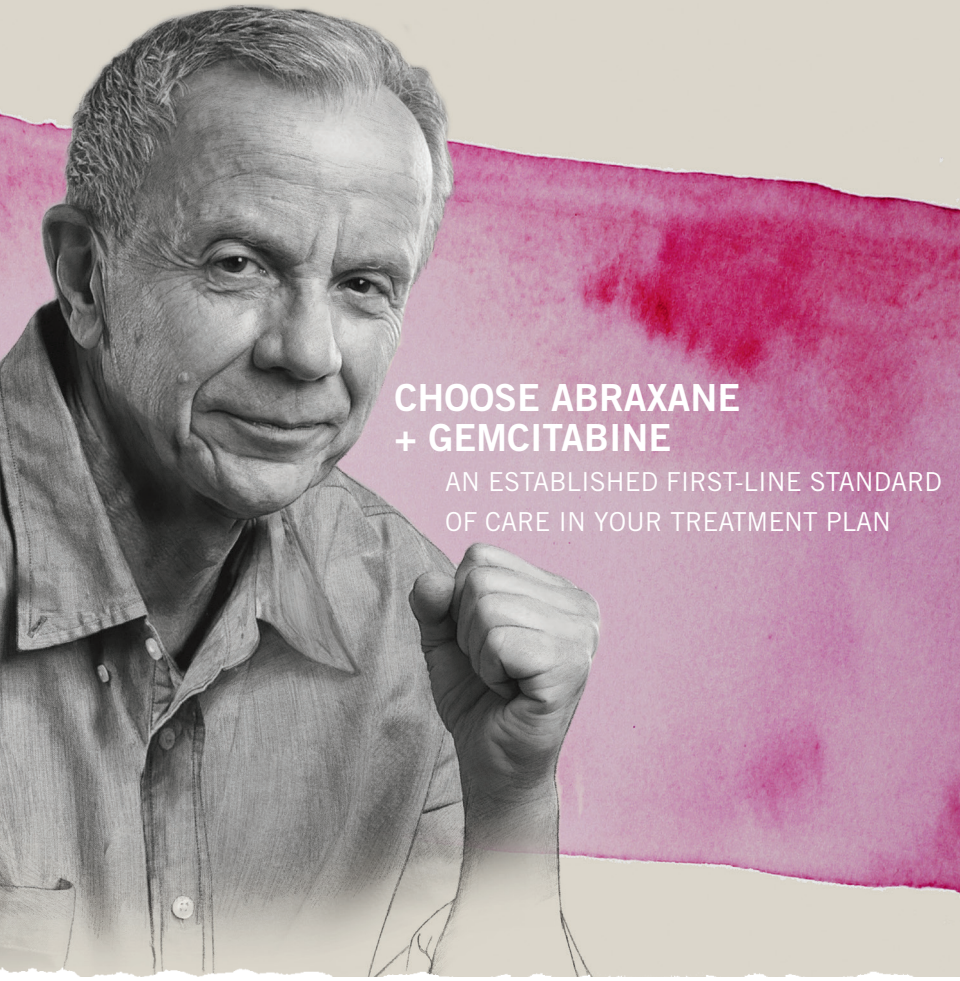
Abraxane®
for Injectable Suspension

(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

ABRAXANE + gemcitabine for first-line metastatic pancreatic cancer (mPC): FDA-approved dosing regimen and modifications



INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNING - NEUTROPENIA

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE**
- **Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS**

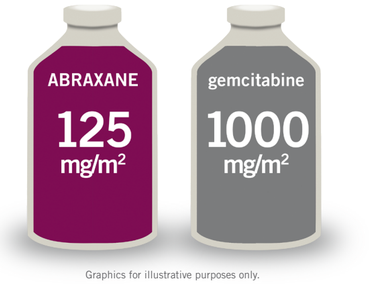
Please see additional Important Safety Information on page 3 and full Prescribing Information, including Boxed WARNING.

ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas (mPC), in combination with gemcitabine.

