ABRAXANE® Plus gemcitabine Receives European Marketing Authorization for First-Line Treatment of Patients with Metastatic Pancreatic Cancer

First new treatment to be approved for pancreatic cancer in nearly seven years, highlighting the challenges and unmet needs in treating the disease

BOUDRY, Switzerland--(BUSINESS WIRE)--Celgene International Sàrl, a wholly-owned subsidiary of Celgene Corporation (NASDAQ: CELG), today announced that the European Commission (EC) has granted approval for ABRAXANE (paclitaxel formulated as albumin bound nanoparticles, or nab-paclitaxel) in combination with gemcitabine for first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, or metastatic pancreatic cancer.1

“With such low survival rates for this disease, the situation for patients and their families is really very poor. But now, we have been able to show that the addition of nab-paclitaxel to conventional treatment with gemcitabine provides substantial benefits in overall survival, with manageable side effects”

During the last few decades, little progress has been made in improving outcomes for patients diagnosed with pancreatic cancer. According to the European Cancer Observatory, 78,654 people were diagnosed with pancreatic cancer in the EU in 2012, and 77,940 died that same year.2 The mortality of pancreatic cancer is high, making it the fourth deadliest cancer for both men and women.3 Patients diagnosed with metastatic disease have a median life expectancy, after diagnosis, of approximately three to six months.4 There have been no new medications approved for pancreatic cancer in nearly seven years.

Alan Colowick, MD, President of Celgene Europe, the Middle East and Africa (EMEA), added: “ABRAXANE in combination with gemcitabine is the first treatment in Europe to be approved for pancreatic cancer in nearly seven years. In fact, since 1990, more than 30 Phase III trials have failed to lead to regulatory approval in the European Union for advanced or metastatic pancreatic cancer. Today’s announcement is a significant step forward, but it is by no means the end for Celgene. We remain committed to developing innovative treatments to improve the lives of those with this devastating disease.”

The EC decision was based on the results of the MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial), an open-label, Phase III, randomized, international study published in the New England Journal of Medicine in its 31 October 2013 edition. The MPACT study involved 861 chemotherapy-naïve patients with metastatic pancreatic cancer at 151 community and academic centers from 11 countries, including North America, Eastern and Western Europe, and Australia. In the study, ABRAXANE plus gemcitabine demonstrated a statistically significant improvement in median overall survival compared to gemcitabine alone (8.5 vs. 6.7 months) (HR 0.72, P<0.0001); a 28% overall reduction in risk of death.5

Grade 3 and higher adverse events that were reported more often with ABRAXANE plus gemcitabine versus gemcitabine alone were neutropenia, fatigue, and peripheral neuropathy.5

The EC decision follows the positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) in November 2013.6

ABRAXANE will be launched in the European Union in the coming months according to local requirements.
ABOUT ABRAXANE®

ABRAXANE is an albumin-bound form of paclitaxel that is manufactured using patented nab® technology. ABRAXANE is formulated with albumin, a human protein, and is free of solvents.

In the European countries covered by the European Commission, ABRAXANE was approved in January 2008 as monotherapy for the treatment of metastatic breast cancer (MBC) in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.

In the United States, ABRAXANE was first approved in January 2005 by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. ABRAXANE has been globally approved in more than forty countries for the treatment of MBC.

In October 2012, ABRAXANE was approved by the FDA for first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. ABRAXANE is also approved for the treatment of NSCLC in Argentina, Australia, Japan and New Zealand.

In September 2013, the FDA approved ABRAXANE as first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

IMPORTANT SAFETY INFORMATION BASED ON APPROVED U.S. LABEL

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 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 myelotoxicity 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 ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/mm³
- In the case of severe neutropenia (<500 cells/mm³ for 7 days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC
- In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1500 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 ABRAXANE 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
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 or 2 for MBC or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer 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

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
- For MBC and NSCLC, the starting dose should be reduced for patients with moderate or severe hepatic impairment
- For pancreatic adenocarcinoma, ABRAXANE is not recommended for patients with moderate or severe hepatic impairment

Albumin (Human)

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

Use in Pregnancy: Pregnancy Category D

- ABRAXANE can cause fetal harm when administered to a pregnant woman
- If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus
- Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE

Use in Men

- Men should be advised not to father a child while receiving ABRAXANE

ADVERSE REACTIONS

Randomized Metastatic Breast Cancer (MBC) Study
The most common adverse reactions (≥20%) with single-agent use of ABRAXANE vs paclitaxel injection in the MBC study are alopecia (90%, 94%), neutropenia (all cases 80%, 82%; severe 9%, 22%), sensory neuropathy (any symptoms 71%, 56%; severe 10%, 2%), abnormal ECG (all patients 60%, 52%; patients with normal baseline 35%, 30%), fatigue/asthenia (any 47%, 39%; severe 8%, 3%), myalgia/arthralgia (any 44%, 49%; severe 8%, 4%), AST elevation (any 39%, 32%), alkaline phosphatase elevation (any 36%, 31%), anemia (any 33%, 25%; severe 1%, <1%), nausea (any 30%, 22%; severe 3%, <1%), diarrhea (any 27%, 15%; severe <1%, 1%) and infections (24%, 20%), respectively

Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients

Renal dysfunction (any 11%, severe 1%) was reported in patients treated with ABRAXANE (n=229)

In all ABRAXANE-treated patients (n=366), ocular/visual disturbances were reported (any 13%; severe 1%)

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients and 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.

Non–Small Cell Lung Cancer (NSCLC) Study

The most common adverse reactions (≥20%) of ABRAXANE in combination with carboplatin are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue

The most common serious adverse reactions of ABRAXANE in combination with carboplatin for NSCLC are anemia (4%) and pneumonia (3%)

The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%)

The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (24%), thrombocytopenia (13%), and anemia (6%)

The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%)

The following common (≥10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE 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 ABRAXANE plus carboplatin treatment group

Adverse reactions with a difference of ≥2%, Grade 3 or higher, with combination use of ABRAXANE and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anesthesia (28%, 7%), neutropenia (47%, 58%), thrombocytopenia (18%, 9%), and peripheral neuropathy (3%, 12%), respectively

Adverse reactions with a difference of ≥5%, Grades 1-4, with combination use of ABRAXANE and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are asthenia (98%, 91%), anemia (50%, 47%), peripheral neuropathy (68%, 55%), peripheral edema (10%, 4%), epistaxis (7%, 2%), arthralgia (13%, 25%), and myalgia (10%, 19%), respectively

Neutropenia (all grades) was reported in 85% of patients who received ABRAXANE and carboplatin vs 83% of patients who received paclitaxel injection and carboplatin

Pancreatic Adenocarcinoma Study

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.
- 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

Nursing Mothers

- It is not known whether paclitaxel is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric

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

Geriatric

- No toxicities occurred notably more frequently among patients ≥65 years of age who received ABRAXANE for MBC.
- Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients ≥65 years of age treated with ABRAXANE and carboplatin in NSCLC.
- 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

- The use of ABRAXANE has not been studied in patients with renal impairment.

DOSAGE AND ADMINISTRATION

- For MBC and NSCLC, dose adjustment is recommended for patients with moderate and severe hepatic impairment. Withhold ABRAXANE if AST >10 x ULN or if bilirubin >5 x ULN.
- For adenocarcinoma of the pancreas, withhold ABRAXANE if bilirubin ≥1.26 x ULN or if AST >10 x ULN.
- Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicity.
- Monitor patients closely.

Please see full Prescribing Information, including Boxed WARNING at http://abraxane.com/downloads/Abraxane_PrescribingInformation.pdf

About Celgene
Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global pharmaceutical company engaged primarily in the discovery, development and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through gene and protein regulation. Celgene International Sàrl, located in Boudry, Switzerland, is a wholly owned subsidiary and international headquarters of Celgene Corporation. For more information, please visit www.celgene.com.

Forward-Looking Statements

This press release contains forward-looking statements, which are generally statements that are not historical facts. Forward-looking statements can be identified by the words "expects," "anticipates," "believes," "intends," "estimates," "plans," "will," "outlook" and similar expressions. Forward-looking statements are based on management's current plans, estimates, assumptions and projections, and speak only as of the date they are made. Celgene Corporation undertakes no obligation to update any forward-looking statement in light of new information or future events, except as otherwise required by law. Forward-looking statements involve inherent risks and uncertainties, most of which are difficult to predict and are generally beyond our control. Actual results or outcomes may differ materially from those implied by the forward-looking statements as a result of the impact of a number of factors, many of which are discussed in more detail in Celgene Corporation's Annual Report on Form 10-K and its other reports filed with the Securities and Exchange Commission.

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References

1 ABRAXANE Summary of Product Characteristics


3 Malvezzi M et al. Ann Oncol 2013;24:792-800


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