EU-RISK MANAGEMENT PLAN FOR ABRAXANE® (PACLITAXEL [FORMULATED AS ALBUMIN BOUND NANOPARTICLES])

VERSION 17.1, 06 DEC 2018

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EU-RISK MANAGEMENT PLAN FOR ABRAXANE

RMP Version to be Assessed as Part of this Application	Version 17.1
Data Lock Point for this Current European Union–Risk Management Plan (EU-RMP)	06 Jan 2018
Date of Final Sign Off	06 Dec 2018
Rationale for Submitting an Updated RMP	Updated in line with Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur Updated Assessment Report for RMP Version 17.0. Reclassification of important identified risks to align with Revision 2 of the Good Pharmacovigilance Practices (GVP) Module V and the new published template of the the EU-RMP.

Table 1: Summary of Significant Changes in this RMP

Part	Module/Annex	Significant Changes in Each Module
Part I	--	**Changes to align with the updated RMP template.**
Part II Safety Specification	**Module SI** Epidemiology of the Indication and Target Population(s)	No changes
	Module SII Nonclinical Part of the Safety Specification	No changes
	Module SIII Clinical Trial Exposure	No changes
	Module SIV Populations Not Studied in Clinical Trials	No changes
	Module SV Postauthorization Experience	No changes
	Module SVI Additional EU Requirements for the Safety Specification	No changes
	Module SVII Identified and Potential Risks	Reclassification of important identified risks.
	Module SVIII Summary of the Safety Concerns	Reclassification of important identified risks.
Part III Pharmacovigilance Plan (Including Postauthorization Safety Studies)	--	Updated to reflect changes in the list of safety concerns.

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Part IV Plan for Postauthorization Efficacy Studies	--	No changes.
Part V Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	--	Updated to reflect changes in the list of safety concerns.
Part VI Summary of the Risk Management Plan	--	Updated to reflect changes in the list of safety concerns.
Part VII Annexes	**ANNEX 1** Eudravigilance Interface	Updated to reflect changes in the list of safety concerns.
	ANNEX 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	No changes
	ANNEX 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan	No changes
	ANNEX 4 Specific Adverse Drug Reaction Follow-up Forms	Not applicable
	ANNEX 5 Protocols for Proposed and Ongoing Studies in RMP Part IV	Not applicable
	ANNEX 6 Details of Proposed Additional Risk Minimization Activities (if Applicable)	Not applicable
	ANNEX 7 Other Supporting Data (Including Referenced Material)	Updated.
	ANNEX 8 Summary of Changes to the Risk Management Plan Over Time	No changes

Other RMP Versions under Evaluation:

RMP Version Number	Submitted On	Procedure Number
None		

Details of the Currently Approved RMP:

Version Number	16.0
Approved with Procedure	Procedure number (PSUSA): PSUSA/00010123/201501 eCTD sequence: 0159
Date of Approval (Opinion Date)	09 Jul 2015

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QPPV NAME AND CONTACT PERSON FOR THIS EU-RISK MANAGEMENT PLAN

Qualified Person for Pharmacovigilance (QPPV) and Contact Person for this RMP	Priv. Doz. Dr. Stefan Kaehler
Signature	{See appended electronic signature page}
Position	Exec. Dir., EEA-QPPV, Global Drug Safety and Risk Management International
E-mail Address or Telephone Number of Contact Person	[redacted]

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LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
ABX/ABI-007	ABRAXANE
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AI	Aromatase inhibitor(s)
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUC-6	Area under the curve 6 mg/mL x min
AUC_{0-24h}	Area under the curve 0 to 24 hours
BMI	Body Mass Index
CCDS	Company Core Data Sheet
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
ChT	Chemotherapy
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLE	Cutaneous lupus erythematosus
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance
CSR	Clinical Study Report
CT	Computerized tomography
CYP	Cytochrome P450
dFdU	2',2'-difluoro-2' deoxyuridine
DHPC	Direct Healthcare Professional Communication

[redacted]

LIST OF ABBREVIATIONS (CONTINUED)

DILE	Drug-induced lupus erythematosus
DILI	Drug-induced liver injury
DLT(s)	Dose-limiting toxicit(y/ies)
DNA	Deoxyribonucleic acid
E	Evaluation
ECOG	Eastern Cooperative Oncology Group
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EML4	Echinoderm microtubule-associated protein-like 4
EML4-ALK	A fusion protein between the N-terminal portion of the EML4 protein and the intracellular signaling portion of the ALK tyrosine kinase receptor
EP	European Pharmacopoeia
EPAR	European Public Assessment Reports
EPIC	European Prospective Investigation into Cancer and Nutrition
EPITT	European Pharmacovigilance Issues Tracking Tool
ER	Estrogen receptor
ET	Endocrine therapy
EU	European Union
EUROCARE	European Concerted Action on Survival and Care of Cancer Patients
FDA	Food and Drug Administration
FOLFIRINOX	Folinic acid (leucovorin), fluorouracil, irinotecan, and oxaliplatin
G3	Grade 3
G4	Grade 4
G-CSF	Granulocyte-colony stimulating factor
Gem	Gemcitabine
GLP	Good Laboratory Practice
GPRD	General Practice Research Database
GVP	Good Pharmacovigilance Practices
HCP	Health Care Provider
Her2	Human epidermal growth factor receptor 2
HER2	Her2-directed therapy

LIST OF ABBREVIATIONS (CONTINUED)

HGPRT	Hypoxanthine guanine phosphoribosyl transferase
HLA	Human leukocyte antigen
HLGT	High-Level Group Term
HLT	High-Level Term
HSA	Human serum albumin
HUS	Hemolytic-uremic syndrome
ICH	International Conference on Harmonisation
IHA	Immune hemolytic anemia
IIT(s)	Investigator Initiated Trial(s)
ILD	Interstitial lung disease
INN	International Nonproprietary Name
IV	Intravenous(ly)
KPS	Karnofsky Performance Status
L&Z	Xanthophylls-lutein, zeaxanthin, and meso-zeaxanthin
LD_{10}	Dose that is lethal to 10% of the tested group
LD_{50}	Dose that is lethal to 50% of the tested group
LDH	Lactate dehydrogenase
LVD	Left ventricular dysfunction
MA	Marketing Authorization
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEDPAR	Medicare Provider Analysis and Review
MRP2	Multidrug resistance-associated protein-2
NDA	New Drug Application
NEC	Not elsewhere classified
NOAEL	No-observed-adverse-effect-level
NSCLC	Non–small cell lung cancer
OR(s)	Odds ratio(s)
OS	Overall survival
PCR	Patient case record

LIST OF ABBREVIATIONS (CONTINUED)

PD	Pharmacodynamic(s)
PFS	Progression free survival
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic/Pharmacodynamic
PSUR	Periodic Safety Update Report
PT(s)	Preferred term(s)
Q3W	Once every 3 weeks
QPPV	Qualified Person Responsible for Pharmacovigilance
R	Reporting
RMP	Risk Management Plan
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SCLE	Subacute cutaneous lupus erythematosus
SEER	Surveillance, Epidemiology and End Results
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPARC	Secreted Protein Acidic Rich in Cysteine
STA	Specialized Therapeutics Australia
T	Trastuzumab
TEAE(s)	Treatment-emergent adverse event(s)
TEN	Toxic epidermal necrolysis
UK	United Kingdom
ULN	Upper limit of normal
US/USA	United States/United States of America
USPI	United States Prescribing Information
UVL	Ultraviolet light

LIST OF ABBREVIATIONS (CONTINUED)

VM_{EL}	Maximum elimination rate
VTE	Venous thromboembolism
WBC	White blood cell

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PART I - PRODUCT(S) OVERVIEW

Table 2: Product Overview ABRAXANE

Active Substance(s) (International Nonproprietary Name [INN] or common name)	Paclitaxel albumin (formulated as albumin bound nanoparticles)
Pharmacotherapeutic Group(s) (Anatomical Therapeutic Chemical Classification [ATC] Code)	Taxanes L01CD01
Marketing Authorization Holder (MAH) or Applicant	Celgene Europe BV Winthontlaan 6 N 3526 KV Utrecht Netherlands
Medicinal Products to which this Risk Management Plan (RMP) Refers	1
Invented Name in the European Economic Area (EEA)	ABRAXANE®
Marketing Authorization Procedure	Central marketing authorization granted 11 Jan 2008; Authorization Number(s) EU/1/07/428/001-002
Brief Description of Product Including Chemical Class, Summary of Mode of Action, Important Information About its Composition (e.g. Origin of Active Substance of Biologicals, Relevant Adjuvants or Residual Vaccines)	Chemical Class: Taxane Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerisation. 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. In addition, paclitaxel induces unusually stable tubulin complexes and abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules, which interfere with mitosis resulting in cell death. The paclitaxel in ABRAXANE is derived from herbal sources (yew trees, Taxus spp). Human albumin derived from blood/plasma is sourced from third party suppliers with a Plasma Master File. ABRAXANE (paclitaxel formulated as albumin bound nanoparticles) contains human serum albumin (HSA) paclitaxel nanoparticles of approximately 130 nm in size, where the paclitaxel is present in a noncrystalline, amorphous state. Upon intravenous (IV) administration, the nanoparticles dissociate rapidly into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size. Albumin is known to mediate endothelial caveolar transcytosis of plasma constituents, and in vitro studies demonstrated that the presence of albumin in ABRAXANE enhances transport of paclitaxel across endothelial cells. It is hypothesized that this enhanced transendothelial caveolar transport is mediated by the gp 60 albumin receptor, and that there is enhanced accumulation of paclitaxel in the area of tumor due to the albumin binding protein Secreted Protein Acidic Rich in Cysteine (SPARC). The medicinal product is provided as a powder in a vial containing nanoparticles of HSA bound paclitaxel. The powder is reconstituted with 20 mL sodium chloride 9 mg/mL (0.9%) solution for infusion to form a suspension for infusion.

Hyperlink to the Product Information	*Summary of Product Characteristics (SmPC)*
Indication(s) in the EEA	
Current	ABRAXANE in Combination With Carboplatin ABRAXANE in combination with carboplatin is indicated for the first-line treatment of non–small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. ABRAXANE in Combination With Gemcitabine ABRAXANE in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. ABRAXANE Monotherapy ABRAXANE monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.
Proposed	None
Dosage in the EEA	
Current	ABRAXANE in Combination With Carboplatin The recommended dose of ABRAXANE is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each 21-day cycle. The recommended dose of carboplatin is area under the curve (AUC) = 6 mg•min/mL on Day 1 only of each 21-day cycle, beginning immediately after the end of ABRAXANE administration. ABRAXANE in Combination With Gemcitabine The initial recommended dose of ABRAXANE is 125 mg/m^2 administered intravenously (IV) over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1000 mg/m^2 administered IV over 30 minutes beginning immediately after the completion of ABRAXANE administration on Days 1, 8 and 15 of each 28-day cycle. ABRAXANE Monotherapy The initial recommended dose of ABRAXANE is 260 mg/m^2 administered IV over 30 minutes every 3 weeks.
Proposed	None

Pharmaceutical Form(s) and Strength(s)	
Current	Powder for suspension for infusion. White-to-yellow powder. The reconstituted suspension has a pH of 6 to 7.5, and an osmolality of 300 to 360 mOsm/kg. Each vial contains 100 mg or 250 mg of paclitaxel formulated as albumin bound nanoparticles. After reconstitution with 20 mL (100 mg vials) or 50 mL (250 mg vials) sodium chloride 9 mg/mL (0.9%) solution for infusion, each milliliter of suspension contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.
Proposed	None
Is the Product Subject to Additional Monitoring in the European Union (EU)?	No

PART II - SAFETY SPECIFICATION

PART II - MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

1. INDICATION

The approved indications of ABRAXANE in the EU are described below.

ABRAXANE in Combination With Carboplatin

ABRAXANE in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

ABRAXANE in Combination With Gemcitabine for Pancreatic Cancer

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

ABRAXANE Monotherapy for Metastatic Breast Cancer

ABRAXANE monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.

2. EPIDEMIOLOGY OF THE DISEASE

2.1. Incidence, Prevalence, Mortality and Demographic Profile of the Non–small Cell Lung Cancer Population

The incidence, prevalence, mortality, and demographics of the population of patients with NSCLC are summarized in Table 3.

Table 3: Epidemiology of Patients with Non–small Cell Lung Cancer

Indication/Target Population	**NSCLC**
Incidence of Target Indication	In Europe, lung cancer was the fourth most common cause of cancer in 2012 (Ferlay, 2013). Lung cancer incidence and mortality, worldwide, follows the historical patterns of smoking, albeit with a 20- to 30-year lag (Garcia, 2007). A recent estimate of the age-standardised incidence rate of lung cancer in Europe is 29.0 per 100,000 person-years based on data from GLOBCAN 2012 (Ferlay, 2013).
Prevalence of Target Indication	Cancer of the lung and bronchus had a 5-year prevalence of 410,201 in Europe based on the GLOBOCAN 2012 data (315,335 men, 127,475 women) in Europe (Ferlay, 2013). According to GLOBOCAN 2012 data, lung cancer accounted for 12.0% of all cancers in Europe (Ferlay, 2013).
Natural History, Including Mortality and Morbidity	Due to low survival in most lung cancer patients, the incidence and mortality rates are very similar. A recent estimate of the mortality rate of lung cancer in Europe is 24.0 per 100,000 person-years based on available data and projection for 2012 (Ferlay, 2013). Mortality rates of lung cancer in men range from 31.1 to 114.6 per 100,000 person-years in men and 5.2 to 41.3 per 100,000 person-years in women (Bray, 2010). In the Netherlands, the 1-year relative survival rate for NSCLC remained almost 45%, whereas the 5-year survival rate remained about 17% between 1970 and 1997. The 5-year survival rate in patients younger than 70 years remained about 18%, but for patients aged 70 years or older, the 5-year relative survival rate increased from 9% in the 1970s to 16% in the mid 1990s. Relative 1- and 5-year survival rates for patients diagnosed with localized (Stages I or II) NSCLC in the southeastern Netherlands were 74% and 40%, respectively, and 27% and 6%, respectively, for patients with non-localized NSCLC (Janssen-Heijnen, 2003). Based on a UK cancer registry analysis, the median 1-year survival rate for NSCLC was 33.9% (Khakwani, 2013).
Risk Factors for the Disease	Cigarette smoking is the most important risk factor for lung cancer, accounting for about 80% of cases in men and 50% in women worldwide. However, rates of smoking have been declining over time in the European population resulting in declines in prevalence of smoking associated lung cancers and mortality (Didkowska, 2016). Other risk factors include second-hand smoke, air pollution, diet, alcohol, occupational exposure and genetic susceptibility (Garcia, 2007; Bray, 2010; Molina, 2008). Lung cancer in non-smokers is a public health concern. Smoking is a well-established risk factor for lung cancer (Didkowska, 2016). A large population-based study showed a significant increase in the risk of lung cancer in current smokers as compared to former/never smokers (hazard ratio = 1.37 [95% confidence interval (CI): 1.18-1.59]) (Tammemagi, 2004). Second-hand smoking accounts for 1.6% of lung cancer, and studies reported a relative risk between 1.14 and 5.2 in non-smokers living with smokers (Molina, 2008).

Table 3: Epidemiology of Patients with Non–small Cell Lung Cancer (Continued)

Indication/Target Population	NSCLC
	The proportion of lung cancers attributable to urban air pollution in Europe is estimated to be 11% (Molina, 2008). A study of the association between air pollution and lung cancer reported a hazard ratio of 1.22 (95% CI: 1.03-1.45) when the air concentration was 10 μg/m³ for particulate matter less than 10 μm (Raaschou-Nielsen, 2013). Certain genetic risk factors have also been identified to be associated with lung cancer. A meta-analysis of genetic studies showed that patients with NSCLC have a higher frequency of methylation in the O(6)-methylguanine-deoxyribonucleic acid (DNA)-methyltransferase promoter (pooled odds ratio [OR] = 4.43, random effects model) (Gu, 2013). Previous pulmonary disease also appeared to increase the risk of lung cancer. Results of a meta-analysis showed that previous history of chronic obstructive pulmonary disease (COPD), chronic bronchitis or emphysema conferred relative risk of lung cancer of 2.22 (95% CI: 1.66-2.97) (from 16 studies), 1.52 (95% CI: 1.25-1.84) (from 23 studies) and 2.04 (95% CI: 1.72-2.41) (from 20 studies), respectively, and for all these diseases combined, 1.80 (95% CI: 1.60-2.11) (from 39 studies). The relative risk of lung cancer for patients with a previous history of pneumonia was 1.43 (95% CI: 1.22-1.68) (from 22 studies) and for patients with a previous history of tuberculosis was 1.76 (95% CI: 1.49-2.08) (from 30 studies) (Brenner, 2011).
Demographic Profile of Target Population	The age of patients at which lung cancer is diagnosed varies widely, with a median age at diagnosis of approximately 70 years. Non–small cell lung cancer accounts for approximately 85% of lung cancers (Movsas, 2013). Incidence and mortality rates in men are higher than women. Ratios of men to women from reviews of many published studies range from around 1.5 to 20 (Kiyohara, 2010). The incidence rate of lung cancer in men range from 32 to 109 per 100,000 person-years and 6.3 to 52 per 100,000 person-years in women (Ferlay, 2013; Janssen-Heijnen, 2003). In the 2008 release of GLOBOCAN data, lung cancer represented 16.5% of all new cancers in men and 8.5% in women (Ferlay, 2010a). In the updated GLOBOCAN 2012 data, lung cancer represented 16% of all new cancers in men and 7.4% of all new cancers in women (Ferlay, 2013). In an analysis of the Thames Cancer Registry database in the UK, the prevalence of NSCLC in the lung cancer population was 16.6% in men and 15.4% in women from 1970 to 2007 (Riaz, 2012). Analysis of trends over time have shown a decrease in incidence of lung cancer in men and an increase in incidence in women. This trend appears to be associated with changes over time to exposures related to lung cancer, such as smoking (Kiyohara, 2010).
Main Treatment Options	Surgical resection remains the mainstay of treatment for all patients with Stage I and II NSCLC, i.e., for those patients who have no evidence of mediastinal disease or invasion of local organs (Tan, 2014). The role of surgery for Stage III disease is controversial. Patients with completely resectable primary tumors (i.e., T4 N0) have a much better prognosis than those patients whose tumors have spread to ipsilateral mediastinal or subcarinal lymph nodes (i.e., N2), signifying that spread beyond the primary tumor is associated with a poor prognosis. Patients with resectable disease who are not candidates for surgery can be treated with potentially curative local radiation therapy, alone or concurrent with chemotherapy. Patients with Stage IIIb or IV tumors are not surgical candidates (Tan, 2014), and are treated with systemic therapy (e.g., chemotherapy). Radiation therapy may also be used for palliation of patients with unresectable disease, either to the chest, brain for the treatment of brain metastases, or bones for the treatment of bone metastases.

