Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for nanoparticle albumin-bound (nab) paclitaxel

Proprietary Product Name: Abraxane

Sponsor: Abraxis Biosciences Pty Ltd

June 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
5-FU	Fluorouracil
ACS	American Cancer Society
AE	Adverse Event
ALT	(SGPT) Alanine aminotransferase
ANC	Absolute neutrophil count
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
$AUC_{0\text{-}24hr}$	Area under the plasma concentration-time curve from time 0
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CA19-9	Carbohydrate Antigen 19-9
CapOx	Capecitabine plus oxaliplatin
Cav-1	Caveolin-1
CI	Confidence Interval
Cmax	Peak plasma concentration of drug
CNS	Central nervous system
CR	Complete Response
CrEL	Cremophor EL
CRF	Case report form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEHP	di-(2-ethylhexyl)phthalate, a plasticizer

Abbreviation	Meaning
DIC	Disseminated intravascular coagulation
DLT	Dose-limiting Toxicities
DMC	Data monitoring committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of study
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
Flutax	Fluorescent-labelled paclitaxel
FOLFIRINOX	Folinic Acid (Leucovorin), Fluorouracil, Irinotecan, and Oxaliplatin
G-CSF	Granulocyte colony-stimulating factor
GEM	Gemcitabine
GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
HMEC	Human Mammary Epithelial Cell
HMVE	Human Microvascular Endothelial
HMVEC	Human Microvascular Endothelial Cell
HR	Hazard Ratio
$HR_{A+G/G}$	Hazard Ratio of ABI-007 followed by Gemcitabine / Gemcitabine alone
HSA	Human Serum Albumin
HUVE	Human Umbilical Vascular Endothelial
HUVEC	Human Umbilical Vascular Endothelial Cell

Abbreviation	Meaning
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRR	Independent Radiologic Review
ITT	Intent-to-treat
IV	Intravenous(ly)
IVRS	Interactive voice recognition system
KM	Kaplan Meier
KPS	Karnofsky Performance Status
MBC	Metastatic breast cancer
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
Mrp2	Multidrug resistance-associated protein 2
MTD	Maximum tolerated dose
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not Evaluable
NEM	N-(3,4-dimethoxyphenethyl)-maleimide
NIH	National Institutes of Health
No.	Number
NOAEL	No Observed Adverse Effect Level
NoMA	Norwegian Medicines Agency
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Overall Response Rate

Abbreviation	Meaning
OS	Overall Survival
p_{A+G}/p_G	Response rate ratio of ABI-007 followed by gemcitabine/gemcitabine alone
PAGE	Polyacrylamide gel electrophoresis
PD	Pharmacodynamics
PD	Progressive Disease
PET	Positron-emission Tomography
PFS	Progression-free Survival
P-gp	P-glycoprotein
PI	Prescribing Information
PK	Pharmacokinetics
PR	Partial Response
PT	Patient
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
sNDA	Supplemental New Drug Application
SPARC	Secreted Protein Acidic and Rich in Cysteine
TEAE	Treatment-emergent Adverse Event
TGA	Therapeutic Goods Administration
T_{max}	Time to peak plasma concentration of drug
TTF	Time to Treatment Failure

Abbreviation	Meaning
ULN	Upper Limit of Normal
US	United States
Vdss	Volume of distribution at steady state
WBC	White Blood Cell

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	13 March 2014
Active ingredient:	Nanoparticle albumin-bound (*nab*) paclitaxel
Product name:	Abraxane
Sponsor's name and address:	Abraxis Bioscience Australia Pty Ltd PO Box 250 East Kew Victoria 3102
Dose form:	Lyophilised powder for injection after reconstitution
Strength:	100 mg paclitaxel (and 900 mg human albumin)
Container:	Vial
Pack size:	One
Approved therapeutic use:	New indication: Abraxane, in combination with gemcitabine, is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas.
Route of administration:	Intravenous (IV)
Dosage:	125 mg/m^2 followed by gemcitabine 1000 mg/m^2 on days 1, 8, 15 repeated every 28 days.
ARTG number:	133500

