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

A BRAXANE® and gemcitabine in first-line MPAC: 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

ABRAXANE® is a registered trademark of Celgene Corporation.

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WARNING - NEUTROPENIA

Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1500 cells/μL. 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 absence form of paclitaxel may substantially affect a drug’s functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR DRUG WITH OTHER PACLI TAXEL FORMULATIONS

CONTRAINDICATIONS

Neutropenia Counts
• ABRAXANE should not be used in patients who have baseline neutrophil counts of ≥1500 cells/μL.

Hypersensitivity
• Patients should experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug.

WARNINGS AND PRECAUTIONS

Hepatic Impairment
• Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting factor of ABRAXANE. In a clinical study, Grade 3-4 neutropenia occurred in 36% of patients with pancreatic cancer.

• For safety reasons, the starting dose of ABRAXANE should be reduced in patients with moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN, or total bilirubin ≤1.5 x ULN and AST >10 x ULN). The starting dose of ABRAXANE should be reduced to 60% of the recommended dose in patients with severe hepatic impairment (AST greater than 10 x ULN).

• Hepatic impairment or end stage renal disease (estimated creatinine clearance <30 mL/min) may be at an increased risk of toxicity, and dose adjustments for ABRAXANE may be needed for development of profound myelosuppression.

If For pancreatic adenocarcinomas, ABRAXANE is not recommended for patients with mild (total bilirubin ≤1.5 x ULN and AST ≤5 x ULN) or moderate (total bilirubin >1.5 x ULN and AST ≤5 x ULN) hepatic impairment.

An Albumin (Human)
• ABRAXANE contains albumin (human), a derivative of human blood.

ABRAXANE in combination with gemcitabine
• ABRAXANE (25 mg/m²) should be administered 24 hours after the first dose of gemcitabine (1000 mg/m²).

• In patients with moderate hepatic impairment (total bilirubin >1.5 x ULN and AST ≤5 x ULN) or with impaired renal function (creatinine clearance <60 mL/min), starting dose of ABRAXANE should be 25 mg/m².

• In patients with impaired renal function (creatinine clearance <60 mL/min) and moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST >10 x ULN), starting dose of ABRAXANE should be 12.5 mg/m².

• In patients with impaired renal function (creatinine clearance <60 mL/min) and severe hepatic impairment (AST greater than 10 x ULN), a starting dose of ABRAXANE should not be used.

• In patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/μL and total bilirubin ≤1.5 x ULN, ABRAXANE should not be used.

• In patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/μL or platelet (PLT) count of less than 100,000 cells/μL, a starting dose of ABRAXANE should be used at the lowest level that results in neutrophil counts ≥750 cells/μL.

• In patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/μL, then resume treatment at reduced dose levels

• Among the most common (≥20%) adverse reactions in the phase III study, those with a ≥2% incidence in the ABRAXANE/gemcitabine group compared with the gemcitabine group were: asthenia (75%), nausea (57%), dysgeusia (17%), headache (10%), decreased appetite (5%), diarrhea (5%), vomiting (4%), pyrexia (4%) and peripheral neuropathy (4%).

• 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, were: asthenia (12%), nausea (10%), dysgeusia (9%), headache (6%), decreased appetite (6%), diarrhea (6%), vomiting (5%), pyrexia (4%), and peripheral neuropathy (4%).

• In patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/μL and total bilirubin ≤1.5 x ULN, the incidence of adverse reactions with a ≥2% higher incidence of Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared with the gemcitabine group, were: asthenia (18%), nausea (9%), dysgeusia (9%), headache (6%), decreased appetite (6%), diarrhea (6%), vomiting (5%), pyrexia (4%), and peripheral neuropathy (4%).

• 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, were: asthenia (12%), nausea (10%), dysgeusia (9%), headache (6%), decreased appetite (6%), diarrhea (6%), vomiting (5%), pyrexia (4%), and peripheral neuropathy (4%).