Table 3: Epidemiology of Patients with Non–small Cell Lung Cancer (Continued)

Indication/Target Population	NSCLC
	The current standard of care for patients with Stage IIIb or IV NSCLC who cannot be treated with curative surgery or radiation therapy remains a platinum-containing chemotherapy doublet. For an unselected group of NSCLC patients, carboplatin/paclitaxel is comparable to other regimens, including cisplatin/gemcitabine and cisplatin/pemetrexed; all are approved in both the US and the EU. As a result, carboplatin/paclitaxel remains a commonly used choice for all histologies. For non-squamous patients, European Society for Medical Oncology guidelines recommend cisplatin/pemetrexed (Peters, 2012). However, that regimen has never been prospectively compared head-to-head in non-squamous patients against any regimen, including carboplatin/paclitaxel. For a selected group of patients with non-squamous histology, no prior history of brain metastases, hypertension or bleeding/coagulation abnormalities, bevacizumab (approved in both the US and the EU) can be added to carboplatin/paclitaxel. While pemetrexed and bevacizumab have offered advances for non-squamous patients, those patients with squamous cell carcinoma (SCC) remain underserved by innovation, with limited improvement in therapeutic options since the advent of platinum-doublet chemotherapy. As a result, for patients with SCC histology, carboplatin/paclitaxel remains a commonly used regimen. In the subset of patients who are positive for epidermal growth factor receptor (EGFR) mutation (~10% of the Caucasian population) or EML4-ALK (a fusion protein between the N-terminal portion of the echinoderm microtubule-associated protein-like 4 [EML4] protein and the intracellular signaling portion of the anaplastic lymphoma kinase [ALK] tyrosine kinase receptor) abnormalities (~5% of adenocarcinomas), treatment options include EGFR inhibitors or ALK inhibitors, respectively (Peters, 2012).
Important Comorbidities	• COPD (Janssen-Heijnen, 1998; Lopez-Encuentra, 2002; Moro-Sibilot, 2005). • Cardiovascular Events (Janssen-Heijnen, 1998; Lopez-Encuentra, 2002; Moro-Sibilot, 2005). • Cerebrovascular Events (Janssen-Heijnen, 1998; Lopez-Encuentra, 2002; Moro-Sibilot, 2005). • Other Malignancies (Janssen-Heijnen, 1998; Lopez-Encuentra, 2002). • Hypertension (Janssen-Heijnen, 1998). • Diabetes Mellitus (Janssen-Heijnen, 1998; Lopez-Encuentra, 2002; Moro-Sibilot, 2005). • Peptic Ulcer (Moro-Sibilot, 2005; Klabunde, 2007).

2.2. Incidence, Prevalence, Mortality and Demographic Profile of the Pancreatic Cancer Population

The incidence, prevalence, mortality, and demographics of the population of patients with pancreatic cancer are summarized in Table 4.

Table 4: Epidemiology of Patients with Pancreatic Cancer

Indication/Target Population	**Pancreatic Cancer**
Incidence of Target Indication	In Europe, pancreatic cancer is the eighth leading cause of cancer-related deaths with approximately 65,000 deaths each year and over 95% of affected patients dying of their disease (Ferlay, 2010a). The age-standardized incidence rate of pancreatic cancer in Europe in 2012 was 6.8 per 100,000 people (Ferlay, 2013). The incidence was higher among men, with an age-standardized incident rate of 8.2 per 100,000 men compared to 5.5 per 100,000 women. US Surveillance, Epidemiology and End Results (SEER) estimate annual incidence of pancreatic cancer (1975 to 2015) was 11.97 per 100,000 person-years (Noone, 2018).
Prevalence of Target Indication	The estimated 5-year prevalence of pancreatic cancer in Europe in 2012 was 56,336 people (9 per 100,000) (Ferlay, 2013). Of these, 29,222 (9.8 per 100,000) were men and 27,114 (8.3 per 100,000) were women.
Natural History Including Mortality and Morbidity	The age-standardized mortality rate for pancreatic cancer in Europe in 2012 was 6.6 per 100,000 overall and 8.2 and 5.3 for men and women, respectively (Ferlay, 2013). In 2007, the highest mortality rates (per 100,000) in men were observed in Lithuania (11.1), the Czech Republic (10.7), Hungary (10.7), and Estonia (10.7) (Bosetti, 2012b). For women, the highest mortality rates (per 100,000) were in Iceland (7.9), Hungary (7.2), the Czech Republic (7.0), and Finland (6.7) (Bosetti, 2012b). Conversely, the lowest mortality rates observed for men were in Luxembourg (5.9; in 2006), Portugal (6.2; in 2006), Spain (6.3; in 2005), and UK (6.6; in 2007) and for women were in Luxembourg (2.7; in 2006), Portugal (3.0; in 2006), Belarus (3.2; in 2002 to 2003), and Spain (3.8; in 2005) (Bosetti, 2012b). Five-year survival rates associated with pancreatic cancer are generally less than 5% (Bosetti, 2012b). A registry-based study in England and Wales reported one-year and five-year survival rates for those diagnosed with pancreatic cancer in 1996 to 1999 of 13% and 2% to 3%, respectively (Wood, 2006).
Risk Factors for the Disease	Smoking is an established risk factor for pancreatic cancer with a relative risk of about 2 for current smokers versus patients who have never smoked (Bosetti, 2012b; Ilic, 2016). In the Netherlands Cohort Study, the hazard ratio (95% CI) for current smokers was 1.82 (1.40, 2.38) (Heinen, 2010). In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, the hazard ratio (95% CI) for current smokers was 1.71 (1.36, 2.15) (Vrieling, 2010). Other risk factors include diabetes, chronic pancreatitis, obesity, and heavy alcohol consumption (Bosetti, 2012b; Ilic, 2016). • A case-control study conducted in Australia, two European countries (Netherlands and Poland), and Canada reported statistically significant associations with diabetes and chronic pancreatitis (Maisonneuve, 2010). The odds ratios (ORs; 95% CI) were 2.16 (1.60, 2.91) and 4.68 (2.23, 9.84) for diabetes and chronic pancreatitis, respectively. • A case-control study in the Czech Republic and Slovakia reported an increased risk of pancreatic cancer for those in the highest Body Mass Index (BMI) quartile relative to those in the lowest quartile (Urayama, 2011). The association was stronger in younger patients such that the OR (95% CI) at 20 years of age was 1.79 (1.23, 2.61) and at 40 years of age it was 1.57 (1.09, 2.27). The EPIC study reported a significant association between central adiposity (measured by waist-to-hip ratio and waist circumference) and the risk of pancreatic cancer (Berrington de González, 2006). • In the Netherlands Cohort Study, an increased risk of pancreatic cancer was associated with heavy alcohol consumption (≥ 30 g per day) (Heinen, 2009). The age-adjusted rate ratio (95% CI) was 1.83 (1.24, 2.71).

Table 4: Epidemiology of Patients with Pancreatic Cancer (Continued)

Indication/Target Population	Pancreatic Cancer
Demographic Profile of Target Population	The incidence of pancreatic cancer increases with age, with 55 cases per 100,000/year in patients over 65 years of age and almost 90% diagnosed after age 55 (Ferlay, 2010b; Ilic, 2016). Incidence rates in England and Wales from 1996 to 1999 were highest among those > 84 years of age (Wood, 2006). In Nordic countries from 1996 to 2000, the mean (95% CI) age at diagnosis was 69 (67, 70) years for men and 72 (70, 74) years for women (Nagenthiraja, 2007). Age-standardized incidence rates reported in Europe were 8.2 per 100,000 in men compared to 5.5 per 100,000 in women (Ferlay, 2013). Thus, the male to female ratio for incidence of pancreatic cancer in Europe is 1.49.
Main Treatment Options	Currently, surgical resection, using procedures such as pancreaticoduodenectomy (Whipple procedure) or total pancreatectomy, offers patients the best chance of long-term survival, especially with advances in perioperative and postoperative care. However, only about 15% of patients with adenocarcinoma have resectable disease, and in addition, many patients are not candidates for surgery because of advanced age (Helm, 2008; Lowenfels, 2004). For pancreatic cancer patients who are ineligible for surgery, including those with locally advanced unresectable or metastatic disease, chemotherapy is administered to palliate symptoms and prolong survival. Gemcitabine has been the standard drug therapy for the treatment of patients with locally advanced or metastatic disease pancreatic cancer (Burris, 1997) and is the only agent approved in the EU and US as monotherapy for the first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas. In a comparative study of gemcitabine and 5-fluorouracil (5-FU), gemcitabine produced significant improvement in disease-related symptoms and prolonged survival, resulting in 1-year overall survival (OS) rates of 18% for gemcitabine versus 2% for 5-FU in metastatic pancreatic cancer patients. With gemcitabine, median OS was 5.7 months compared with 4.4 months for 5-FU treatment (Gemzar Summary of Product Characteristics [SmPC]). Although gemcitabine was well tolerated, median OS was still poor in patients with metastatic pancreatic cancer, and newer agents and combination therapies continue to be evaluated. Gemcitabine plus erlotinib, an oral epidermal growth factor inhibitor, achieved modest improvements in survival, with 1-year OS rates of 23.8% for the erlotinib doublet compared to 19.4% for gemcitabine monotherapy (Moore, 2007). For the erlotinib doublet, median OS was 6.4 months, compared to 6.0 months for gemcitabine monotherapy. However, no significant difference was observed in overall tumor response rates between the treatments, and increased adverse events (AEs) were observed with the gemcitabine plus erlotinib doublet compared with gemcitabine monotherapy (Tarceva SmPC). Based on modest improvement in median OS, erlotinib in combination with gemcitabine was approved in Europe and the US. A Phase 2/3 French consortium group study was conducted in patients with metastatic pancreatic cancer to evaluate the combination of folinic acid (leucovorin), fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) compared with gemcitabine alone. The study reported a median OS of 11.1 months for FOLFIRINOX compared with 6.8 months for gemcitabine alone (Conroy, 2011). However, the FOLFIRINOX regimen has not been approved in any country/region and broad application of the original dose regimen to the clinical setting may be limited by its associated toxicities (Kindler, 2012).

Table 4: Epidemiology of Patients with Pancreatic Cancer (Continued)

Indication/Target Population	Pancreatic Cancer
Main Treatment Options (Continued)	The randomized MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) of gemcitabine with or without *nab*-paclitaxel (Von Hoff, 2013) was the first Phase 3 trial to demonstrate a significant survival benefit of adding a second cytotoxic agent to gemcitabine (median OS of 8.5 versus 6.7 months for gemcitabine alone; p = 0.000015). Other clinical endpoints were all significantly greater in patients on the gemcitabine/*nab*-paclitaxel arm. As a result of this study, the US Food and Drug Administration (FDA) approved paclitaxel protein-bound for first-line treatment of pancreatic cancer in Sep 2013, followed by approval in the EU/EEA in Dec 2013. Improvements in patient outcomes with other combination chemotherapy regimens have been limited thus far, and consensus has not been reached on the relative efficacy of regimens involving chemoradiation (Twombly, 2008).
Important Comorbidities	• Diabetes (Urayama, 2011; Heinen, 2010; Maisonneuve, 2010; Vrieling, 2010). • Chronic Pancreatitis (Urayama, 2011; Maisonneuve, 2010). • Venous Thromboembolism (Horsted, 2012). • Depression (Massie, 2004; Massie, 2010).

2.3. Incidence, Prevalence, Mortality and Demographic Profile of the Breast Cancer Population

The incidence, prevalence, mortality, and demographics of the population of patients with breast cancer are summarized in Table 5.

Table 5: Epidemiology of Patients with Breast Cancer

Indication/Target Population	Breast Cancer
Incidence of Target Indication	The age-standardized incidence rate of breast cancer in Europe in 2012 was 69.9 per 100,000 women (Ferlay, 2013). The highest incidence rates of breast cancer per 100,000 women in Europe were observed in Belgium (101.3), Switzerland (99.1), France (98.1), and Italy (88.4 to 94.4) and the low rates were observed in Belarus (35.6), Lithuania (43.7), and Latvia (44.1) (Curado, 2011). At the time of diagnosis, 3% to 10% of breast cancer patients present with metastatic disease (Ernst, 2007). In the European Concerted Action on Survival and Care of Cancer Patients (EUROCARE) registry, representing 6 countries (Estonia, France, Italy, Spain, Netherlands, and the UK), 6.2% of incident primary breast cancer cases presented with metastatic disease (Sant, 2004). In the Eindhoven Cancer registry study (South-East Netherlands), 4.5% of breast cancer patients presented with metastatic disease from 1995 through to 2002 (Ernst, 2007). The most common metastatic site was bone (55%), followed by liver (23%), and lung (18%). The least common sites were skin (7%) and brain (3%). In a population-based cohort study in Denmark, 5% of women with newly-diagnosed breast cancer presented with metastases (Jensen, 2011). The most common site of metastases was bone, with 4% of patients diagnosed with bone metastases at either diagnosis or during the follow-up period (median 3.5 years). The 5-year incidence rate of bone metastasis was 10 per 1,000 person-years.

Table 5: Epidemiology of Patients with Breast Cancer (Continued)

Indication/Target Population	Breast Cancer
Incidence of Target Indication (Continued)	In a Swedish National Cancer Registry study, 1.4% of patients with breast cancer were admitted to the hospital with brain metastases and 6.9% were admitted with other distant metastases during a median follow-up period of 3.5 years (Frisk, 2012). The incidence of hospital admission for brain metastases during the first year following a breast cancer diagnosis was 1.1 to 3.1 per 1,000 person-years. The incidence during the first two years was 2.7 to 4.4 per 1,000 person-years. US SEER estimate annual incidence (1975 to 2009) of metastatic breast cancer (MBC): 126.42 per 100,000 person-years (Noone, 2018).
Prevalence of Target Indication	The estimated prevalence of breast cancer in Europe over a 5-year period is 1,814,572 women (553.8 per 100,000 women) (Ferlay, 2013). Prevalence data for MBC are not readily available since many cancer registries do not capture relapses (Cardoso, 2012).
Natural History, Including Mortality and Morbidity	The age-standardized mortality rate associated with breast cancer in Europe in 2012 was 16.1 per 100,000 women (Ferlay, 2013). Mortality rates in the EU in 2006 per 100,000 were 7.74, 55.6, and 96.0 for women aged 20 to 49 years, 50 to 69 years, and 70 to 79 years, respectively (Bosetti, 2012a). Across Europe in 1998 to 2005, breast cancer mortality rates ranged from 7 to 25 per 100,000 women. The highest rates were observed in Denmark, Netherlands, and Ireland. The lowest rates were observed in Spain, Bulgaria, and Finland. Mortality rates have been declining over the past two decades in western European countries (Curado, 2011). In the Eindhoven Cancer Registry study, the median survival time for patients with MBC was 20.5 months (Ernst, 2007). A German study reported a 5-year survival rate for MBC of 21% (Holleczek, 2011).
Risk Factors for the Disease	In addition to a family history of breast cancer, known risk factors for breast cancer include reproductive history, exposure to endogenous and exogenous hormones, and health behaviors (Menvielle, 2011). Specifically, later age at first full-term pregnancy, lower parity or nulliparity, shorter duration of breast-feeding, earlier age at menarche, later age at menopause, use of oral contraceptives or hormone replacement therapy, obesity, smoking, high alcohol intake, and physical inactivity have been associated with an increased risk of breast cancer (Menvielle, 2011; DeRoo, 2010; Kruk, 2007).
Demographic Profile of Target Population	The risk of breast cancer increases for women over 50 years of age and the mortality rate is higher in postmenopausal women (Curado, 2011). In the Eindhoven Cancer Registry study, patients with MBC tended to be in the older age groups: 23% were less than 50 years, 39% were between 50 and 69 years, and 37% were 70 years or older (Ernst, 2007). A study from the Thames Cancer Registry reported a higher incidence of breast cancer in white women. However, white women were least likely to have MBC. Seven percent of white women with breast cancer in the study had metastatic disease, while Pakistani women had the highest rate (17%) of metastatic disease (Jack, 2009). Breast cancer in men is very rare. Reported incidence in men ranges from 0.23 to 1.24 per 100,000 man-years (Ly, 2012). In comparison to female incidence, the rate ratio (females to males) ranges from 64.3 to 204.5 (Ly, 2012). A higher incidence of breast cancer has been observed in the least socioeconomically deprived groups in the UK with a relative risk (95% CI) of 0.84 (0.82, 0.85) among the most deprived group compared to the least deprived group (Shack, 2008). Similarly, higher education is associated with an increased risk of breast cancer (Menvielle, 2011).