Product background

This AusPAR describes the application by the sponsor to register Abraxane for the following indication;

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

Cancer of the exocrine pancreas is a highly lethal malignancy, with a five-year survival rate of fewer than 5%. It is the fifth leading cause of cancer-related death in Australia (Cancer Council Australia) accounting for 5% of all cancer deaths, and second only to colorectal cancer as a cause of digestive cancer-related death. Ductal adenocarcinoma of the pancreas (including its subtypes) represents about 85 percent of all pancreatic neoplasms. Of the several subtypes of ductal adenocarcinoma, most share a similar poor long-term prognosis, with the exception of colloid carcinomas, which have a somewhat better prognosis.

Surgical resection is the only potentially curative treatment but, because by the time most patients develop symptoms and/or present, only 15 to 20 percent of patients are candidates for pancreaticoduodenectomy. Even after a complete resection, the five-year survival rate after pancreaticoduodenectomy is about 25-30 percent for node-negative and 10 percent for node-positive disease. Median survival is 8-12 months for patients with locally advanced unresectable disease and only three to six months for those who present with metastases. Thus with so many patients presenting with unresectable or metastatic disease, there is a significant need for effective chemotherapeutic regimens. Two agents have been registered for the treatment of locally advanced or metastatic disease. The first of these, gemcitabine, demonstrated a very modest objective response rate (11%) but a 27% improvement in symptoms (that is, pain, weight loss) and performance status compared with fluorouracil (5-FU). This study led to the approval of single agent gemcitabine for the treatment of locally advanced and metastatic pancreatic cancer and emphasised the importance of assessing efficacy by defining symptom control as a beneficial endpoint for evaluating treatments in this disease.

The other agent approved for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine, is the Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor, erlotinib. There was a slight improvement in survival compared with gemcitabine alone, but there was significantly more toxicity (Hazard Ratio (HR) 0.81, p = 0.038, median 6.2 versus 5.9 months, one year survival 23 versus 17 percent, respectively).

Another regimen with a reported improvement in survival is Folfirinox (5-FU, leucovorin, irinotecan and oxaliplatin) but this has significant toxicity and requires a good baseline performance status.

Thus there remains a significant unmet need for those patients presenting with advanced or metastatic disease.

Abraxane is a proprietary human albumin-bound nanoparticle formulation of paclitaxel with a mean particle size of approximately 130 nm, designed to improve the chemotherapeutic effects of paclitaxel by exploiting endogenous transport pathways to deliver higher doses of paclitaxel to the tumour and to reduce the solvent-related hypersensitivity (and the need for premedication with corticosteroids) and other toxicities associated with solvent-based paclitaxel injections.

Molecular profiling of patients' pancreatic cancers demonstrated that the albumin-binding protein, secreted protein acidic and rich in cysteine (SPARC), was present, in particular in the tumour stroma. This finding has suggested that nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel, Abraxane) may bind to SPARC and be useful for the treatment of pancreatic cancer.

Furthermore, Abraxane has been shown to have single agent activity in mouse models of pancreatic cancer, and to be synergistic with gemcitabine in preclinical models by increasing intratumoral gemcitabine levels compared with gemcitabine alone. Based in part on these findings, a Phase I/II dose escalation study of Abraxane combined with gemcitabine was conducted in patients with metastatic adenocarcinoma of the pancreas. The tolerability of this combination and the promising early activity in Study CA040 led to the conduct of the pivotal randomized Phase III study of Abraxane in combination with gemcitabine compared with gemcitabine monotherapy, Study CA046.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 October 2008.

At the time the TGA considered this application, Abraxane was approved for the following 2 indications:

> *Abraxane is indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.*
>
> *Abraxane, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.*

Orphan drug designation for Abraxane for the treatment of pancreatic cancer was approved by the TGA Australia on the 1 December 2009.