ABRAXANE + gemcitabine in first-line mPC: Starting dose, schedule, and appropriate dose modifications

Results achieved in the phase III MPACT trial were based on a starting dose of 125 mg/m² given QW3/4[1,2]

Administer ABRAXANE intravenously at a dose of 125 mg/m²



Graphics for illustrative purposes only.

- ABRAXANE is administered over 30-40 minutes

Administer ABRAXANE immediately followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle

WEEK 1	1	2	3	4	5	6	7
WEEK 2	8	9	10	11	12	13	14
WEEK 3	15	16	17	18	19	20	21
WEEK 4	22	23	24	25	26	27	28

Patients with hepatic impairment[1]

Do not administer ABRAXANE to 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) or if total bilirubin > 5 x ULN or AST > 10 x ULN.

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The majority of ABRAXANE doses were administered at full dose and as scheduled[2]

71%
(4116/5770)
of administered doses were given at 125 mg/m² across all study cycles

85%
(5568/6514)
of doses were given as scheduled QW3/4
- **15%** (964/6514) were delayed or withheld

Percentage of patients who had at least one ABRAXANE dose modification[2]

41%
of 421 patients had at least one ABRAXANE dose reduction

71%
of 421 patients had at least one ABRAXANE dose delayed or withheld

Timing of dose modifications in the MPACT trial[3]

60%
(155/257)
of **ABRAXANE dose reduction** occurred **after 3 months*** of treatment

72%
(679/946)
of **ABRAXANE dose delays** occurred **after 3 months*** of treatment

*First 2 cycles.

Adverse reactions in the phase III MPACT trial[1]

- Randomized phase III study of ABRAXANE + gemcitabine vs gemcitabine alone in first-line metastatic pancreatic cancer (N=861). ABRAXANE (125 mg/m²) + gemcitabine (1000 mg/m²) was given QW3/4. In the gemcitabine arm, gemcitabine (1000 mg/m²) was given QW7/8 then QW3/4.
- The most common (≥20%) selected (with a ≥5% higher incidence) adverse reactions of ABRAXANE are:
  - neutropenia
  - fatigue
  - peripheral neuropathy
  - nausea
  - alopecia
  - peripheral edema
  - diarrhea
  - pyrexia
  - vomiting
  - decreased appetite
  - rash
  - dehydration

References: 1. ABRAXANE Prescribing Information. Bristol-Myers Squibb Company. **2.** Data on file. Bristol-Myers Squibb Company. **3.** Scheithauer W, Ramanathan RK, Moore M, et al. Dose modification and efficacy of *nab*-paclitaxel plus gemcitabine vs. gemcitabine for patients with metastatic pancreatic cancer phase III MPACT trial. *Gastrointest Oncol.* 2016;7(3):469-478.

Please see additional Important Safety Information on page 3 and full Prescribing Information, including Boxed WARNING.

Appropriate treatment adjustments for peripheral neuropathy

Grades 1 or 2: No dose modification of ABRAXANE is recommended[2]

Grade 3: Withhold ABRAXANE until improvement to ≤Grade 1; resume at next lower dose level[1,2]

17% of patients developed Grade 3 peripheral neuropathy in the ABRAXANE + gemcitabine arm (70/421)

- **Nearly half of these patients (44%)** resumed ABRAXANE at a reduced dose (31/70)
- The median time to improvement to ≤Grade 1 after withholding dose was **29 days**
- **Median time to onset of Grade 3 neuropathy was ~5 months** (140 days, 9-336)

- **54% of patients experienced peripheral neuropathy of any grade in the ABRAXANE + gemcitabine arm (227/421)**

Clearly defined dose modifications[1]

Dose level	ABRAXANE dose (mg/m²)	Gemcitabine dose (mg/m²)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Appropriate treatment adjustments for hematologic ARs[1]

Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Days 1, 8, and 15
- Febrile neutropenia Grade 3 or 4: Withhold until fever resolves and ANC ≥1500; resume at next lower dose level