Table 5: Epidemiology of Patients with Breast Cancer (Continued)

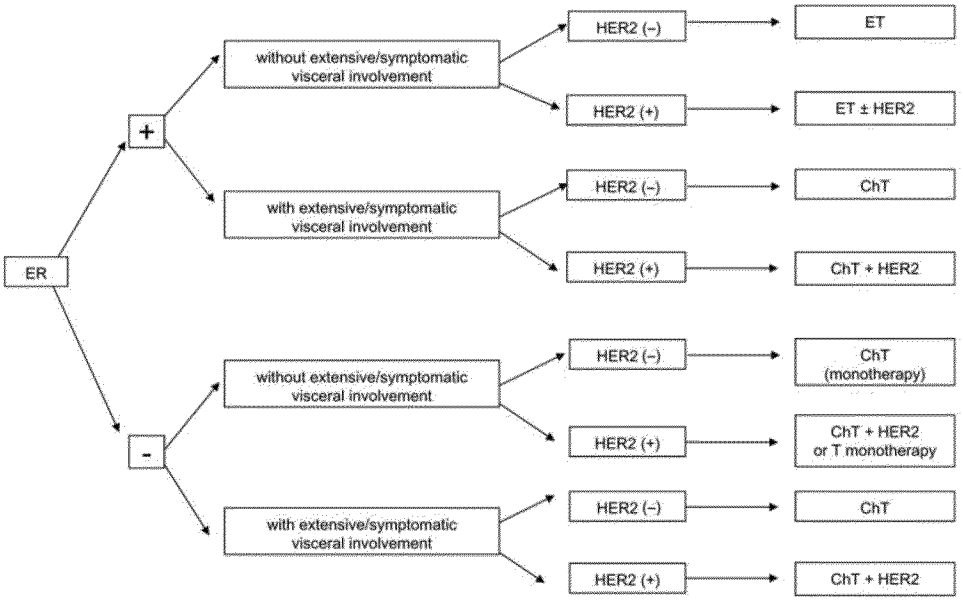
Indication/Target Population	**Breast Cancer**
Main Treatment Options	The treatment of MBC should be multidisciplinary, including specialists in the areas of medical oncology, radiation therapy, surgery, palliative care and imaging. Treatment is palliative in principle, as MBC is in its majority not curable. Radiation therapy is commonly used in cases of painful bone metastasis, brain metastasis, fungating masses or bleeding complications. Systemic therapy can include hormonal therapy, chemotherapy and targeted agents, and to date, clinical trials should be considered as priority as for those patients there are only few proven standards of care. Treatment has to be individualized according to hormone receptor/Human epidermal growth factor receptor 2 (Her2) status, bulk of disease and patient's clinical condition. The use of sequential single agent treatment should be considered and OS is similar to patients who receive combination treatment, and combination treatment should be indicated for patients with aggressive disease, rapid disease progression or visceral involvement. Patients with Her2 positive disease should receive Her2 antibody therapy early on, patients with hormonal receptor positive disease should start their treatment with hormonal therapy (as long as there is no urgent need of rapid response, and hormonal therapy should not be combined with chemotherapy). Bone targeted agents are used in case of bone metastasis and include bisphosphonates and denosumab. Cytotoxic chemotherapy is the mainstay of treatment in the group of MBC patients. There are many agents that can be used alone or in combination, among them anthracyclines (doxorubicin, epirubicin, liposomal doxorubicin), taxanes (paclitaxel, docetaxel and *nab*-paclitaxel, which is indicated for the treatment of MBC in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated) and other cytotoxic agents (platinums, gemcitabine, capecitabine, vinorelbine, etc).  ChT = chemotherapy; ER = estrogen receptor; ET = endocrine therapy; HER2 = Her2-directed therapy; T = trastuzumab. Tumor response should be assessed every 2 to 4 cycles of chemotherapy, and throughout treatment lines, quality of life should be assessed and prioritized (Cardoso, 2012).

Table 5: Epidemiology of Patients with Breast Cancer (Continued)

Indication/Target Population	**Breast Cancer**
Important Comorbidities	• Hypertension (Soler, 1999). • Cardiovascular Disease (Louwman, 2005; Hooning, 2007). • Diabetes (Louwman, 2005; Larsson, 2007). • Previous Cancer (Louwman, 2005; Kenney, 2004). • COPD (Louwman, 2005; Halbert, 2003). • Depression[a] (Caplette-Gingras, 2008; Kessler, 1993).

[a] A comorbidity specific to MBC

PART II - MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

1. NONCLINICAL PART OF THE SAFETY SPECIFICATION

Full details of the nonclinical safety data for ABRAXANE are presented in the Nonclinical Overview (Marketing Authorization Application [MAA], Module 2, Section 2.4 Nonclinical Overview).

1.1. Outline of Nonclinical Safety Concerns

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 6.

Table 6: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Toxicity Studies: • **Single and Repeat-dose Toxicity** In the development of ABRAXANE, the nonclinical toxicology program has been focused on evaluating the safety of paclitaxel in ABRAXANE compared with Taxol. The toxicity studies conducted were therefore primarily single-dose studies conducted in rodent species. Only limited evaluation was conducted on the repeat-dose toxicity of ABRAXANE since safety and efficacy of the known active substance paclitaxel is well understood in animals and humans and the necessary comparative toxicology data could be obtained from single-dose studies. Single-dose studies show that ABRAXANE is well tolerated in rats and mice. The doses that were lethal to 50% of the tested group (LD_{50}) and the doses that were lethal to 10% of the tested group (LD_{10}) were notably higher for animals treated with ABRAXANE compared to animals treated with Taxol. ABRAXANE produced less myelosuppression in rats than Taxol (white blood cell [WBC] nadir 24% and 55% below baseline, respectively). Furthermore, the time to recovery from the WBC suppression was less for ABRAXANE, at about 7 days, compared to 14 days for the Taxol-treated animals. The vehicle for Taxol produced neutropenia, which was similar in extent (approximately 61% below baseline) and recovery period to Taxol-induced neutropenia. The vehicle for Taxol, therefore, contributed substantially to the reduction in WBC count. In contrast, the ABRAXANE vehicle produced no significant myelosuppression. There was severe, dose-related atrophy of seminiferous tubules seen in the testes and aspermia in rats administered ≥ 30 mg/kg ABRAXANE. Cerebral cortical necrosis was seen in the 9 mg/kg dose of Taxol-treated rats. In contrast, no cerebral lesions were seen in rats treated with	Repeated dose toxicity testing is used to evaluate drug chronic toxic effects on various organ systems. The target organs/systems evaluated may include liver, kidney, lung, central nervous system (CNS), reproductive organs, the hematopoietic system, the immune system, and the endocrine system. Myelosuppression, particularly neutropenia, and peripheral neuropathy have been validated in the clinic, either during monotherapy with ABRAXANE or in combination regimens. Both are known to be reversible, and can be addressed by dose reduction or discontinuation. Because of the clinical experience with ABRAXANE, an acceptable and manageable safety profile has been observed in patients who received ABRAXANE. In the clinics, ABRAXANE should not be given to patients with known hypersensitivity to the active ingredient, paclitaxel, or to human serum albumin.

Table 6: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
ABRAXANE. The toxicity of ABRAXANE has not been fully assessed in large animal species because the HSA used as a stabilizer for paclitaxel and to facilitate solvent-free administration causes a xenoimmune reaction in dogs. Administration of ABRAXANE in the dog resulted in toxicity that was consistent with an immune reaction to HSA and similar to that expected from serum sickness. A subsequent study in the dog using HSA controls confirmed that both ABRAXANE and control groups exhibited similar symptoms attributed to serum sickness. A non-Good Laboratory Practice (GLP) pilot study was conducted to determine the 5-day repeat dose tolerability of ABRAXANE compared to Taxol in CD-1 mice. The LD_{50} for ABRAXANE was calculated to be 76.2 mg/kg, compared to 8.07 mg/kg for Taxol, demonstrating that ABRAXANE is considerably less toxic to mice than Taxol. A GLP repeat-dose toxicity study was conducted in rats given ABRAXANE at 0, 10, 20, and 30 mg/kg, and paclitaxel at 10 mg/kg, IV a total of 6 times every 5 days over a 30-day period. Reversibility was assessed after a 4-week drug-free period. Mortality occurred in 1/32, 4/32, and 23/32 rats in ABRAXANE 10, 20, and 30 mg/kg groups, respectively. On the contrary, all animals in the 10 mg/kg paclitaxel group survived throughout the study. The toxicity observed in rats intermittently treated with ABRAXANE consisted mainly of atrophic changes in the lymphatic/hematopoietic tissues, male reproductive organs, and skin and degenerative changes in the nervous system and eyes. The no-observed-adverse-effect level (NOAEL) was considered to be less than 10 mg/kg of ABRAXANE. In the paclitaxel group, the toxicological findings were qualitatively similar to those in the ABRAXANE 10 mg/kg group. Notably, however, neuronal necrosis and gliosis in the CNS seen in the paclitaxel group were not observed in rats administered ABRAXANE. The toxic changes attributed to ABRAXANE were mostly reversible by recovery sacrifice, except for the changes in the reproductive organs, nervous system, or eye in the ABRAXANE and paclitaxel groups. The toxicokinetics data in this study showed that the maximum plasma concentration (C_{max}) and area under the curve 0 to 24 hours (AUC_{0-24h}) increased dose-dependently and there were no remarkable gender differences on each dosing day in ABRAXANE groups. In the paclitaxel group, C_{max} and AUC_{0-24h} were higher than those in ABRAXANE 10 mg/kg for both sexes. The C_{max} and AUC_{0-24h} increased in all dosing groups at the final dosing, in comparison with those at the first dosing.	

Table 6: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
In cynomolgus monkeys, administration of 9 mg/kg ABRAXANE by IV infusion on a weekly schedule for 3 weeks led to adverse clinical observations, decreased food consumption, decreased body weights in females, and changes in urinalysis, hematology, and serum chemistry. Postmortem changes included decreased thymic size, organ weight changes, and histopathologic lesions (including hepatic leucocytosis and centrilobular vacuolation). In addition to single agent treatment with ABRAXANE, other arms in this study included combination treatment with nanoparticle albumin bound 17-AAG (*nab*-17-AAG) and trastuzumab. Generally, exposures on Day 8 and Day 15 were comparable to those on Day 1, with the exception of a single male animal on Day 15 that had approximately 3-fold higher C_{max} and AUC. No consistent gender differences in the pharmacokinetic (PK) parameters were apparent.	
• **Reproductive and Developmental Toxicity** Developmental toxicity in rats was evident in all test groups above 0.5 mg/kg/day with incidence and severity increasing as the dose was escalated (Study 4701-001). In particular, ABRAXANE caused early resorption, and there were no live fetuses at 21 days in the 4 and 8 mg/kg/day groups. The mating index was reduced in male rats receiving 7 and 16 mg/kg ABRAXANE, as was sperm count and fertility (Study 4701-002). This was considered to be due to an inhibition of mitosis in germ cells as a consequence of incorrect microtubule organization. This resulted in a suppression of spermatogenesis at the higher dose levels and lowering of fertilization. Effects on fertility were partially reversible in the male rat at 7 mg/kg. The NOAEL for fertility in the male rat was 2 mg/kg.	Clinicians and patients prescribing/receiving products containing paclitaxel should be advised about the likely adverse reactions on the male and female reproductive systems, since there are recorded effects in rodents that include reduction in male fertility and embryo/fetal toxicity. These effects may occur at exposure levels that are not in excess of those to be encountered in human clinical use. Therefore, a risk-benefit analysis should be made relative to the indication. Due to the fetal toxicity effects of paclitaxel in animals and the limited data of its effects during human pregnancy, ABRAXANE should not be used to treat pregnant women or women of childbearing potential not using effective contraception, unless the clinical condition of the mother requires treatment with paclitaxel. Similarly, as it is not known whether paclitaxel is excreted in human milk and because of potential serious adverse reactions in breast-feeding infants, ABRAXANE should not be used during lactation and breast-feeding must be discontinued for the duration of therapy. Male patients treated with ABRAXANE should be advised not to father a child during and up to six months after treatment. Since ABRAXANE induced infertility in male rats, it is possible that it may have a similar effect in humans. Therefore, male patients should be advised to seek advice on conservation of sperm prior to treatment.

Table 6: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
• **Nephrotoxicity** No separate studies were performed to investigate nephrotoxicity. The repeat-dose toxicity studies, described above, did, however, assess all organ systems and no ABRAXANE-related nephrotoxicity was observed.	The absence of definitive findings of nephrotoxicity in the repeat dose toxicity studies leads to the conclusion that clinical data are the most appropriate to assess effects in this organ system.
• **Hepatotoxicity** No separate studies were performed to investigate hepatotoxicity. The repeat-dose toxicity studies, described above, did, however, assess all organ systems and no ABRAXANE-related hepatotoxicity was observed.	The absence of definitive findings of hepatotoxicity in the repeat dose toxicity studies leads to the conclusion that clinical data are the most appropriate to assess effects in this organ system.
• **Genotoxicity** Genotoxicity studies have not been conducted with ABRAXANE either in the clinical or nonclinical setting. However, the potential for genotoxic effects of paclitaxel has been widely studied and reported in the literature. The overall conclusion from a number of genotoxicity studies with paclitaxel is that it affects the chromosomal spindle via microtubule disorganization but does not react directly with DNA. The consequence of this is apoptosis or necrosis (Wang, 2000).	Paclitaxel has been shown to be genotoxic in vivo (micronucleus test in mice), but it did not induce mutagenicity in the Ames test or the Chinese hamster ovary/hypoxanthine guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay. Therefore, paclitaxel is a potentially genotoxic agent at clinical doses, based upon its pharmacodynamic (PD) mechanism of action.
• **Carcinogenicity** In accordance with the International Conference on Harmonisation (ICH) *S1A: Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals*, carcinogenicity studies in animals were not conducted with ABRAXANE as this is an anticancer agent. This guideline notes that carcinogenicity testing is not recommended for a medicinal product that will be used intermittently for less than 6 months. Additionally, carcinogenicity testing is not recommended if the life expectancy of the indicated population intended for treatment is short (i.e., less than 2 to 3 years). There are no published data for paclitaxel as a potential initiator of tumors and no studies have been conducted with ABRAXANE. Neither the US National Toxicology Program nor the International Agency for Research on Cancer has listed paclitaxel as a carcinogen.	Although the carcinogenic potential of paclitaxel has not been formally studied, based on the published literature, the drug has been demonstrated to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). Therefore, paclitaxel is a potentially carcinogenic agent at clinical doses, based upon its PD mechanism of action.
General Safety Pharmacology The standard core battery of safety pharmacology tests were not conducted because paclitaxel is a well-known active substance with well-defined safety and efficacy.	The absence of specific safety pharmacology data for ABRAXANE leads to the conclusion that data for solvent-based paclitaxel, inasmuch as they exist, are deemed to be the best surrogate to assess potential off-target effects.

Table 6: Nonclinical Risks and Relevance to Human Use (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Mechanisms for Drug Interactions In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by cytochrome P450 (CYP) 2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. In vitro, the metabolism of paclitaxel to 6α-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, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel in vitro. The PK 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. With the exception of gemcitabine, possible interactions of ABRAXANE with concomitantly administered medications have not been formally investigated because the distribution of paclitaxel to liver (and hence to CYP3A4 and CYP2C8) was not altered significantly from that of the Taxol formulation. A study was conducted in rats to evaluate the PK interaction between ABRAXANE and gemcitabine (Gemzar®) when administered concurrently versus as single agents. Each rat (n = 8 per dose group) received an IV bolus dose of the assigned compound at a target paclitaxel dose level of 21 mg/kg and gemcitabine dose level of 167 mg/kg. Blood samples were collected at various time points up to 48 hours post dose and liquid chromatography-tandem mass spectrometry analysis was performed to quantitate paclitaxel, gemcitabine, and its inactive metabolite, 2',2'-difluoro-2'-deoxyuridine (dFdU). There were no statistically significant differences in plasma paclitaxel and gemcitabine C_{max} and AUC between ABRAXANE + gemcitabine concurrent administration and single-agent treatment groups, suggesting that the concurrent administration of ABRAXANE and gemcitabine has no significant impact on the PK profile of either drug.	Since paclitaxel is metabolized by CYP2C8 and CYP3A4, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures. Although PK interactions between ABRAXANE and gemcitabine have not been evaluated in humans, both compounds do not share a common metabolic pathway. Paclitaxel clearance is primarily determined by CYP2C8- and 3A4-mediated metabolism, while gemcitabine is inactivated by cytidine deaminase. Thus PK-based interactions between the two compounds are not anticipated. A PK study (Study CA031 sub-study 08-DA33) was conducted with ABRAXANE and carboplatin in NSCLC patients. There were no clinically relevant interactions for ABRAXANE on the PK of carboplatin and for carboplatin on the PK of ABRAXANE.