Similar applications were lodged in the European Union (European Medicines Agency (EMA)) on 20 December 2013, and in the United States (Food and Drug Administration (FDA)) on 6 September 2013.

A similar application was lodged in Switzerland but no outcome has been determined.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

Data submitted consisted of pharmacology studies to support the proposed indication, a study assessing potential pharmacokinetic drug interactions between the two drugs, and toxicity studies with Abraxane alone. While toxicity studies with the combination would have been ideal, in accordance with The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH S9) (Nonclinical Evaluation for Anticancer Pharmaceuticals), the absence of such studies is not considered a deficiency given the extensive clinical use of both gemcitabine and paclitaxel-containing products, and the currently approved use of gemcitabine with paclitaxel (albeit not Abraxane per se, but Taxol and similar solvent-based paclitaxel generics).

Pharmacology

Primary pharmacology

In vitro, both Abraxane and gemcitabine had inhibitory activity on pancreatic ductal adenocarcinoma cell lines. The IC50 values for gemcitabine were significantly lower in the presence of Abraxane.

The in vivo efficacy of the combination of Abraxane and gemcitabine was assessed in mice bearing human xenografts of pancreatic ductal adenocarcinoma (PDA) (both subcutaneous (SC) and intraperitoneal (IP) implants) and a genetically-engineered mouse

model for pancreatic cancer (KPC model). All models are acceptable, but the KPC model is the best of the models used, as the disease in this model recapitulates some of the aspects of the human form of the disease (PDA formation and metastases) which are lacking from the xenograft models.[1] Nonetheless, similar findings were seen in all models, while individually both agents showed some efficacy, reduced tumour growth and greater animal survival were observed with the Abraxane/gemcitabine combination compared with either agent alone. In the presence of paclitaxel, higher intratumour concentrations of gemcitabine and, where tested, its active metabolite, dFdCTP, were observed. The mechanism leading to increased intratumour concentrations is not fully known but the data indicate increased penetration of the tumour due to effects on the stroma (xenograft model) and decreased protein levels of cytidine deaminase (KPC model), an enzyme that deactivates gemcitabine and dFdCTP and whose levels have correlated with gemcitabine resistance.[2]

Some evidence was provided to suggest cytidine deaminase levels were reduced as a result of paclitaxel-induced reactive oxygen species (ROS).

Regardless of the mechanism, synergistic or additive anti-tumour activity was seen with Abraxane and gemcitabine. The efficacious doses ranged from 30–360 mg/m^2 Abraxane (IV or IP) and 300 mg/m^2 IP gemcitabine, every 3 to 5 days. Overall, the pharmacology data support the proposed clinical use of Abraxane and gemcitabine for the treatment of patients with adenocarcinoma of the pancreas.

Pharmacokinetics

Potential pharmacokinetic interactions between paclitaxel and gemcitabine were assessed in rats given IV doses of the combination of Abraxane and Gemzar. Paclitaxel had no impact on the plasma kinetics of gemcitabine, and vice versa. Both the maximum concentration (Cmax) and the area under the curve (AUC) values for the metabolite, dFdU, were higher in animals that received the combination compared with those that received Gemzar alone. Given that this metabolite is not active, this difference is not expected to impact the safety/efficacy assessment. Cellular levels of dFdCTP were not assessed. Both the Gemzar Product Information document and published data[3] indicate that when administered in combination with paclitaxel to human subjects, the gemcitabine pharmacokinetics are not affected and gemcitabine had no effect on paclitaxel pharmacokinetics. However, the Cmax (but not AUC) for dFdCTP was higher during coadministration with paclitaxel,[3] the reason for which is unknown. No clinical pharmacokinetic interaction studies have been conducted with Abraxane and gemcitabine, but the effects described above for "paclitaxel" are expected to also be relevant for Abraxane.