DAY 1	DAY 8	DAY 15	Treatment adjustments at Day 15 depend upon action taken at Day 8
Recommended starting dose of ABRAXANE[a]: 125 mg/m²	ANC ≥1000[b] AND PLATELETS[b] ≥75,000	ANC ≥1000[b] AND PLATELETS ≥75,000[b]	Maintain DAY 1 dose
		ANC 500 - <1000[b] AND PLATELETS 50,000 - <75,000[b]	Reduce by 1 dose level
		ANC <500[b] AND PLATELETS <50,000[b]	Withhold doses
	Maintain DAY 1 dose		
Recommended starting dose of ABRAXANE[a]: 125 mg/m²	ANC 500 - <1000[b] OR PLATELETS[b] 50,000 - <75,000	ANC ≥1000[b] AND PLATELETS ≥75,000[b]	Maintain DAY 8 dose
		ANC 500 - <1000[b] AND PLATELETS 50,000 - <75,000[b]	Reduce by 1 dose level from DAY 8
		ANC <500[b] AND PLATELETS <50,000[b]	Withhold doses
	Reduce by 1 dose level		
Recommended starting dose of ABRAXANE[a]: 125 mg/m²	ANC 500 - <500[b] OR PLATELETS <50,000[b]	ANC ≥1000[b] AND PLATELETS ≥75,000[b]	Resume treatment at dose 1 level lower than DAY 1
		ANC 500 - <1000[b] AND PLATELETS 50,000 - <75,000[b]	Resume treatment at dose 2 levels lower than DAY 1
		ANC <500[b] AND PLATELETS <50,000[b]	Withhold doses
	Withhold doses		

[a]Patients must have ANC ≥1500 cells/mm³ to initiate a cycle. If counts are not at these levels, delay the start of the cycle until recovery. [b]All ANC and platelet counts are shown in cells/mm³.

Appropriate treatment adjustments for nonhematologic ARs[1]

Adverse Drug Reaction	
Gastrointestinal toxicity Grades 3 or 4	Withhold until improves to ≤Grade 1; resume at next lower dose level
Cutaneous toxicity Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists

ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas (mPC), in combination with gemcitabine.

ABRAXANE + gemcitabine in first-line mPC: Starting dose and appropriate dose modifications

INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNING - NEUTROPENIA

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1500 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE**
- **Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS**

CONTRAINDICATIONS

Neutrophil Counts

- ABRAXANE should not be used in patients who have baseline neutrophil counts of <1500 cells/mm³

Hypersensitivity

- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug

WARNINGS AND PRECAUTIONS

Hematologic Effects

- Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE. In a clinical study, Grade 3-4 neutropenia occurred in 38% of patients with pancreatic cancer
- Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Days 1, 8, and 15 for pancreatic cancer
- Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/mm³
- In patients with adenocarcinoma of the pancreas, withhold ABRAXANE 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

Nervous System

- Sensory neuropathy is dose- and schedule-dependent
- The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification
- If ≥ Grade 3 sensory neuropathy develops, withhold ABRAXANE treatment until resolution to ≤ Grade 1 followed by a dose reduction for all subsequent courses of ABRAXANE

Sepsis

- Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE 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 ABRAXANE and gemcitabine until fever resolves and ANC ≥1500 cells/mm³, then resume treatment at reduced dose levels

Pneumonitis

- Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine
- Monitor patients for signs and symptoms and interrupt ABRAXANE and gemcitabine during evaluation of suspected pneumonitis
- Permanently discontinue treatment with ABRAXANE and gemcitabine upon making a diagnosis of pneumonitis

Hypersensitivity

- Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported
- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with this drug
- Cross-hypersensitivity between ABRAXANE and other taxane products has been reported and may include severe reactions such as anaphylaxis. Patients with a previous history of hypersensitivity to other taxanes should be closely monitored during initiation of ABRAXANE therapy

Hepatic Impairment

- Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution
- Patients with hepatic impairment may be at an increased risk of toxicity, particularly from myelosuppression, and should be monitored for development of profound myelosuppression
- For pancreatic adenocarcinoma, ABRAXANE is not recommended for patients with moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN)