PART II - MODULE SIII: CLINICAL TRIAL EXPOSURE

1. CLINICAL TRIAL EXPOSURE

Cumulatively, up to 06 Jan 2018 (the data cutoff date for the most recent annual ABRAXANE Periodic Safety Update Report [PSUR]; 07 Jan 2017 to 06 Jan 2018), approximately 18,557 subjects have been treated with ABRAXANE in clinical studies, with 5516 in the Celgene development program worldwide and an estimated 13,041 in non-Celgene-sponsored studies globally.

The data cutoff dates for the ABRAXANE clinical studies in the RMP are listed in Table 7.

Table 7: Data Cutoff Dates for ABRAXANE Clinical Studies (Safety Population)

Study		Data Cutoff Date
NSCLC Studies	CA028	31 Jan 2011
	CA031	31 Jan 2011[a]
Pancreatic Cancer Studies	CA040	31 Dec 2010
	CA046	17 Sep 2012
Monotherapy Studies	DM97-123	16 Mar 2000[b]
	CA101	23 Mar 2005
	CA002-0LD	06 Sep 2001[b]
	CA012-0	07 Apr 2003[c]
	CA008	20 Aug 2005[d]
	CA018	10 Jun 2005
	CA002	29 Sep 2001[b]
	CA005	07 Dec 2004[c]
	CA013	11 Jun 2005[f]
	CA014	23 Mar 2006[g]
	CA015	10 Mar 2006
	CA024	31 Jan 2010[h]
	CA201	18 Dec 2006[f]
	CA009	27 Mar 2006
	CA042	25 Jan 2011[j]

[a] At the time of the final analysis of Study CA031 with a data cutoff date of 31 Jan 2011, there were 3 patients in the ABRAXANE in combination with carboplatin arm who had therapy ongoing. The last of the 3 patients discontinued the study on 21 Dec 2012. A summary of key safety data for these 3 patients has been included in the CSR.
[b] Date of last patient assessment.
[c] Date of 9-week assessment for last patient entered (study was ongoing). Close of data collection: 16 Nov 2004.
[d] Includes data through Cycle 13 dosing for 1 ongoing patient (study was ongoing).
[e] Last telephone interview.
[f] Serious adverse event (SAE) cutoff.
[g] Date all data in-house. Last patient completed 03 Apr 2007.
[h] Date of final overall survival data cutoff.

[i] Follow-up was ongoing.
[j] Last patient discontinued 19 Dec 2012.

ABRAXANE in Combination With Carboplatin for Non–small Cell Lung Cancer

Planned doses in Studies CA028 and CA031 were between 100 and 140 mg/m^2 per administration for ABRAXANE and AUC 6 mg/mL x min (AUC-6) for carboplatin. The overall average planned dose for these studies with a weekly regimen was 103 mg/m^2 and the average number of cycles was 6.1.

Patient exposure by dose and number of cycles is presented in Table 8 and Table 9, respectively.

Table 8: Patient Exposure by Dose Weekly Regimen

Planned Study Doses of ABRAXANE Per Administration	Study Numbers	Number (%) of Patients
ABRAXANE + Carboplatin Weekly Regimen for NSCLC[a]		
100 mg/m^2 (Day 1, 8, and 15)	CA028, CA031	539 (92%)
125 mg/m^2 (Day 1, 8, and 15)	CA028	25 (4%)
140 mg/m^2 (Day 1, and 8)	CA028	25 (4%)
TOTAL		**589**
Overall average planned dose	103 mg/m^2	Not applicable

[a] Planned dose of carboplatin was AUC-6

Table 9: Patient Exposure by Number of Cycles Weekly Regimen

Total Cycles Administered	Study Numbers	Number (%) of Patients
ABRAXANE + Carboplatin Weekly Regimen for NSCLC		
1 cycle	CA028, CA031	31 (5%)
2 cycles	CA028, CA031	67 (11%)
3 cycles	CA028, CA031	54 (9%)
4 cycles	CA028, CA031	77 (13%)
5 cycles	CA028, CA031	51 (9%)
6 cycles	CA028, CA031	124 (21%)
7 cycles	CA028, CA031	38 (6%)
8 cycles	CA028, CA031	34 (6%)
9 cycles	CA028, CA031	28 (5%)
10 cycles	CA031	16 (3%)
11 to 17 cycles	CA028, CA031	52 (9%)
≥ 18 cycles	CA028, CA031	17 (3%)
TOTAL		**589**
Overall average number of cycles	6.1 cycles	Not applicable

In addition, 176 patients were exposed to the "every-3-week" dosing regimen for ABRAXANE in combination with carboplatin. Of these patients, 101 (57%) received a dose of 340 mg/m^2 per

[redacted]

administration. Of the remaining 75 patients, 25 (14%) each received 225 mg/m^2, 260 mg/m^2 and 300 mg/m^2 per administration.

Patient exposure by dose and by number of cycles for the patients exposed to the "every-3-week" dosing regimen is presented in Table 10 and Table 11, respectively.

Table 10: Patient Exposure by Dose ("Every 3 Weeks" Regimen)

Planned Study Doses Per Administration	**Study Number**	**Number of Patients**
225 mg/m^2	CA028	25
260 mg/m^2	CA028	25
300 mg/m^2	CA028	25
340 mg/m^2	CA028	101
TOTAL		**176**
Overall average planned dose	**307 mg/m^2**	

Table 11: Patient Exposure by Number of Cycles ("Every 3 Weeks" Regimen)

Total Cycles Administered	**Study Numbers**	**Number of Patients**
1 cycle	CA028	9
2 cycles	CA028	14
3 cycles	CA028	33
4 cycles	CA028	15
5 cycles	CA028	10
6 cycles	CA028	34
7 cycles	CA028	10
8 cycles	CA028	10
9 cycles	CA028	22
10 cycles	CA028	5
11 to 17 cycles	CA028	13
≥ 18 cycles	CA028	1
TOTAL		**176**
Average number of cycles	**6.0 cycles**	

Patient exposure to ABRAXANE in combination with carboplatin for NSCLC in Studies CA028 and CA031 is presented by age group and gender, and by ethnic origin in Table 12 and Table 13, respectively.

Table 12: Patient Exposure by Age Group and Gender (Studies CA028 and CA031) Weekly Regimen

ABRAXANE + Carboplatin Weekly Regimen for NSCLC	**Number (%) of Patients**	
Age Group	**Male**	**Female**
≤ 45 years	27 (5%)	18 (10%)
> 45 to 55 years	163 (28%)	37 (21%)
> 55 to 65 years	225 (38%)	69 (39%)
> 65 years	175 (30%)	51 (29%)
TOTAL	590	175

Table 13: Patient Exposure by Ethnic Origin (Studies CA028 and CA031) Weekly Regimen

Ethnic Origin	**Study Numbers**	**Patients Enrolled (%)**
ABRAXANE + Carboplatin Weekly Regimen for NSCLC		
Asian	CA031	77 (10%)
Black	CA031	12 (2%)
Indian-Eastern	CA031	1 (< 1%)
Hispanic	CA028, CA031	12 (2%)
Caucasian	CA028, CA031	661 (86%)
Other	CA031	2 (< 1%)
TOTAL	**CA028, CA031**	**765**

ABRAXANE in Combination With Gemcitabine for Pancreatic Cancer

The safety database for ABRAXANE in combination with gemcitabine (weekly for 3 weeks followed by a week of rest) in pancreatic cancer comprised trials CA040 and CA046.

Planned study doses in Studies CA040 and CA046 were between 100 and 150 mg/m^2 per administration for ABRAXANE. The overall average planned dose for these studies with a weekly regimen for 3 weeks was 124.1 mg/m^2 and the average number of cycles was 4.7.

Patient exposure by dose and number of cycles is presented in Table 14 and Table 15, respectively.

Table 14: Patient Exposure by Dose (Studies CA040 and CA046)

Planned Study Doses of ABRAXANE Per Administration	Number (%) of Patients
ABRAXANE + Gemcitabine Weekly for 3 Weeks	
100 mg/m^2	20 (4%)
< 125 mg/m^2	465 (95%)
< 150 mg/m^2	3 (1%)
TOTAL	**488**

Table 15: Patient Exposure by Number of Cycles (Studies CA040 and CA046)

Total Cycles Administered	Number (%) of Patients
ABRAXANE + Gemcitabine Weekly for 3 Weeks	
1 cycle	135 (28%)
2 cycles	41 (8%)
3 cycles	56 (11%)
4 cycles	33 (7%)
5 cycles	48 (10%)
6 cycles	44 (9%)
7 cycles	39 (8%)
8 cycles	31 (6%)
9 cycles	19 (4%)
10 cycles	8 (2%)
11 cycles	11 (2%)
12 cycles	3 (1%)
13 cycles	9 (2%)
14 cycles	2 (< 1%)
15 cycles	1 (< 1%)
17 cycles	1 (< 1%)
18 cycles	1 (< 1%)
19 cycles	1 (< 1%)
20 cycles	2 (< 1%)
22 cycles	1 (< 1%)
23 cycles	1 (< 1%)
24 cycles	1 (< 1%)
TOTAL	**488**

A breakdown of treated patients by age group and sex, and by ethnic origin, is presented in Table 16 and Table 17, respectively.

Table 16: Patients Exposed by Age Group and Sex (Studies CA040 and CA046)

	Study CA046		Study CA040		
	ABX 125 mg/m²/ Gem (N = 421)	**Gem (N = 402)**	**ABX 100 mg/m²/ Gem (N = 20)**	**ABX 125 mg/m²/ Gem (N = 44)**	**ABX 150 mg/m²/ Gem (N = 3)**
Age Group, n (%)					
≤ 45 years	30 (7%)	9 (2%)	2 (10%)	1 (2%)	0
> 45 to 55 years	92 (22%)	77 (19%)	5 (25%)	10 (23%)	1 (33%)
> 55 to 65 years	132 (31%)	154 (38%)	5 (25%)	19 (43%)	0
> 65 to 75 years	138 (33%)	128 (32%)	5 (25%)	12 (27%)	2 (67%)
> 75 years	29 (7%)	34 (8%)	3 (15%)	2 (5%)	0
Sex, n (%)					
Female	183 (43%)	161 (40%)	9 (45%)	25 (57%)	1 (33%)
Male	238 (57%)	241 (60%)	11 (55%)	19 (43%)	2 (67%)

ABX = ABRAXANE; Gem = Gemcitabine.

Table 17: Patients Exposed by Ethnic Origin (Studies CA040 and CA046)

	Study CA046		Study CA040		
	ABX 125 mg/m²/ Gem (N = 421)	**Gem (N = 402)**	**ABX 100 mg/m²/ Gem (N = 20)**	**ABX 125 mg/m²/ Gem (N = 44)**	**ABX 150 mg/m²/ Gem (N = 3)**
Ethnic Origin, n (%)					
Asian	8 (2%)	9 (2%)	1 (5%)	1 (2%)	0
Black of African Heritage	15 (4%)	15 (4%)	0	2 (5%)	0
Native Hawaiian or Other Pacific Island	1 (< 1%)	0	0	0	0
White, Non-Hispanic and Non-Latino	369 (88%)	351 (87%)	16 (80%)	37 (84%)	1 (33%)
White, Hispanic or Latino	25 (6%)	23 (6%)	2 (10%)	4 (9%)	2 (67%)
Other	3 (1%)	4 (1%)	1 (5%)	0	0

ABX = ABRAXANE; Gem = Gemcitabine.

ABRAXANE Monotherapy Studies

The clinical trial integrated safety database for the monotherapy studies was developed from trials with mature safety information (as of Jan 2011) where patients were treated with ABRAXANE monotherapy for indications including MBC, advanced solid tumors and advanced NSCLC. As shown above, the trials included were DM97-123 (n = 19), CA101 (n = 22),

CA002-0 (n = 63), CA002-0LD (n = 43), CA008 (n = 14), CA012-0 (n = 241), CA018 (n = 43), CA005 (n = 39), CA013 (n = 181), CA009 (n = 43), CA014 (n = 74), CA015 (n = 75), CA024 (n = 226), CA201 (n = 104) and CA042 (n = 123).

The patients not included in the integrated safety databases (n = 1978) were from ABRAXANE combination therapy trials (i.e., CA016, CA023, CA025, CA028, CA031, CA034, CA040, CA043, CA046), or a trial where the safety data collection currently is ongoing (i.e., CA033), trials in other nononcology indications (CVR001, CVR002, CVR003, HD001), literature studies (INT33/98, INT16/00), adjuvant therapy trials (CA030, CA045), a PK crossover design trial (CA019), and a special population trial in patients with hepatic dysfunction (CA037).

A total of 1310 patients were treated with ABRAXANE monotherapy for MBC and other monotherapy indications, of whom 336 were exposed for at least 6 months, and 92 for at least 1 year. A total of 3923 cycles were administered to patients, of which 3459 (88%) were at the approved dose or higher. A total of 332 patients (52%) were exposed to ABRAXANE for between 3 and 6 months, 107 patients (17%) were exposed to the drug for 6 months or more and 203 (32%) for less than 3 months.

Of the 1310 patients included in the monotherapy integrated safety database, 642 patients were exposed to the "every-3-week" dosing regimen for ABRAXANE, the approved dosing schedule. Of these, 405 patients (63%) received the recommended dose for the target indication (260 mg/m^2). Of the 642 patients who received "every 3-week" dosing of ABRAXANE monotherapy, 61% received ≥ 6 cycles of treatment.

Patient exposure by dose and by number of cycles for the patients exposed to the "every-3-week" dosing regimen is presented in Table 18 to Table 19, respectively. The overall average planned ABRAXANE dose was 264 mg/m^2 and the average number of cycles was 6.0.

Table 18: Patients in the Monotherapy Studies by Dose ("Every-3-Weeks" Regimen)

Planned Study Doses Per Administration	Study Numbers	Number of Patients
135 mg/m^2	DM97-123, CA101	7
175 mg/m^2	CA002-0LD, CA101	47
200 mg/m^2	DM97-123	3
225 mg/m^2	CA101	3
260 mg/m^2	CA012, CA008, CA018, CA101, CA201	405
300 mg/m^2	CA002, DM97-123, CA024, CA101, CA009	168
350 mg/m^2	CA101	3
375 mg/m^2	DM97-123	6
TOTAL		**642**
Overall average planned dose	**264 mg/m^2**	

[redacted]

Table 19: Patient Exposure by Number of Cycles (Monotherapy Studies with an "Every-3-Weeks" Regimen)

Total Cycles Administered	Study Numbers	Number of Patients
1 cycle	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201, CA009	29
2 cycles	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201, CA009	75
3 cycles	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201, CA009	62
4 cycles	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201, CA009	42
5 cycles	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201	42
6 cycles	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201, CA009	193
7 cycles	CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201, CA009	38
8 cycles	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201	67
9 cycles	CA012, CA008, CA018, CA024, CA201	28
10 cycles	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA024, CA201	18
11 to 17 cycles	DM97-123, CA101, CA012, CA008, CA018, CA002, CA024, CA201, CA009	33
≥ 18 cycles	CA012, CA008, CA018, CA024, CA201	15
TOTAL		**642**
Overall average number of cycles	**6.0 cycles**	

The remaining 668 patients in the monotherapy integrated safety database received ABRAXANE at a dosing regimen of "once a week for 3 weeks followed by 1 week of rest". Doses administered in these studies were between 80 and 200 mg/m^2. The total number of cycles (irrespective of dose) administered to this population was 4,198. Sixty-five percent of patients on this dosing schedule were exposed to ABRAXANE for more than 3 months.

Patient exposure by dose for these 668 patients is presented in Table 20.

Table 20: Patients Exposure by Dose (Monotherapy Studies with a "Once a Week for 3 Weeks Followed by 1 Week of Rest" Regimen)

Planned Study Doses Per Administration	Study Numbers	Number of Patients
80 mg/m^2	CA005	3
100 mg/m^2	CA005, CA013, CA014, CA015, CA024, CA009, CA042	383
125 mg/m^2	CA005, CA013, CA015	149
150 mg/m^2	CA005, CA014, CA015, CA024	125
175 mg/m^2	CA005	6
200 mg/m^2	CA005	2
TOTAL		**668**
Overall average planned dose	**116 mg/m^2**	

A breakdown of patients in the monotherapy studies by age group and gender, and by ethnic origin, is presented in Table 21 and Table 22, respectively.