Toxicology

Repeat-dose toxicity studies with Abraxane alone in rats (up to 4 weeks) and monkeys (up to 3 weeks) further characterised the toxicity profile of this drug, as only a very limited toxicity package was submitted previously (SN 2006-2696-4). In general, the toxicity profile of Abraxane was similar in both species and was similar to that reported previously with Abraxane and paclitaxel.[4] Target organs included the bone marrow and lymphoid organs (hypocellularity), correlating with reduced levels of circulating white blood cells as well as reduced red blood cell parameters, and the male reproductive organs (testicular degeneration, prostate gland and seminal vesicle atrophy). In rats, where higher

[1] Herreros-Villanueva et al., 2012; Hruban et al., 2006.
[2] Ogawa et al., 2005; Yoshida et al., 2010.
[3] Kroep et al., 1999.
[4] Kadota et al., 1994a; 1994b.

exposures were achieved, central and peripheral neuropathy were evident (myelin ovoid in the spinal cord, sciatic nerve, cerebrum and brain stem), and effects were seen in the eyes (single cell necrosis, cataracts) and skin (single cell necrosis and atrophy of the skin/subcutis). Infectious lesions were evident in some animals, likely due to the impaired immune system. Toxicity (clinical signs and effects on haematology parameters) appeared to be greater affected with Abraxane than Taxol in rats, similar to previously evaluated single dose toxicity studies in the same species, although Abraxane was better tolerated than Taxol in repeat dose studies in mice.

Gemcitabine, based on its mode of action, targets rapidly dividing cells and has an overlapping toxicity profile with paclitaxel — myelosuppression, gastrointestinal toxicity and effects on the reproductive organs and skin. Hepatotoxicity has also been reported.[5]

No toxicity studies have been conducted with the combination of Abraxane and gemcitabine. As the 3 week cumulative dose of Abraxane (125 mg/m^2/week) is higher than the currently approved dose (260 mg/m^2/3 weeks) and higher than that for Taxol in combination with gemcitabine (175 mg/m^2/3 weeks), and the toxicity profile of paclitaxel and gemcitabine are, in part, overlapping, more severe toxicity (in particular myelosuppression with a higher risk for infections, gastrointestinal toxicity, reproductive toxicity and dermal toxicity) would be expected with the proposed dose/dosage regimen of the Abraxane/gemcitabine combination.

The tolerability of the proposed doses and dosage regimen with Abraxane and gemcitabine needs to rely solely on clinical data.

Nonclinical summary and conclusions

In vitro, both Abraxane and gemcitabine had inhibitory activity on pancreatic ductal adenocarcinoma cell lines. The IC50 values for gemcitabine were significantly lower in the presence of Abraxane.

In mouse models of pancreatic ductal adenocarcinoma, reduced tumour growth and greater animal survival were observed with the Abraxane/gemcitabine combination compared with either agent alone. Overall, the pharmacology data support the proposed clinical use of Abraxane and gemcitabine for the treatment of patients with adenocarcinoma of the pancreas.

No pharmacokinetic interactions were evident in rats.

Significant toxicity concerns exist with the proposed use of Abraxane as:

- the 3 week cumulative dose of Abraxane is higher than the currently approved dose and higher than that for Taxol when used in combination with gemcitabine;
- the toxicity profile of paclitaxel and gemcitabine are, in part, overlapping – more severe toxicity may be expected. In particular:
  - myelosuppression with a higher risk for infections
  - gastrointestinal toxicity
  - dermal toxicity
  - reproductive toxicity

The tolerability of the proposed doses and dosage regimen with Abraxane and gemcitabine needs to rely solely on clinical data.

[5] Lund et al., 1993.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2 (Clinical Evaluation Report Extract).