Albumin (Human)

- ABRAXANE contains albumin (human), a derivative of human blood

Embryo Fetal Toxicity

- Based on mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman
- 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 ABRAXANE and for at least six months after the last dose of ABRAXANE
- Advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE

ADVERSE REACTIONS

- Among the most common (≥20%) adverse reactions in the phase III study, those with a ≥5% higher incidence in the ABRAXANE/gemcitabine group compared with the gemcitabine group are neutropenia (73%, 58%), fatigue (59%, 46%), peripheral neuropathy (54%, 13%), nausea (54%, 48%), alopecia (50%, 5%), peripheral edema (46%, 30%), diarrhea (44%, 24%), pyrexia (41%, 28%), vomiting (36%, 28%), decreased appetite (36%, 26%), rash (30%, 11%), and dehydration (21%, 11%)
- Of these most common adverse reactions, those with a ≥2% higher incidence of Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared with the gemcitabine group, respectively, are neutropenia (38%, 27%), fatigue (18%, 9%), peripheral neuropathy (17%, 1%), nausea (6%, 3%), diarrhea (6%, 1%), pyrexia (3%, 1%), vomiting (6%, 4%), decreased appetite (5%, 2%), and dehydration (7%, 2%)
- Thrombocytopenia (all grades) was reported in 74% of patients in the ABRAXANE/gemcitabine group vs 70% of patients in the gemcitabine group
- The most common serious adverse reactions of ABRAXANE (with a ≥1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%)
- The most common adverse reactions resulting in permanent discontinuation of ABRAXANE were peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%)
- The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (10%) and peripheral neuropathy (6%)
- The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%)
- Other selected adverse reactions with a ≥5% higher incidence for all-grade toxicity in the ABRAXANE/gemcitabine group compared to the gemcitabine group, respectively, are asthenia (19%, 13%), mucositis (10%, 4%), dysgeusia (16%, 8%), headache (14%, 9%), hypokalemia (12%, 7%), cough (17%, 7%), epistaxis (15%, 3%), urinary tract infection (11%, 5%), pain in extremity (11%, 6%), arthralgia (11%, 3%), myalgia (10%, 4%), and depression (12%, 6%)
- Other selected adverse reactions with a ≥2% higher incidence for Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared to the gemcitabine group are thrombocytopenia (13%, 9%), asthenia (7%, 4%), and hypokalemia (4%, 1%)

Postmarketing Experience With ABRAXANE and Other Paclitaxel Formulations

- Severe and sometimes fatal hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied. In postmarketing experience, cross-hypersensitivity between ABRAXANE and other taxanes has been reported
- There have been reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block with ABRAXANE, primarily among individuals with underlying cardiac history or prior exposure to cardiotoxic drugs
- There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for possible infiltration during drug administration

DRUG INTERACTIONS

- Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4

USE IN SPECIFIC POPULATIONS

Pregnancy

- Based on the mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman. Advise females of the potential risk to a fetus and to avoid becoming pregnant while receiving ABRAXANE

Lactation

- Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Nursing must be discontinued when receiving treatment with ABRAXANE and for two weeks after the last dose

Females and Males of Reproductive Potential

- Females of reproductive potential should have a pregnancy test prior to starting treatment with ABRAXANE
- Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with and for at least six months after the last dose of ABRAXANE *[see Warnings and Precautions]*
- Advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE *[see Warnings and Precautions]*
- Based on findings in animals, ABRAXANE may impair fertility in females and males of reproductive potential

Pediatric

- The safety and effectiveness of ABRAXANE in pediatric patients have not been established

Geriatric

- Diarrhea, decreased appetite, dehydration, and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old who received ABRAXANE and gemcitabine in adenocarcinoma of the pancreas

Renal Impairment

- 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 AND ADMINISTRATION

- Do not administer ABRAXANE to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment
- Do not administer ABRAXANE to any patient with total bilirubin greater than 5 x ULN or AST greater than 10 x ULN
- Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicity
- Monitor patients closely

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Bristol Myers Squibb™

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