Table 21: Patients in the Monotherapy Studies by Age Group and Gender

		Number (%) of Patients	
Age Group	**Study Numbers**	**Male**	**Female**
≤ 45 years	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA005, CA013, CA014, CA015, CA024, CA201, CA009, CA042	19 (12%)	270 (23%)
> 45 to 55 years	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA005, CA013, CA014, CA015, CA024, CA201, CA009, CA042	38 (25%)	436 (38%)
> 55 to 65 years	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA005, CA013, CA014, CA015, CA024, CA201, CA009, CA042	38 (25%)	282 (24%)
> 65 years	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA005, CA013, CA014, CA015, CA024, CA201, CA009, CA042	58 (38%)	169 (15%)
TOTAL		**153**	**1157**
GRAND TOTAL		**1310**	

Table 22: Patients in the Monotherapy Studies by Ethnic Origin

Ethnic Origin	Study Numbers	Patients Enrolled (%)
Asian	DM97-123, CA101, CA012, CA008, CA018, CA002, CA013, CA201, CA009, CA042	140 (11%)
Black	CA002-0LD, CA012, CA008, CA018, CA002, CA005, CA013, CA015, CA009, CA042	34 (3%)

[redacted]

Table 22: Patients in the Monotherapy Studies by Ethnic Origin (Continued)

Ethnic Origin	Study Numbers	Patients Enrolled (%)
Indian-Eastern	CA002-0LD, CA012, CA008, CA018, CA002	87 (7%)
Hispanic	DM97-123, CA101, CA012, CA008, CA018, CA002, CA005, CA013, CA014, CA015, CA024, CA009, CA042	45 (3%)
Caucasian	DM97-123, CA101, CA002-0LD, CA012, CA008, CA018, CA002, CA005, CA013, CA014, CA015, CA024, CA009, CA042	991 (76%)
Other	CA012, CA008, CA018, CA013, CA014, CA015, CA042	13 (< 1%)
TOTAL		**1310**

PART II - MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 23: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for Being an Exclusion Criterion	Is it Considered to be Included as Missing Information? If No, Rationale.
All Studies		
Patients < 18 years of age	Taxanes as a class of chemotherapeutic agents have not shown major antitumor activity in pediatric malignancies, and so their use in this population is typically limited.	No Based on Study ABI-007-PST-001, a Phase 1/2 study to assess the safety, tolerability, and preliminary efficacy of weekly *nab*-paclitaxel in pediatric patients with recurrent or refractory solid tumours, use in patients < 18 years of age is no longer considered missing information. Further, ABRAXANE is authorized to be used in adult patients only.
Pregnancy	Data are limited regarding use of paclitaxel in human pregnancy and it is suspected to cause serious birth defects. Animal studies have shown reproductive toxicity.	No ABRAXANE should not be used in pregnancy, and in women of childbearing potential not using effective contraception, unless the clinical condition of the mother requires treatment with paclitaxel. Women of childbearing potential should have a pregnancy test prior to starting treatment with ABRAXANE.
Lactation	It is not known whether paclitaxel is excreted in human milk. Animal studies have shown that paclitaxel and/or its metabolites are excreted into the milk in lactating rats.	No Because of potential serious adverse reactions in nursing infants, ABRAXANE is contraindicated during lactation. Breast-feeding must be discontinued for the duration of therapy.
Patients with impaired bone marrow function (baseline neutrophil counts < 500 cells/mm^3	Because ABRAXANE and other cytotoxic chemotherapeutic agents can cause myelosuppression, patients with impaired bone marrow function are typically not entered into clinical trials or treated with the chemotherapeutic agent once it has been approved. Bone marrow suppression (primarily neutropenia) occurs frequently with ABRAXANE. Neutropenia is dose dependent and a dose-limiting toxicity (DLT).	No ABRAXANE is contraindicated in patients who have baseline neutrophil counts < 1500 cells/mm^3. Frequent monitoring of blood cell counts should be performed during ABRAXANE therapy. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to > 500 cells/mm^3 and platelets recover to > 100,000 cells/mm^3.

Table 23: Important Exclusion Criteria in Pivotal Clinical Studies (Continued)

Exclusion Criteria	Reason for Being an Exclusion Criterion	Is it Considered to be Included as Missing Information? If No, Rationale.
Hypersensitivity to the active substance or to any of the excipients.	To protect patient safety by ensuring that patients with known hypersensitivity to the medicinal product were not included in the clinical studies.	No ABRAXANE is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.
All Studies Excluding Monotherapy Study DM97-123		
Brain metastasis	CNS disease, which typically is not well controlled by systemic chemotherapy, can be the major limiting factor for survival of patients. Concomitant brain metastasis may therefore influence interpretation of the study data	No Patients with CNS metastases are excluded from clinical trials because their CNS disease, which typically is not well controlled by systemic chemotherapy, can be the major limiting factor for their survival. In practice, the use of ABRAXANE in this patient population would not be expected to have a higher risk profile if the CNS disease is under control.
All Studies Excluding Monotherapy Studies DM97-123 and CA024		
Pre-existing peripheral neuropathy of Grade ≥ 1	Sensory neuropathy occurs frequently during ABRAXANE therapy. Therefore pre-existing disease may influence interpretation of the study data.	No
Study CA046 (ABRAXANE in Combination With Gemcitabine)		
History of interstitial lung disease (ILD), slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies	Such concomitant diseases may influence interpretation of the study data.	No
Monotherapy Study CA024		
Cumulative life-time dose of doxorubicin > 360 mg/m^2	Prior chemotherapeutic treatment may influence interpretation of the study data, in particular whilst trying to delineate the effects of ABRAXANE from those of doxorubicin treatment.	No ABRAXANE is presently not indicated in combination with doxorubicin, there might be hypothetically a carryover effect from previous exposure.

[redacted]

Table 23: Important Exclusion Criteria in Pivotal Clinical Studies (Continued)

Exclusion Criteria	**Reason for Being an Exclusion Criterion**	**Is it Considered to be Included as Missing Information?** **If No, Rationale.**
Concurrent immunotherapy or hormonal therapy for breast cancer	Such concomitant medication may influence interpretation of the study data, in particular whilst trying to delineate the effects of ABRAXANE from those of another drug.	No ABRAXANE is indicated as monotherapy for breast cancer.
History of Class II to IV congestive heart failure	Congestive heart failure and left ventricular dysfunction have been reported, albeit rarely, in ABRAXANE treated patients. Such concomitant disease may therefore influence interpretation of the study data.	No Section 4.4 of the SmPC includes a warning of congestive heart failure and left ventricular dysfunction, and provides advice for monitoring for the occurrence of cardiac events.

2. LIMITATIONS TO DETECT ADVERSE REACTIONS DETECTION IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical development program is unlikely to detect rare adverse reactions. The majority of patients are not diagnosed with NSCLC until the tumor has progressed beyond the primary site. Generally, median survival of treated patients is 10 to 12 months (Schiller, 2013; Schiller, 2002). Patients with metastatic pancreatic cancer have a very short mean survival time without active treatment (2 to 3 months; Stathis and Moore, 2010), and patients with MBC have a short median survival time (20.5 months; Ernst, 2007), meaning that the trial program may be limited in its ability to assess effects with a long latency. Due to the target patient population for which ABRAXANE is indicated, the clinical trial program may be limited in its ability to assess the effects of prolonged exposure beyond 6 months.

3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

To ensure patient safety, specific populations of patients were excluded from the clinical studies. Thus, experience in these populations is limited.

Table 24: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Lactating women	Not included in the clinical development program.
Patients with relevant comorbidities:	
• Patients with impaired bone marrow function	Not included in the clinical development program.
• Patients with central nervous system metastases	Not included in the clinical development program.
• Patients with cardiac disease/dysfunction	Patients with high cardiovascular risk, including but not limited to, recent coronary stenting or myocardial infarction in the past year were excluded from Study CA046 (ABRAXANE in combination with gemcitabine).
Patients with renal impairment	Among the 229 patients randomized to ABRAXANE in Study CA012, 14 (6%) had a high creatinine level at baseline. Population PK analysis (Study Report ABI-007-CP-001) of pooled data from 8 clinical studies (150 patients with advanced solid tumors and under the nab-paclitaxel monotherapy) included 61 patients classified as having mild renal impairment (CrCl ≥ 60 to < 90 mL/min); 23 patients as having moderate renal impairment (CrCl ≥ 30 to < 60 mL/min), and one patient as having severe renal impairment (CrCl < 30 mL/min), as defined in the 2010 FDA guidance (FDA PK in Patients with Impaired Renal Function).
Patients with hepatic impairment	Population PK analysis (Study Report ABI-007-CP-001) of pooled data from clinical studies included patients with normal hepatic function (n = 130), and pre-existing mild (n = 8), moderate (n = 7) or severe (n = 5) hepatic impairment (according to National Cancer Institute Organ Dysfunction Working Group criteria).
Patients with cardiovascular impairment	No specific data are available.
Immunocompromised patients	No specific data are available.

Table 24: Exposure of Special Populations Included or Not in Clinical Trial Development Programs (Continued)

Type of Special Population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials • Patients with low performance status	Studies CA028 and CA031 (ABRAXANE in combination with carboplatin) in NSCLC had an Eastern Cooperative Oncology Group (ECOG) performance of 0 (fully active) or 1 (restrictive but ambulatory) as an inclusion criterion. In Study CA031, most patients had an ECOG performance status of 1 (76%) or 0 (23%); 5 (< 1%) patients had an ECOG status of 2. Results from Study ABI-007-NSCL-004 indicate that *nab*-paclitaxel/carboplatin was well tolerated and efficacious in patients with advanced NSCLC with an ECOG performance status of 2 (40 patients enrolled). Study CA046 (ABRAXANE in combination with gemcitabine) in pancreatic cancer had Karnofsky Performance Status (KPS) ≥ 70 as an inclusion criterion. Patients with ≥ 10% decreases in KPS between Baseline and within 72 hours prior to randomization were excluded from the study. An ECOG performance status of > 2 was an exclusion criterion in the pivotal, randomized comparative study in MBC (Study CA012). Of the 229 patients who received ABRAXANE, 65% had impaired performance status (ECOG 1, 2 or 3) at study entry.
Population with relevant different ethnic origin	The majority of patients were Caucasian (86%) or Asian (10%) in the ABRAXANE in combination with carboplatin NSCLC studies; White, non-Hispanic and non-Latino in the ABRAXANE in combination with gemcitabine pancreatic cancer studies (87%); and Caucasian (76%) or Asian (11%) in the ABRAXANE monotherapy studies. In Phase 2 Study ABI-007-PANC-001, the safety and efficacy of *nab*-paclitaxel plus gemcitabine was investigated in Chinese patients with metastatic pancreatic adenocarcinoma. Eighty-three patients were enrolled; all received investigational product and were analyzed for efficacy and safety. The results of this study were consistent with Study CA046 and showed a clinically meaningful and compelling improvement in tumour control and clinical benefit in Chinese patients with advanced adenocarcinoma of the pancreas. The safety profile in Study ABI-007-PANC-001was comparable to Study CA046. The data generated in Chinese patients were consistent with an improved benefit-risk demonstrated in Study CA046 and an improvement over that observed, historically, with gemcitabine alone.
Subpopulations carrying relevant genetic polymorphisms	The clinical trials did not identify a subpopulation of patients that seemed to be markedly more sensitive to ABRAXANE than the general population. At present the MAH is not aware of specific subpopulations that need to be dosed differently based upon their genetic makeup.

Table 24: Exposure of Special Populations Included or Not in Clinical Trial Development Programs (Continued)

Type of Special Population	Exposure
Other	**Pediatric Population:** The safety and efficacy of ABRAXANE in children aged 0 to 17 years has not been established. There is no relevant use of ABRAXANE in the pediatric population in the indications of NSCLC, pancreatic adenocarcinoma or MBC. Study ABI-007-PST-001 was a Phase 1/2 study to assess the safety, tolerability, and preliminary efficacy of weekly *nab*-paclitaxel in pediatric patients with recurrent or refractory solid tumours. A total of 65 and 42 patients were enrolled in Phase 1 and Phase 2, respectively. The overall safety profile of *nab*-paclitaxel was consistent with the known safety profile in adults. No meaningful clinical activity or survival benefit was seen in pediatric patients with Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma in the Phase 2 portion of the study. The overall findings from Study ABI-007-PST-001 do not support the further development of *nab*-paclitaxel in pediatric patients. **Elderly Population:** Of the 514 patients with NSCLC in the randomized study who received ABRAXANE in combination with carboplatin, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression events, peripheral neuropathy events, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years. No additional dose reductions, other than those recommended for all patients, are necessary for patients 65 years or older. Of the 421 patients with metastatic pancreatic adenocarcinoma in the randomized study who received ABRAXANE and gemcitabine, 41% were 65 years or older and 10% were 75 years or older. In patients aged 75 years and older who received ABRAXANE and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation including hematologic toxicities, peripheral neuropathy, decreased appetite and dehydration. Of the 229 patients in the randomized study who received ABRAXANE monotherapy for breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among patients at least 65 years of age who received ABRAXANE. A subsequent analysis was conducted in 981 patients receiving ABRAXANE monotherapy for MBC, of which 15% were ≥ 65 years old and 2% were ≥ 75 years old. Higher incidences of epistaxis, diarrhea, dehydration, fatigue and peripheral edema were found in patients ≥ 65 years old. Additionally, results from Study ABI-007-NSCL-005 indicate that *nab*-paclitaxel/carboplatin was well tolerated and efficacious in elderly patients (≥ 70 years) with advanced NSCLC (143 patients were randomised).

PART II - MODULE SV: POSTAUTHORIZATION EXPERIENCE

1. POSTAUTHORIZATION EXPOSURE

1.1. Method Used to Calculate Exposure

The current total cumulative estimate of unique patients who received *nab*-paclitaxel through the most recent PSUR data cutoff point (06 Jan 2018) is calculated based on the growth rate of shipped units sold in aggregate during the most recent time periods leading up to the current reporting interval. The regional/country distribution of patient exposure is based on the proportion of drug units shipped to the various regions/countries around the world for the same time periods. The estimate of unique patients receiving *nab*-paclitaxel for the specified reporting interval is calculated based on the ratio of moving averages between new interval patients and the total interval patients during the most recent intervals leading up to the current reporting interval.

1.2. Exposure

As of 06 Jan 2018, ABRAXANE is approved in 73 countries worldwide, for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease. ABRAXANE is also approved in 62 countries for the first-line treatment of locally advanced or metastatic NSCLC; in 67 countries for the first-line treatment of metastatic adenocarcinoma of the pancreas, and in Japan for the treatment of gastric cancer.

As of 06 Jan 2018, it is estimated that approximately 591,819 patients have received commercial ABRAXANE globally since initial approval in the USA in Jan 2005, and of those, approximately 90,497 patients have received ABRAXANE in the EEA.

PART II - MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

1. POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

ABRAXANE is a cytotoxic agent to be used in the hospital setting for the treatment of solid tumors. The potential for misuse for illegal purposes is therefore considered negligible, and no special coloring or packaging is required.

The risk of accidental unintended use of ABRAXANE by children is negligible as it is a product used in the hospital setting only.

PART II - MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The summary of the safety concerns in the initial RMP submission (Version 9.0) at time of authorization in the EEA (11 January 2008) is presented in Table 25. A description of the changes to the list of safety concerns in the approved EU-RMPs is presented in Annex 8.

Table 25: Summary of Safety Concerns in the Initial RMP Submission

Important Identified Risks	Myelosuppression Neurotoxicity Gastrointestinal events Myalgia and arthralgia Hypersensitivity reactions Cranial nerve palsies Cardiotoxicity Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN)
Important Potential Risks	Infusion site reactions/extravasation Off-label use Concomitant therapy and interactions requiring dose adjustments
Missing Information	Patients with impaired renal function Use in children CNS metastases

1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Adverse reactions where the risk is considered to be fully characterized and appropriately managed in clinical practice at this time include myelosuppression (neutropenia, anemia and thrombocytopenia), peripheral neuropathy, cranial nerve palsies, hypersensitivity reactions, pneumonitis, severe infections resulting in sepsis, gastrointestinal events, myalgia and arthralgia, cardiotoxicity, cystoid macular edema, Stevens-Johnson syndrome/toxic epidermal necrolysis, infusion site reactions/extravasation, and safety in geriatric patients older than 65 years, and are not considered for inclusion in the list of important safety concerns. Potential risks not considered for inclusion in the list of important safety concerns safety concerns based on cumulative evidence include hepatic toxicity (drug-induced liver injury), acute renal failure and hemolytic-uremic syndrome (including HUS in combination with gemcitabine), use in patients with hepatic impairment, concomitant therapy and interactions requiring dose adjustments, medication errors, off-label use, and drug-induced lupus erythematosus (DILE). Justification for reclassification of these identified and potential adverse reactions is provided in Part II Module SVII Section 2.

1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks

There are no important identified risks for the purpose of risk management planning.

Important Potential Risks

There are no important potential risks for the purpose of risk management planning.

Missing Information

There is no missing information for the purpose of risk management planning.

2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Reasons for the removal/addition to the list of safety concerns:

Important identified risks reclassified as an identified risk (not important)

- Myelosuppression (Neutropenia, Anemia and Thrombocytopenia)

  The MAH is proposing to reclassify Myelosuppression (Neutropenia, Anemia and Thrombocytopenia) from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  Myelosuppression refers to impaired bone marrow function due to reduced bone marrow reserve usually reversible upon dose reduction or discontinuation of treatment. Myelosuppression is a common side effect of cancer chemotherapy. The most prominent myelosuppressive effect associated with the use of paclitaxel albumin is neutropenia, with anemia and thrombocytopenia less frequent manifestations. Neutropenia, anemia and thrombocytopenia are listed as very common adverse drug reactions (ADRs) of ABRAXANE (Section 4.8 of the SmPC), representing major dose-limiting toxicities.