• In patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/μL and total bilirubin >1.5 x ULN, the incidence of adverse reactions with a ≥2% higher incidence of Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared with the gemcitabine group, were: asthenia (27%), nausea (14%), dysgeusia (10%), headache (6%), decreased appetite (6%), diarrhea (6%), vomiting (5%), pyrexia (4%), and peripheral neuropathy (4%).

• 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, were: asthenia (12%), nausea (10%), dysgeusia (9%), headache (6%), decreased appetite (6%), diarrhea (6%), vomiting (5%), pyrexia (4%), and peripheral neuropathy (4%).

• The most common serious adverse reactions of ABRAXANE (with a ≥1% higher incidence) were pneumonitis, including some cases that were fatal, occurring in 4% of patients receiving ABRAXANE in combination with gemcitabine.

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• Do not administer ABRAXANE in patients who have baseline hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN). The starting dose of ABRAXANE should be 25 mg/m².

• In patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/μL, ABRAXANE should not be used.

• In patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/μL and moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST >10 x ULN), ABRAXANE should not be used.

• In patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/μL and severe hepatic impairment (AST greater than 10 x ULN), ABRAXANE should not be used.

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ABRAXANE® and gemcitabine in first-line MPAC:
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.**

Administer ABRAXANE intravenously at a dose of 125 mg/m²

The majority of ABRAXANE doses were administered at full dose and as scheduled.

- 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.

**Percentage of patients who had at least one ABRAXANE dose modification**

- 41% of 421 patients had at least one ABRAXANE dose reduction.
- 71% of 421 patients had at least one ABRAXANE dose delayed or withdrawn.

**Timing of dose modifications in the MPACT Trial**

- 60% (155/257) of ABRAXANE dose reductions occurred after 3 months of treatment.
- 72% (180/250) of ABRAXANE dose delays occurred after 3 months of treatment.

**Adverse reactions in the phase III MPACT trial**

- 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 QW3/4.
- Median time to onset of Grade 3 neuropathy was 15 months (9, 136).
- Median time to improvement to ≤ Grade 1 after withholding dose was 29 days.
- 17% of patients developed ≥ Grade 3 peripheral neuropathy in the ABRAXANE + gemcitabine arm (282/1790).
- 54% of patients experienced peripheral neuropathy of any grade in the ABRAXANE + gemcitabine arm (22/421).

**Appropriate treatment adjustments for peripheral neuropathy**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Treatment adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recommend dose reduction of ABRAXANE®; 125 mg/m²</td>
</tr>
<tr>
<td>2</td>
<td>Reduce to next lower dose level; discontinue treatment if toxicity persists</td>
</tr>
<tr>
<td>3</td>
<td>Withhold dose</td>
</tr>
<tr>
<td>4</td>
<td>Withhold dose</td>
</tr>
</tbody>
</table>

**Appropriate treatment adjustments for hematologic ARs**

<table>
<thead>
<tr>
<th>ANC</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500</td>
<td>&lt;50,000</td>
</tr>
<tr>
<td>500 - &lt;1000</td>
<td>50,000 - &lt;75,000</td>
</tr>
<tr>
<td>1000 - &lt;1500</td>
<td>75,000 - &lt;100,000</td>
</tr>
<tr>
<td>≥1500</td>
<td>≥100,000</td>
</tr>
</tbody>
</table>

**Clearly defined dose modifications**

- Full dose: 125 mg/m²
- 1st dose reduction: 100 mg/m²
- 2nd dose reduction: 75 mg/m²
- If additional dose reduction required: Discontinue

**References:**
1. ABRAXANE Prescribing Information, Celgene Corporation.

**Please see additional Important Safety Information inside and accompanying full Prescribing Information, including Boxed WARNING.**
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**ABRAXANE® + gemcitabine in first-line MPAC: Starting dose and appropriate dose modifications**

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