  In the registration clinical studies, the proportions of patients experiencing general myelosuppression were 50% for ABRAXANE monotherapy, 73% for ABRAXANE in combination with gemcitabine and 79% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing myelosuppression in the comparative arms were 60% for taxol, 64% for gemcitabine and 65% for taxol plus carboplatin. The incidences of serious adverse events (SAEs) of myelosuppression were 8% for ABRAXANE monotherapy, 8% for ABRAXANE in combination with gemcitabine and 5% for ABRAXANE in combination with carboplatin versus 19% for taxol, 2% for gemcitabine and 2% for taxol plus carboplatin. The incidences of Grade 3 and Grade 4 myelosuppression, respectively, were 23% and 8% for ABRAXANE monotherapy; 36% and 17% for ABRAXANE in combination with gemcitabine, and 40% and 21% for ABRAXANE in combination with carboplatin. The incidences of Grade 3 and Grade 4 myelosuppression were 29% and 19% for taxol; 28% and 8% for gemcitabine, and 27% and 26% for taxol plus carboplatin. There were no myelosuppression events with fatal outcomes in the registration clinical studies.

  The incidences of neutropenia, anemia and thrombocytopenia were 40%, 21% and 4% for ABRAXANE monotherapy; 52%, 52% and 38% for ABRAXANE in combination with gemcitabine, and 61%, 53% and 45% for ABRAXANE in combination with carboplatin versus 57%, 6% and 2% for taxol; 36%, 39% and 34% for gemcitabine, and 57%, 28% and 27% for taxol plus carboplatin. The rates of febrile neutropenia were 2%, 3% and 1% for ABRAXANE monotherapy, ABRAXANE in combination with gemcitabine, and ABRAXANE in combination with carboplatin, respectively, versus < 1%, 1% and 2% for taxol, gemcitabine, and taxol plus carboplatin, respectively. The proportions of patients experiencing SAEs of neutropenia were 8% for ABRAXANE monotherapy; 4% for ABRAXANE in combination with gemcitabine and 1% for ABRAXANE in combination with carboplatin, and 18%, < 1% and 1% for taxol, gemcitabine, and taxol plus

carboplatin, respectively. The incidences of SAEs of febrile neutropenia, anemia and thrombocytopenia were ≤ 4% across all study treatment arms in the registration clinical studies. The incidences of Grade 3 and Grade 4 neutropenia were 21% and 8% for ABRAXANE monotherapy; 27% and 15% for ABRAXANE in combination with gemcitabine, and 31% and 14% for ABRAXANE in combination with carboplatin. The incidences of Grade 3 and Grade 4 neutropenia were 28% and 18% for taxol; 20% and 5% for gemcitabine, and 24% and 25% for carboplatin plus carboplatin. The incidences of Grade 3 anemia were 4% for ABRAXANE monotherapy; 14% for ABRAXANE in combination with gemcitabine, and 23% for ABRAXANE in combination with carboplatin versus 2%, 9% and 7% for taxol, gemcitabine and taxol plus carboplatin, respectively. The proportions of patients experiencing Grade 3 thrombocytopenia were 2% for ABRAXANE monotherapy; 13% for ABRAXANE in combination with gemcitabine and 14% for ABRAXANE in combination with carboplatin and < 1%, 8% and 5% for taxol, gemcitabine, and taxol plus carboplatin, respectively. The incidences of Grade 4 anemia and thrombocytopenia were ≤ 5% across all study treatment arms. Grade 3 or 4 febrile neutropenia was reported for ≤ 2% of patients across all study treatment arms.

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for general myelosuppression was 0.64% (890/139,633) versus 0.72% (992/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.53% (751/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016. The annual reporting rates versus the previous PSURs were 0.44% (616/139,633) versus 0.49% (668/137,451) and 0.38% (544/142,490) for neutropenia; 0.19% (260/139,633) versus 0.17% (239/137,451) and 0.09% (129/142,490) for anemia, and 0.20% (278/139,633) versus 0.23% (323/137,451) and 0.13% (184/142,490) for thrombocytopenia.

Neutropenia is a known major dose-limiting toxicity of ABRAXANE and HCPs in this area are aware of managing this risk as part of routine clinical practice. Regular blood counts are recommended before and during treatment, as per the SmPC Sections 4.2 and 4.4, and dose adjustment advice is included. Dosing recommendations for ABRAXANE in combination with carboplatin or gemcitabine and ABRAXANE monotherapy in the event of neutropenia and/or thrombocytopenia can be found in Section 4.2 of the SmPC. These routine risk minimization measures are considered sufficient after more than 10 years' real world setting experience and well-integrated into clinical practice. No additional risk minimization measures are in place. Therefore the safety concern of Myelosuppression (Neutropenia, Anemia and Thrombocytopenia) is proposed to be reclassified as an identified risk and no longer considered important.

- Peripheral neuropathy

  The MAH is proposing to reclassify Peripheral neuropathy from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  Paclitaxel treatment has produced a distal sensory neuropathy with glove and stocking distribution sensory loss, paresthesia, and occasionally pain, leading to deficits in gait and fine motor skills and seems to be related to cumulative dose (Park, 2008; Wolf, 2008).

Peripheral neuropathy is a very common side effect of taxane chemotherapy, including ABRAXANE, and is listed in Section 4.8 of the SmPC. The definition of peripheral neuropathy as presented in the RMP and labelling documents, including the SmPC for ABRAXANE, is based on the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) Peripheral neuropathy, regardless of a specific MedDRA preferred term (PT).

In the registration clinical studies, the proportions of patients experiencing peripheral neuropathy were 68% for ABRAXANE monotherapy, 56% for ABRAXANE in combination with gemcitabine and 47% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing peripheral neuropathy in the comparative arms were 63% for taxol, 13% for gemcitabine and 64% for taxol plus carboplatin. The incidences of peripheral neuropathy SAEs were < 1% for ABRAXANE monotherapy, < 1% for ABRAXANE in combination with gemcitabine and 0% for ABRAXANE in combination with carboplatin versus 0% for taxol, < 1% for gemcitabine and < 1% for taxol plus carboplatin. The incidences of Grade 3 and Grade 4 peripheral neuropathy were 13% and < 1% for ABRAXANE monotherapy; 17% and 0% for ABRAXANE in combination with gemcitabine, and 4% and 0% for ABRAXANE in combination with carboplatin. The incidences of Grade 3 and Grade 4 peripheral neuropathy in the comparative arms were 3% and 0% for taxol, < 1% and 0% for gemcitabine, and 12% and < 1% for taxol plus carboplatin. There were no peripheral neuropathy events with fatal outcomes in the registration clinical studies.

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for peripheral neuropathy was 0.35% (492/139,633) versus 0.37% (502/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.16% (232/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

Peripheral neuropathy is a known major dose-limiting toxicity of ABRAXANE and HCPs in this area are aware of managing this risk as part of routine clinical practice. Dose delay and adjustment recommendations for ABRAXANE in the event of peripheral neuropathy can be found for all indications in Sections 4.2 and 4.4 of the SmPC. These routine risk minimization measures are considered sufficient after more than 10 years' real world setting experience and well-integrated into clinical practice. Other measures based on genetic (and other) predictors of peripheral neuropathy that the MAH has been requested to include in the PSUR for ABRAXANE are not yet sufficiently mature to be included into routine clinical practice. No additional risk minimization measures are in place. Therefore the safety concern of Peripheral neuropathy is proposed to be reclassified as an identified risk and no longer considered important.

- Cranial nerves palsies

  The MAH is proposing to reclassify Cranial nerve palsies from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  Cranial nerve palsies are events occurring in less than 1% of 465 patients treated with ABRAXANE in combination with gemcitabine and 1310 patients receiving ABRAXANE monotherapy in the registration clinical trials. No such events were

reported in patients receiving ABRAXANE in combination with carboplatin in clinical trials for NSCLC.

Cranial nerves palsies have been reported during postmarketing surveillance of ABRAXANE (Section 4.8 of the SmPC). In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for cranial nerve palsies was 0.002% (3/139,633) versus 0.005% (7/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.0% (0/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

No new information has been identified that would alter the current understanding of the identified risk of Cranial nerve palsies, and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Hypersensitivity reactions

  The MAH is proposing to reclassify Hypersensitivity reactions from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  Hypersensitivity reactions cover a wide range of severity from mild facial swelling or an itchy rash, to a life-threatening reaction. Adjudicating hypersensitivity is a medical judgment and alternative etiologies may include cardiovascular or pulmonary disease, edema, and skin reactions and may be caused by other agents in conjunction with *nab*-paclitaxel. Hypersensitivity reactions including rare reactions with fatal outcomes are listed in Section 4.4 of the SmPC.

  In the registration clinical studies, the proportions of patients experiencing hypersensitivity reactions were 45% for ABRAXANE monotherapy, 60% for ABRAXANE in combination with gemcitabine and 30% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing hypersensitivity reactions in the comparative arms were 29% for taxol, 38% for gemcitabine and 29% for taxol plus carboplatin. Allergic reactions, such as rash, occurred as a very common AE in the clinical trials (frequency ≥ 1/10), but more severe forms were much less common. The incidences of SAEs of hypersensitivity reactions were 1% for ABRAXANE monotherapy, 2% for ABRAXANE in combination with gemcitabine and < 1% for ABRAXANE in combination with carboplatin versus < 1% for taxol, 1% for gemcitabine and 2% for taxol plus carboplatin. The incidences of Grade 3 and Grade 4 hypersensitivity reactions were 5% and < 1% for ABRAXANE monotherapy; 7% and < 1% for ABRAXANE in combination with gemcitabine, and 3% and 0% for ABRAXANE in combination with carboplatin. The incidences of Grade 3 and Grade 4 hypersensitivity reactions were 3% and 0% for taxol; 4% and < 1% for gemcitabine, and 5% and < 1% for taxol plus carboplatin.

  Two patients (< 1%) treated with ABRAXANE in combination with carboplatin experienced hypersensitivity reactions with fatal outcomes. In addition, 3 (< 1%) patients in the carboplatin plus taxol arm experienced hypersensitivity reactions with an outcome of death. One patient (< 1%) treated with ABRAXANE in combination with gemcitabine experienced a fatal hypersensitivity reaction. In addition, 3 (< 1%) patients in the

gemcitabine arm experienced fatal hypersensitivity reactions. A total of 7 (< 1%) patients treated with ABRAXANE monotherapy experienced hypersensitivity reactions with an outcome of death.

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rates for hypersensitivity reactions, serious hypersensitivity reactions, and serious hypersensitivity reactions with fatal outcome during the most recent PSUR were 0.05% (70/139,633), 0.02% (33/139,633) and 0.0007% (1/139,633), respectively, versus 0.05% (62/137,451), 0.04% (52/137,451) and 0.001% (2/137,451), respectively, for the PSUR interval 07 Jan 2016 to 06 Jan 2017, and 0.03% (43/142,490), 0.02% (35/142,490) and 0.001% (1/142,490), respectively, for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

Routine clinical practice includes eliciting patient history of allergies, including drug allergies, in order for the prescriber to assess the benefit-risk of prescribing drugs such as ABRAXANE. Hypersensitivity to the active substance or to any of the excipients is a contraindication (SmPC, Section 4.3). Occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic shock with fatal outcome, have been reported and are acknowledged in Section 4.4 of the SmPC. Routine risk minimization is considered effective, as reflected in Sections 4.3 and 4.4 of the SmPC, and no additional risk minimization measures are in place. Healthcare professionals in this area are familiar with the prevention and treatment of hypersensitivity reactions due to paclitaxel products. Due to the absence of Cremophor EL, the risk of serious hypersensitivity reactions with ABRAXANE is considered to be lower than for solvent-based paclitaxel, and there is no special requirement for specific premedications. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Pneumonitis

  The MAH is proposing to reclassify Pneumonitis from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  Drug-induced pneumonitis is a general term for drug-induced nonspecific interstitial pneumonitis and drug-induced hypersensitivity pneumonitis. Interstitial pneumonitis is characterized by minimal inflammation and heterogeneous fibrosis of the lung, most prominent in the peripheral areas, without infection, which distinguishes pneumonitis from pneumonia. The definition of pneumonitis as presented in the RMP and labelling documents, including the SmPC for ABRAXANE, is based on the SMQ Interstitial lung disease.

  Pneumonitis is listed in Section 4.8 of the SmPC and is a dose-limiting toxicity for ABRAXANE resulting in permanent discontinuation of ABRAXANE treatment (SmPC, Sections 4.2 and 4.4).

  In the registration clinical studies, the proportions of patients experiencing pneumonitis were 1% for ABRAXANE monotherapy, 4% for ABRAXANE in combination with gemcitabine and < 1% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing pneumonitis in the comparative arms were < 1% for taxol, 1% for gemcitabine and < 1% for taxol plus carboplatin. The incidences of pneumonitis SAEs were < 1% for ABRAXANE monotherapy, 2% for ABRAXANE in

combination with gemcitabine and 0% for ABRAXANE in combination with carboplatin versus 0% for taxol, < 1% for gemcitabine and 0% for taxol plus carboplatin. The incidences of Grade 3 and Grade 4 pneumonitis were < 1% and < 1% for ABRAXANE monotherapy; 1% and < 1% for ABRAXANE in combination with gemcitabine, and 0% and 0% for ABRAXANE in combination with carboplatin. The incidences of Grade 3 and Grade 4 peripheral neuropathy in the comparative arms were 0% and 0% for taxol, < 1% and < 1% for gemcitabine, and 0% and 0% for taxol plus carboplatin. Fatal outcomes were reported for 2 (< 1%) patients treated with ABRAXANE in combination with gemcitabine who experienced acute respiratory distress syndrome and diffuse alveolar damage (1 [< 1%] patient each). Both patients were aged < 75 years.

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for pneumonitis and pneumonitis with a fatal outcome was 0.08% (116/139,633) and 0.01% (18/139,633) versus 0.09% (119/137,451) and 0.01% (14/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017, and 0.07% (106/142,490) and 0.01% (14/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

Health Care Providers in this area are managing this risk as part of routine clinical practice. As per the SmPC Section 4.4, patients are monitored for signs and symptoms of pneumonitis. These routine risk minimization measures are considered sufficient after more than 10 years' real world setting experience and well-integrated into clinical practice. No additional risk minimization measures are in place. Therefore, the safety concern of Pneumonitis is proposed to be reclassified as an identified risk and no longer considered important.

- Severe infections resulting in sepsis

  The MAH is proposing to reclassify Severe infections resulting in sepsis from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  Sepsis is a serious medical condition characterized by a whole-body inflammatory state (called a systemic inflammatory response syndrome) caused by severe infection. Septicemia is a related term referring to the presence of pathogenic organisms in the bloodstream that may or may not lead to sepsis.

  Sepsis is listed in Section 4.8 of the SmPC.

  In the registration clinical studies, the proportions of patients experiencing sepsis were < 1% for ABRAXANE monotherapy, 5% for ABRAXANE in combination with gemcitabine and < 1% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing sepsis in the comparative arms were < 1% for taxol, 2% for gemcitabine and < 1% for taxol plus carboplatin. The incidences of sepsis SAEs were < 1% for ABRAXANE monotherapy, 5% for ABRAXANE in combination with gemcitabine and 0% for ABRAXANE in combination with carboplatin versus < 1% for taxol, 2% for gemcitabine and < 1% for taxol plus carboplatin. The incidences of Grade 3 and Grade 4 sepsis were < 1% and < 1% for ABRAXANE monotherapy; 3% and < 1% for ABRAXANE in combination with gemcitabine, and < 1% and 0% for ABRAXANE

in combination with carboplatin. The incidences of Grade 3 and Grade 4 sepsis in the comparative arms were < 1% and 0% for taxol, 1% and < 1% for gemcitabine, and < 1% and 0% for taxol plus carboplatin. Fatal outcomes were reported for 5 (1%) patients treated with ABRAXANE in combination with gemcitabine who experienced sepsis (2 [< 1%] patients) and septic shock, biliary sepsis, bacterial sepsis and neutropenic sepsis (1 [< 1%] patient each), and 2 (< 1%) patients treated with gemcitabine (septic shock in both patients).

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for fatal sepsis or septic shock was 0.01% (15/139,633) versus 0.03% (39/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.02% (32/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

Section 4.4 of the SmPC includes a warning that complications due to the underlying pancreatic cancer were identified as significant contributing factors to sepsis. Dosing and treatment advice in the case of febrile neutropenia are also provided. These routine risk minimization measures are considered sufficient after more than 10 years' real world setting experience and well-integrated into clinical practice. Neutropenic sepsis is listed across all approved indications. All HCPs who are involved in the treatment and care of patients for whom ABRAXANE is indicated are well aware of the occurrence of neutropenic sepsis, including the increased risk in patients with pancreatic cancer, and the management thereof. No additional risk minimization measures are in place. Therefore the safety concern of Severe infections resulting in sepsis is proposed to be reclassified as an identified risk and no longer considered important.

- Gastrointestinal events

  The MAH is proposing to reclassify Gastrointestinal events from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  Gastrointestinal events, in particular diarrhea, nausea and vomiting, are common side effects of cancer chemotherapy, including ABRAXANE, and are listed in Section 4.8 of the SmPC. Mucositis and diarrhea are additionally listed as dose-limiting toxicities in Section 4.2 of the SmPC.

  In the registration clinical studies, the proportions of patients experiencing gastrointestinal events were 51% for ABRAXANE monotherapy, 74% for ABRAXANE in combination with gemcitabine and 35% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing gastrointestinal events in the comparative arms were 31% for taxol, 62% for gemcitabine and 32% for taxol plus carboplatin. The incidences of gastrointestinal SAEs were 2% for ABRAXANE monotherapy, 9% for ABRAXANE in combination with gemcitabine and < 1% for ABRAXANE in combination with carboplatin versus < 1% for taxol, 5% for gemcitabine and < 1% for taxol plus carboplatin. The incidences of Grade 3 and Grade 4 gastrointestinal events were 6% and < 1% for ABRAXANE monotherapy; 15% and < 1% for ABRAXANE in combination with gemcitabine, and 1% and 0% for ABRAXANE in combination with carboplatin. The incidences of Grade 3 and Grade 4 gastrointestinal events were < 1% for the comparative arms, with the exception of Grade 3 events in the

gemcitabine arm (7%). There were no gastrointestinal events with fatal outcomes in the registration clinical studies.

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for gastrointestinal events was 0.32% (441/139,633) versus 0.29% (403/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.18% (253/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

Health Care Providers in this area are managing this risk as part of routine clinical practice. As per the SmPC Section 4.4, patients experiencing nausea, vomiting and diarrhea following the administration of ABRAXANE may be treated with commonly used anti-emetics and constipating agents. Dosing recommendations for ABRAXANE in combination with carboplatin or gemcitabine and ABRAXANE monotherapy in the event of gastrointestinal toxicity can be found in Section 4.2 of the SmPC. These routine risk minimization measures are considered sufficient after more than 10 years' real world setting experience and well-integrated into clinical practice. No additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Myalgia and arthralgia

  The MAH is proposing to reclassify Myalgia and arthralgia from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  Myalgia and arthralgia are listed in Section 4.8 of the SmPC.

  In the registration clinical studies, the proportions of patients experiencing myalgia and arthralgia were 26% and 24% for ABRAXANE monotherapy, 12% and 11% for ABRAXANE in combination with gemcitabine, and 12% and 9% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing myalgia and arthralgia in the comparative arms were 31% and 30% for taxol, 3% and 3% for gemcitabine, and 25% and 19% for taxol plus carboplatin. The incidences of SAEs of myalgia and arthralgia were < 1% across study treatment arms, and the incidences of Grade 3 myalgia and arthralgia were ≤ 2%. Myalgia and arthralgia are usually mild to moderate in severity and self-limiting, and are less frequent with ABRAXANE than with solvent-based paclitaxel.

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for arthralgia and myalgia was 0.04% (56/139,633), versus 0.05% (69/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.02% (34/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

  No new information has been identified that would alter the current understanding of the nature and the management of the identified risk of Myalgia and arthralgia, and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Cardiotoxicity

  The MAH is proposing to reclassify Cardiotoxicity from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  In the registration clinical studies, the proportions of patients experiencing cardiotoxicity, specifically cardiac disorders, myocardial disorders, bradyarrhythmia, cardiac conduction disorders, sinus node function disorders, congestive heart failure (CHF) and left ventricular dysfunction (LVD), were 5% for ABRAXANE monotherapy, 8% for ABRAXANE in combination with gemcitabine and 3% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing cardiotoxicity in the comparative arms were 2% for taxol, 4% for gemcitabine and 2% for taxol plus carboplatin. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines, or had underlying cardiac history. The incidences of SAEs of cardiotoxicity were < 1% across all study treatment arms.

  The incidences of Grade 3 and Grade 4 cardiotoxicity were ≤ 1% for ABRAXANE monotherapy, ABRAXANE in combination with gemcitabine, and ABRAXANE in combination with carboplatin. The incidences of Grade 3 and Grade 4 cardiotoxicity were < 1% for the comparator arms.

  Fatal outcomes were reported for 3 (< 1%) patients treated with ABRAXANE monotherapy, of whom 2 (< 1%) patients experienced cardiopulmonary failure and 1 (< 1 %) patient experienced cardiac failure acute. Outcomes of death were reported for 1 (< 1%) patient treated with ABRAXANE in combination with gemcitabine (PT cardiac failure congestive), and in 1 (< 1%) patient in the gemcitabine arm (PT cardiopulmonary failure). Outcomes of death were reported for 3 (< 1%) patients treated with ABRAXANE in combination with carboplatin (PTs arrhythmia, cardiopulmonary failure and cardiac failure acute in 1 [< 1%] patient each) and in 2 (< 1%) patients treated with taxol and carboplatin (PTs cardiopulmonary failure and pulmonary oedema).

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for cardiotoxicity overall and for CHF/LVD was 0.02% (31/139,633) and 0.006% (9/139,633), respectively, versus 0.03% (36/137,451) and 0.02% (24/137,451), respectively, for the PSUR interval 07 Jan 2016 to 06 Jan 2017, and 0.02% (25/142,490) and 0.01% (15/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

  Section 4.4 of the SmPC includes a warning of CHF and LVD, and provides advice for monitoring for the occurrence of cardiac events. These routine risk minimization measures are considered sufficient after more than 10 years' real world setting experience and well-integrated into clinical practice. No additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Cystoid macular edema

  The MAH is proposing to reclassify Cystoid macular edema from an important identified risk to an identified risk (not important) as it is deemed no longer important basd on the following.

In the registration clinical trials, cystoid macular edema occurred in less than 1% of 465 patients treated with ABRAXANE in combination with gemcitabine. No such events were reported in patients receiving ABRAXANE as monotherapy or in combination with carboplatin.

During postmarketing surveillance, there have been reports of cystoid macular edema leading to reduced visual acuity with treatment with ABRAXANE (Section 4.8 of the SmPC), and with other taxanes. In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for cystoid macular edema in the postmarketing setting was 0.01% (16/139,633) versus 0.02% (28/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.01% (17/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

Rare reports of reduced visual acuity due to cystoid macular edema and advice to discontinue upon diagnosis during treatment with ABRAXANE are included in Section 4.8 of the SmPC.

No additional information has been identified that would alter the current understanding of Cystoid macular edema, and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN)

  The MAH is proposing to reclassify Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN) from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  In the registration clinical trials, SJS/TEN occurred in less than 1% of 1310 patients treated with ABRAXANE as monotherapy. No such events were reported in patients receiving ABRAXANE in combination with gemcitabine or ABRAXANE in combination with carboplatin.

  Very rarely (frequency <1/10,000), SJS or TEN have been reported in postmarketing surveillance of ABRAXANE (Section 4.8 of the SmPC). In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for SJS/TEN was 0.0007% (1/139,633) versus 0.0% (0/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.001% (1/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

  The risk of severe skin reactions is rare and no predictors specific to ABRAXANE have been identified. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Infusion site reactions/Extravasation

  The MAH is proposing to reclassify Infusion site reactions/Extravasation from an important identified risk to an identified risk (not important) as it is deemed no longer important based on the following.

  In the registration clinical studies, the proportions of patients experiencing infusion site reactions/extravasation were 1% for ABRAXANE monotherapy, 5% for ABRAXANE in

combination with gemcitabine and < 1% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing infusion site reactions/extravasation in the comparative arms were < 1% for taxol, 3% for gemcitabine and 0% for taxol plus carboplatin. There were no infusion site reactions/extravasation SAEs reported in the registration studies. A single patient in the ABRAXANE monotherapy studies experienced a Grade 3 event. There were no other Grade 3 events, or any Grade 4 or 5 events reported in the registration studies.

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for infusion site reactions/extravasation was 0.005% (7/139,633) versus 0.007% (10/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.006% (8/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

Infusion site reaction is listed in Section 4.8 of the SmPC.

No new information has been identified that would alter the current understanding of the identified risk of Infusion site reactions/extravasation, and no additional risk minimization measures are in place. Health Care Providers in this area are very familiar with the diagnosis and management of infusion site reactions/extravasation. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Safety in patients older than 75 years

  The MAH is proposing to reclassify the Important identified risk of Safety in patients older than 75 years from an important identified risk to an identified risk (not important) as it is deemed no longer important; the risk is to be renamed as Safety in Geriatric Patients older than 65 years.

  A review of the data from the pancreatic cancer studies showed numerical imbalances (≥ 5% difference) between the two treatment arms for patients ≥ 75 years versus younger patients in the incidence of hematologic toxicity (myelosuppression), peripheral neuropathy, dehydration, decreased appetite and diarrhea. In the ABRAXANE/gemcitabine treatment arm, the overall rate of AEs leading to death was higher in patients ≥ 75 years of age than those < 75 years of age; however, there were no notable differences for any of the individual preferred terms.

  Pharmacokinetic/pharmacodynamic modelling using data from 125 patients with advanced solid tumors indicates that patients ≥ 65 years of age may be more susceptible to development of neutropenia within the first treatment cycle (Section 4.2 of the SmPC). A warning that patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed before treatment is considered is provided in Section 4.4 of the SmPC. However, no additional dose reductions, other than those recommended for all patients (Section 4.2 of the SmPC), are necessary for patients 65 years or older. While some ADRs specifically listed in the SmPC for each indication may be more frequent or more serious in the elderly, the safety profile of ABRAXANE is similar across all indications and the management of these events does not differ. Across all indications, the management of DLTs is the same, regardless of age group, as reflected in Section 4.2 of the SmPC.

In the PSUR, the MAH has been monitoring safety by age group in patients younger than 65 years, 65 to 74 years, and 75 years and older.

No new signals have emerged during additional non-registration safety studies in elderly patients and patient with low performance status with NSCLC receiving ABRAXANE in combination with carboplatin:

- ABI-007-NSCL-005: A Phase 4, multicenter, open-label, randomized study of *nab*-paclitaxel combination with carboplatin as first-line treatment in elderly subjects (70+) with advanced NSCLC (abound.70+)
- ABI-007-NSCL-004: A Phase 2, single arm, open-label, multicenter, safety and tolerability trial with *nab*-paclitaxel (ABRAXANE®) plus carboplatin followed by *nab*-paclitaxel monotherapy as first-line treatment for subjects with locally advanced or metastatic NSCLC and an ECOG performance status of 2 (abound.ps2)

Inclusion of new identified risk (not considered important)

- Tumor lysis syndrome

  During the most recent annual PSUR reporting period (07 Jan 2017 to 06 Jan 2018), one new report of tumor lysis syndrome (TLS) in the literature identified via quantitative signal detection triggered a cumulative review of this event. Cumulatively through 01 Aug 2017 there were seven reports of TLS in association with ABRAXANE in the Celgene global safety database. Five of a total of seven reports had sufficient information to satisfy the diagnostic criteria of laboratory and/or clinical TLS.

  The MAH determined that Tumor lysis syndrome should be considered as an identified risk (not important), based on the nature of the event and the familiarity of TLS to the HCPs.

  The risk for TLS with ABRAXANE is low and the rate is currently estimated as 7/562,990 = 1.2/100,000 ie, less than 1/10,000 or "very rare" according to the Council for International Organizations of Medical Sciences (CIOMS) III criteria (CIOMS Working Group III, 1995).

  Although the number of reported events of TLS is relatively low and the cases are confounded by the combination treatment setting, considering the possible mechanism of action, the close time to onset in most of the cases and the seriousness of the condition, as well as the fact that the risk is addressed in the SmPCs of several solvent-based paclitaxel formulations, inclusion of Tumor lysis syndrome in Section 4.8 of the SmPC under postmarketing data was considered appropriate by the CHMP.

Important potential risks reclassified as identified risks (not important)

- Use in patients with hepatic impairment

  The MAH is proposing to reclassify Use in patients with hepatic impairment from an important potential risk to an identified risk (not important).

  Hepatic impairment is classified as follows: mild impairment (total bilirubin > 1 to ≤ 1.5 × upper limit of normal [ULN]); moderate impairment (total bilirubin > 1.5 to ≤ 3 x ULN); and severe impairment (total bilirubin > 3 to ≤ 5 x ULN).

[redacted]

Hepatic impairment was an exclusion criterion for most of the registration clinical studies with ABRAXANE. In postmarketing study CA037 conducted with doses of 260, 200, and 130 mg/m^2 in patients with mild, moderate and severe hepatic dysfunction, respectively, no consistent trend was seen relating to level of hepatic dysfunction and the overall incidence of AEs. The most common AEs were neutrophils (62% of patients), fatigue (57%), sensory neuropathy (40%) and hair loss/alopecia (37%). Anorexia was the only AE occurring more often with increasing hepatic dysfunction (0%, 20% and 30% for doses of 260, 200, and 130 mg/m^2, respectively). Grade 4 and 5 AEs were reported in 23% (7/30) and 7% (2/30) of patients, respectively. The only Grade 4 event reported for more than 1 patient was neutrophils (14%; 4/29). Grade 4 neutrophils were reported for 4 (14%) patients including 2 (20%), 1 (11%) and 1 (10%) patients in the 260, 200 and 130 mg/m^2 groups, respectively.

Study ABI-PANC-004 was a Phase 1 study to investigate the safety and PK of *nab*-paclitaxel plus gemcitabine in patients with advanced pancreatic cancer who have cholestatic hyperbilirubinemia secondary to bile duct obstruction. This study was terminated due to the fact that the study population was determined to be more infrequent than the original estimation. This was due to a change of treatment patterns, including biliary stent placement, in patients developing biliary obstruction due to pancreatic cancer.

Section 4.2 of the SmPC provides dosing information for patients with hepatic impairment, including reduced starting dose in patients for mild to moderate hepatic impairment. For metastatic breast cancer patients and NSCLC patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and aspartate aminotransferase (AST) ≤ 10 x ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles. There are insufficient data to permit dosage recommendations for patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment. Regardless of indication, there are insufficient data to permit dosage recommendations for patients with total bilirubin > 5 x ULN or AST > 10 x ULN (SmPC Sections 4.4 and 5.2).

Section 4.4 of the SmPC includes a warning that patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression. These routine risk minimization measures are considered sufficient after more than 10 years' real world setting experience and well-integrated into clinical practice. No additional risk minimization measures are in place. Therefore, the safety concern of Use in patients with hepatic impairment is proposed to be reclassified as an identified risk and no longer considered important.

- Concomitant therapy and interactions requiring dose adjustments

  The MAH is proposing to reclassify Concomitant therapy and interactions requiring dose adjustments from an important potential risk to an identifed risk (not important) as it is deemed no longer important.

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), there were no reports of concomitant therapy and interactions requiring dose adjustments versus one report of drug interaction for each of the previous PSURs (07 Jan 2016 to 06 Jan 2017 and 07 Jan 2015 to 06 Jan 2016, respectively).

Section 4.5 of the SmPC provides details of potential interactions with other medicinal products and advises caution when administering paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4. Most recently, possible interaction with clopidogrel has been added to the SmPC as another example of possible interaction.

No new information has been identified that would alter the current understanding of the risk of Concomitant therapy and interactions requiring dose adjustments, and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is reclassified as an identified risk and no longer considered important.

- Acute renal failure and hemolytic-uremic syndrome (including HUS in combination with gemcitabine)

  The MAH is proposing to reclassify Acute renal failure and hemolytic-uremic syndrome (including HUS in combination with gemcitabine) from an important potential risk to an identified risk (not important) as it is well established in combination with gemcitabine for which acute renal failure and HUS are listed in the SmPC.

  In the registration clinical studies, the proportions of patients experiencing acute renal failure and hemolytic-uremic syndrome were 2% for ABRAXANE monotherapy, 6% for ABRAXANE in combination with gemcitabine and 2% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing acute renal failure and hemolytic-uremic syndrome in the comparative arms were < 1% for taxol, 6% for gemcitabine and 3% for taxol plus carboplatin. The incidences of SAEs and Grade 3 and Grade 4 events of acute renal failure and haemolytic-uremic syndrome were ≤ 2% across all treatment arms. Outcomes of death were reported for 1 (< 1%) patient treated with ABRAXANE monotherapy (PT: renal failure acute), ABRAXANE in combination with gemcitabine (PT: renal failure), and in 1 (< 1%) patient in the gemcitabine arm (PT: renal failure acute).

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for acute renal failure and hemolytic-uremic syndrome was 0.001% (2/139,633) versus 0.004% (5/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.0% (0/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

  No new information has been identified that would alter the current understanding of the potential risk of Acute renal failure and hemolytic-uremic syndrome (including HUS in combination with gemcitabine), which continues to be observed in combination with gemcitabine, and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is no longer considered important.

- Hepatic toxicity (Drug-induced liver injury)

  The MAH is proposing to reclassify Hepatic toxicity (Drug-induced liver injury) from an important potential risk to an identified risk (not important).

  While useful for screening purposes, single clinical, laboratory and investigational adverse event terms *per se* are not diagnostic for drug-induced liver injury (DILI). Instead, a diagnosis of DILI is a clinical judgment based on the evaluation of multiple factors and possible competing etiologies. In reviewing these events for ABRAXANE, Celgene has been applying Hy's Law and other published criteria for the identification of suspected cases of DILI.

  Hepatic toxicity (DILI) generally occurs between 5 and 90 days after drug ingestion. The clinical picture of hepatic toxicity (DILI) is variable, ranging from transient mild elevation of liver enzymes to liver failure. According to CIOMS definitions, hepatic toxicity (DILI) is divided into three types: hepatocellular, cholestatic, and mixed. The hepatocellular type is defined by alanine aminotransferase (ALT) > 2 x ULN or R ≥ 5, where R is the ratio of serum ALT/serum alkaline phosphatase. The cholestatic type is defined by serum alkaline phosphatase > 2 x ULN or R ≤ 2. Lastly, the mixed type is defined by ALT > 2 x ULN and 2< R < 5 (Bénichou, 1990; Tajiri, 2008). Hy's Law refers to transaminase elevations > 3 x ULN concurrent with total bilirubin > 2 x ULN in the absence of plausible alternative explanations (e.g. hepatitis;
  US FDA DILI Guidance, 2009).

  In the registration clinical studies, the proportions of patients experiencing potential hepatic toxicity (DILI) events were 14% ABRAXANE monotherapy, 26% for ABRAXANE in combination with gemcitabine and 18% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing hepatic toxicity (DILI) events in the comparative arms were 13% for taxol, 26% for gemcitabine and 16% for taxol plus carboplatin.

  For patients treated with ABRAXANE monotherapy, Grade 3 potential hepatic toxicity (DILI) events were reported for 7% of patients and Grade 4 events were reported for 1% patients. By comparison, Grade 3 potential hepatic toxicity (DILI) events were reported for 7% of patients and Grade 4 events were reported for 2% patients treated with taxol. An outcome of death was reported for hepatic cirrhosis in 1 (< 1%) patient in the ABRAXANE monotherapy arm.

  For patients treated with ABRAXANE in combination with gemcitabine, Grade 3 potential hepatic toxicity (DILI) events were reported for 10% of patients and Grade 4 events were reported for < 1% patients. By comparison, Grade 3 potential hepatic toxicity (DILI) events were reported for 12% of patients and Grade 4 events were reported for < 1% patients treated with gemcitabine. An outcome of death was reported for hepatic failure in 1 (< 1%) patient in the ABRAXANE in combination with gemcitabine arm who was aged < 75 years. In addition, an outcome of death was reported for hepatic failure in 1 (< 1%) patient in the gemcitabine arm, who was aged < 75 years.

  For patients treated with ABRAXANE in combination with carboplatin, Grade 3 potential hepatic toxicity (DILI) events were reported for 3% of patients and Grade 4

events were reported for < 1% patients. By comparison, Grade 3 potential hepatic toxicity (DILI) events were reported for 1% of patients and Grade 4 events were reported for < 1% patients treated with taxol plus carboplatin. There were no hepatic toxicity events with fatal outcomes in the studies with carboplatin.

In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for initial reports of hepatic events, regardless of cause, was 0.1% (154/139,633) versus 0.09% (128/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.06% (85/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016. Review of the cases received during the current reporting period showed multiple risk factors for hepatic toxicity, including pancreatic cancer with hepatic metastasis, use in combination with investigational agents, checkpoint inhibitors, and investigational use in unapproved combination with other agents. Due to multiple confounding factors, no cases were assessed as DILI secondary to ABRAXANE during this reporting period.

No new information has been identified that would alter the current understanding of the potential risk of Hepatic toxicity (Drug-induced liver injury), and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is no longer considered important.

Important potential risks reclassified as potential risks (not important)

- Medication errors

  The MAH is proposing to reclassify Medication errors from an important potential risk to a potential risk (not important) as it is deemed no longer important based on the following.

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for medication errors was estimated to be 0.003% (4/139,633) versus 0.004% (6/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.003% (4/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

  ABRAXANE is subject to restricted medical prescription. Section 4.2 of the SmPC includes information on ABRAXANE administration, including a statement that ABRAXANE should only be administered under the supervision of a qualified oncologist in units specialized in the administration of cytotoxic agents. Sections 4.2 and 6.6 of the SmPC include a specific instruction to flush the infusion line following ABRAXANE administration.

  No new information has been identified that would alter the current understanding of the potential risk of Medication errors, and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this potential risk is no longer considered important.

- Off-label use

  The MAH is proposing to reclassify Off-label use from an important potential risk to a potential risk (not important) as it is deemed no longer important.

In more than 10 years since ABRAXANE has been available under real-world conditions (placed on the market), there has been a low rate of off-label use. In the most recent annual PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for off-label use was 6% compared to 7% for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 6% for the PSUR interval 07 Jan 2015 to 06 Jan 2016. The safety profile in off-label indications thus far has been consistent with the known safety profile of ABRAXANE and does not affect the overall risk-benefit profile of the product. The current indications for ABRAXANE in the EEA are the same as or similar to the approved indications for ABRAXANE in other countries globally.

ABRAXANE is subject to restricted medical prescription. The SmPC details the approved indications. The package leaflet clearly states the product is not to be shared with others and the indications for product use.

Important potential risk removed from the list of safety concerns

- Drug-induced lupus erythematosus (DILE)

  The MAH is proposing to remove Drug-induced lupus erythematosus (DILE) from the list of safety concerns as it is deemed no longer important based on the following.

  No events of DILE were reported in the registration clinical studies with ABRAXANE monotherapy, ABRAXANE in combination with gemcitabine and ABRAXANE in combination with carboplatin. One case report (Lamond, 2013) of drug-induced subacute cutaneous lupus erythematosus was identified during routine literature surveillance for ABRAXANE.

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for DILE was 0.001% (2/139,633) versus 0% (0/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.0% (0/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

  No new information has been identified that would alter the current understanding of the potential risk of DILE, and no additional risk minimization measures are in place. The current level of information is insufficient to establish a causal relationship and to have any impact on risk/benefit. Going forward, the MAH is proposing to apply standard signal detection methodology. Therefore, the MAH is proposing to remove this safety concern, as it is no longer considered important.

Risk previously classified as missing information, reclassified as potential risk (not important)

- Reproductive toxicity

  The MAH is proposing to reclassify Reproductive toxicity (including suspected pregnancy exposure and fertility disorders) as a potential risk (not important) based on the following.

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for reproductive toxicity was estimated to be 0.0007% (1/139,633) versus 0.001% (2/137,451) in the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.0%

(0/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016. The cumulative reporting rate was estimated to be 0.001% (10/610,376).

Data are limited regarding use of ABRAXANE in human pregnancy. Section 4.6 of the SmPC provides information on the reproductive toxicity of paclitaxel, and includes a warning on the use of ABRAXANE in pregnancy, breast-feeding, and in women of childbearing potential not using effective contraception, as well as the effect on male fertility. Most recently, the SmPC has been amended to include advice that women of childbearing potential should have a pregnancy test prior to starting treatment with ABRAXANE. These routine risk minimization measures are considered sufficient, and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is not considered important.

- Genotoxicity long-term effect

  The MAH is proposing to reclassify Genotoxicity long-term effect as a potential risk (not important) based on the following.

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for genotoxicity was estimated to be 0.002% (3/139,633) versus 0.002% (3/137,451) in the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.001% (2/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016. The cumulative reporting rate was estimated to be 0.002% (11/610,376).

  Section 5.3 of the SmPC includes information on the carcinogenic and genotoxic potential of paclitaxel. No additional studies are planned and routine risk minimization measures are considered sufficient, and no additional risk minimization measures are in place. Therefore, the MAH is proposing that this safety concern is not considered important.

Risks previously classified as missing information, removed from the list of safety concerns

- Patients with severe renal insufficiency (CrCl <30 mL/min), including end-stage renal disease

  The MAH is proposing to remove the specific patient population Patients with severe renal insufficiency (CrCl <30 mL/min), including end-stage renal disease from the list of safety concerns based on the following.

  In a population PK analysis (Study Report ABI-007-CP-001) of pooled data from eight clinical studies, which included 150 patients with advanced solid tumors and under the *nab*-paclitaxel monotherapy, only one patient had severe renal impairment. This patient had an approximately 30% reduction in maximum elimination rate (VMEL) of paclitaxel and 38% higher AUC versus the corresponding median value for normal renal function. Pharmacokinetic data are not available for patients with end-stage renal disease. No further studies in patients with severe renal insufficiency are planned.

  In the two most recent annual ABRAXANE PSURs (reporting periods 07 Jan 2017 to 06 Jan 2018, and 07 Jan 2016 to 06 Jan 2017, respectively), there were no cases with a history of severe renal impairment with a CrCl < 30 mL/min or end-stage renal failure versus two cases for the PSUR for 07 Jan 2015 to 06 Jan 2016.

Sections 4.2 and 5.2 of the SmPC advise that insufficient data are available to recommend dose modifications for patients with severe renal impairment (estimated CrCl < 30 mL/min) or end-stage renal disease. No further PK/PD studies are planned in this subpopulation.

- Patients with central nervous system metastases

  The MAH is proposing to remove the specific patient population Patients with central nervous system metastases from the list of safety concerns based on the following.

  Patients with CNS metastases are excluded from clinical trials because their CNS disease, which typically is not well controlled by systemic chemotherapy, can be the major limiting factor for their survival. In practice, the use of ABRAXANE in this patient population would not be expected to have a higher risk profile if the CNS disease is under control. However, the MAH has been monitoring safety in the PSURs.

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), there were 12 initial cases for the population of patients with central nervous system (CNS) metastases (including five clinical trial cases, three spontaneous cases, two other non-interventional study cases, and two literature cases) and six follow-up cases received. Of the 12 initial cases, seven occurred in patients with NSCLC, four occurred in patients with breast cancer, and one occurred in a patient with pancreatic cancer. There were three cases with a fatal outcome.

  During the PSUR for 07 Jan 2016 to 06 Jan 2017, there were eight initial reports for the population of patients with CNS metastases (including seven clinical trial cases and one spontaneous case). Of the eight initial cases, six occurred in patients with NSCLC, one occurred in a patient with breast cancer and the remaining occurred in an unapproved indication. All eight initial cases noted a history of CNS metastases and one noted disease progression associated with CNS metastases. There was one case with a fatal outcome.

  During the PSUR for 07 Jan 2015 to 06 Jan 2016, there were eight initial reports for the population of patients with CNS metastases (including five clinical trial cases, two spontaneous cases and one literature case). All eight initial cases noted a history of CNS metastases, two noted disease progression associated with CNS metastases and one noted new meningeal metastases. There was one case with a fatal outcome.

  The ADRs reported in these cases, while serious, are not substantially different from those reported in patients without CNS metastases.

  No new information concerning the safety of ABRAXANE in this group of patients has emerged, and no additional risk minimization measures are in place.

  The MAH considers Patients with CNS metastases as information no longer missing and therefore proposes to remove Patients with CNS metastases from the list of safety concerns.

- Children

  The MAH considers (use in) Children as information no longer missing and proposes to remove Children from the list of safety concerns.

Study ABI-007-PST-001 was a Phase 1/2 study to assess the safety, tolerability, and preliminary efficacy of weekly *nab*-paclitaxel in pediatric patients with recurrent or refractory solid tumours. A total of 65 and 42 patients were enrolled in Phase 1 and Phase 2, respectively. The overall safety profile of *nab*-paclitaxel was consistent with the known safety profile in adults. No new safey signals were observed. No meaningful clinical activity or survival benefit was seen in pediatric patients with Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma in the Phase 2 portion of the study. The overall findings from Study ABI-007-PST-001 do not support the further development of *nab*-paclitaxel in pediatric patients.

A Pediatric Investigation Plan (PIP) modification request has been made by the MAH to the European Medicines Agency (EMA) to stop further pediatric development as results from Study ABI-007-PST-001 demonstrated the lack of efficacy of ABRAXANE in the pediatric population. This modification request was submitted on 09 Apr 2018, and approved on 29 Jun 2018 as per opinion EMA/PDCO/238013/2018.

Class Effects Reclassified as Identified Risks (Not Considered Important)

- Alopecia

  The MAH is proposing to reclassify Alopecia as an identified risk (not important).

  Grade 1 to 2 alopecia is known to be very common and affects most patients receiving ABRAXANE, both as a single agent or in combination.

  In the registration clinical studies, the proportions of patients experiencing alopecia were 74% for ABRAXANE monotherapy, 53% for ABRAXANE in combination with gemcitabine and 54% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing alopecia in the comparative arms were 5% for gemcitabine and 60% for taxol plus carboplatin.

  In the most recent annual ABRAXANE PSUR (07 Jan 2017 to 06 Jan 2018), the annual reporting rate for alopecia was estimated as 0.10% (144/139,633) versus 0.11% (145/137,451) for the PSUR interval 07 Jan 2016 to 06 Jan 2017 and 0.04% (62/142,490) for the PSUR interval 07 Jan 2015 to 06 Jan 2016.

  Alopecia is very common (> 80%) in patients treated with ABRAXANE (Section 4.8 of the SmPC). The MAH is closely monitoring reports of alopecia from all sources and reports of persisting alopecia beyond six months after discontinuation.

- Edema

  The MAH is proposing to reclassify Edema as an identified risk (not important).

  In the registration clinical studies, the proportions of patients experiencing edema were 19% for ABRAXANE monotherapy, 44% for ABRAXANE in combination with gemcitabine and 9% for ABRAXANE in combination with carboplatin. The proportions of patients experiencing edema in the comparative arms were 29% for gemcitabine and 4% for taxol plus carboplatin. Grade 3 events of edema were reported for 4% of patients treated with ABRAXANE in combination with gemcitabine, and 3% of patients treated with gemcitabine alone. The incidences of Grade 3 edema were < 1% each in patients

treated with ABRAXANE monotherapy, ABRAXANE in combination with carboplatin and taxol plus carboplatin. Events of Grade 4 edema were reported in < 1% of patients treated with ABRAXANE monotherapy, and no patients in the clinical studies of ABRAXANE in combination with gemcitabine and ABRAXANE in combination with carboplatin.

The MAH considers that edema is an identified risk (not important) for patients treated with ABRAXANE. In addition to peripheral oedema, several other manifestations are included in the SmPC for ABRAXANE (for instance, pleural effusion).

3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

3.1. Presentation of the Important Identified Risks and Important Potential Risks

Not applicable.

3.2. Presentation of the Missing Information

Not applicable.

PART II - MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

1. SUMMARY - ONGOING SAFETY CONCERNS

There are no important identified or potential risks, or missing information.

PART III - PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance activities in Celgene as described in the Celgene Pharmacovigilance System Master File are in accordance with the "Good Pharmacovigilance Practices (GVP)" Guidelines in the EU. Celgene's Routine Pharmacovigilance System is detailed in the Pharmacovigilance System Master File.

In addition to expedited reporting, Celgene vigilantly undertakes follow-up on all ADRs, including serious ADRs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the ADRs.

1.1. Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

1.1.1. Specific Adverse Reaction Follow-up Questionnaires

Specific adverse reaction follow-up questionnaires have been developed by the MAH to ensure that consistent and good quality follow-up information can be obtained.

1.1.1.1. An Analysis of Adverse Drug Reactions of Special Interest within the Required PSURs

Emerging potential safety signals can be detected by periodic and if appropriate, cumulative evaluation of the ADRs. The results will be compiled in the PSUR, in accordance with EU guidance. Periodicity of the PSUR submissions is defined by the International Birth Date.

In addition, data regarding AEs of special interest will be targeted for review and will be specifically discussed in the PSUR document. These data will include all case reports collected during the specified period together with cumulative data.

2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional pharmacovigilance activities for ABRAXANE.

2.1. Summary Table of the Additional Pharmacovigilance Activities

Not applicable.

2.2. Ongoing and Planned Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities for ABRAXANE.

PART IV - PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorization efficacy studies for ABRAXANE.

PART V - RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

1. RISK MINIMIZATION PLAN

1.1. Routine Risk Minimization Measures

Not applicable as there are no important identified or potential risks.

1.2. Additional Risk Minimization Measures

No additional risk minimization measures are proposed for ABRAXANE.

1.3. Summary of Risk Minimization Measures

Not applicable as there are no important identified or potential risks.

PART VI - SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR ABRAXANE (PACLITAXEL [FORMULATED AS ALBUMIN BOUND NANOPARTICLES])

This is a summary of the risk management plan (RMP) for ABRAXANE.

ABRAXANE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ABRAXANE should be used.

This summary of the RMP for ABRAXANE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns will be included in updates of ABRAXANE's RMP.

1.1. The Medicine and what it is Used for

ABRAXANE is authorized for:

ABRAXANE in Combination With Carboplatin

ABRAXANE in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

ABRAXANE in Combination With Gemcitabine for Pancreatic Cancer

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

ABRAXANE Monotherapy for Metastatic Breast Cancer

ABRAXANE monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.

ABRAXANE contains paclitaxel as the active substance and is a powder for suspension for infusion.

Further information about the evaluation of ABRAXANE's benefits can be found in ABRAXANE's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage *http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000778/WC500020431.pdf.*

1.2. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

There are no important identified or potential risks of ABRAXANE.

1.2.1. List of Important Risks and Missing Information

Not applicable as there are no important identified or potential risks, or missing information.

1.2.2. Summary of Important Risks

Not applicable as there are no important identified or potential risks.

1.2.3. Postauthorization Development Plan

1.2.3.1. Studies which are Conditions of the Marketing Authorization

Not applicable as there are no studies in the postauthorization development plan.

1.2.3.2. Other Studies in Postauthorization Development Plan

Not applicable as there are no studies in the postauthorization development plan.

PART VII - ANNEXES

Annex Number	Document Title
1	EudraVigilance Interface
2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program
3	Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan
4	Specific Adverse Drug Reaction Follow-up Forms
5	Protocols for Proposed and Ongoing Studies in RMP Part IV
6	Details of Proposed Additional Risk Minimization Activities (if Applicable)
7	Other Supporting Data (Including Referenced Material)
8	Summary of Changes to the Risk Management Plan Over Time

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

There have been no updates since Version 16.0 of the EU-RMP.