First round benefit-risk assessment

First round assessment of benefit

There are very few treatment options of potential benefit available for the treatment of metastatic adenocarcinoma of the pancreas with gemcitabine the established agent of choice with a potential response rate of < 20% and progression free survival of < 4 months development of new more effective therapies is urgently required. The quite robust and relatively large randomised trial provided in this submission namely CA046 clearly demonstrates that the combination of Abraxane with gemcitabine is significantly superior to gemcitabine alone in terms of overall survival with a median for the combination of 8.5 months compared to gemcitabine at 6.7 months corresponding to a 28% reduction in the risk of death. It is pertinent to point out that this study was quite mature as at the time of the final analysis some 80% of patients had died and only 19% remained in survival follow up. Furthermore the one year survival rate was 59% higher in the combination arm compared with gemcitabine arm at 35% versus 22% and the two year survival was 125% higher at 9% versus 4%. Various sub-group and sensitivity analyses confirmed the significant improvement in overall survival and secondary efficacy parameters including progression free survival and overall response rate are also significantly improved with the combination therapy.

Although this represents a single study it nevertheless is robust and mature giving confidence to the likely benefits of the combination of Abraxane with gemcitabine for the treatment of patients with advanced stage pancreatic adenocarcinoma.

The relatively small Study CA040 adds credibility to the activity levels of the combination of Abraxane and gemcitabine.

First round assessment of risks

The safety data provided in this submission clearly indicates that the addition of Abraxane to gemcitabine results in a somewhat greater degree of adverse effects. This might be anticipated from the known toxicity profiles for the two agents involved. Those adverse effects with the highest incidence for the combination included neutropenia, peripheral neuropathy, infectious sepsis and pneumonitis. Again these are consistent with that well recognised for Abraxane. Its addition to gemcitabine results in a higher incidence of these adverse effects. It is notable however that there were no new adverse effects apparent with the introduction of this combination.

Careful monitoring together with early intervention and relevant prophylaxis particularly in relation to neutropenia with growth factors should help to ameliorate the toxicity profile from the drug combination but nevertheless it is clear that for patients greater than 75 years, great caution needs to be observed when treating this patient population with this particular drug combination.

First round assessment of risk-benefit balance

The pivotal study has demonstrated a clear-cut benefit in terms of survival, progression free survival, overall response rate for the combination of Abraxane and gemcitabine in what is a well-conducted quite large study. Although this represents the only data

available in relation to the combination for the proposed indication the clinical benefits that have ensued from the data are superior to those available for any other assessed combinations including the combination of gemcitabine with Erlotinib. The toxicity profile for the combination is somewhat greater than that observed with gemcitabine but nevertheless as discussed should fall within the expertise of oncologists experienced with the use of these agents.

Taking into account the generally poor outcomes for advanced stage pancreatic adenocarcinoma with currently available therapies particularly gemcitabine alone, the evidence from the pivotal study clearly is supportive of a strongly positive benefit/risk balance.

It is also pertinent to point out that although the study conducted was in patients with metastatic adenocarcinoma of the pancreas all other available data in the literature would strongly suggest that benefits accruing to patients with metastatic adenocarcinoma of the pancreas might be anticipated for those with locally advanced disease and accordingly the proposed indication to include both advanced unresectable and metastatic adenocarcinoma of the pancreas seems appropriate.

First round recommendation regarding authorisation

Taking into account the above discussion and the clear indication of positive benefit versus risk together with recognition that both patients with locally advanced disease and metastatic adenocarcinoma of the pancreas would be benefited by the combination of Abraxane with gemcitabine it is appropriate for this reviewer to recommend approval for Abraxane in combination with gemcitabine is indicated for the first line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas.

Clinical questions

No additional clinical questions arise from this reviewer.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version: 12.0, dated 11 March 2013 with an Australian Specific Annex (ASA) Version: 3.0, dated 6 June 2013) which was reviewed by the TGA.

Table 1. Summary of Risk Management Plan

All figures and tables in this section that have been copied from the original dossier are considered by the evaluator to be an accurate representation of the reviewed data, unless qualified as such in the commentary of the report.

Safety Concern	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
Important Identified Risks:		
Myelosuppression (Neutropenia, anemia and thrombocytopenia) Peripheral neuropathy Cranial nerve palsies Hypersensitivity reactions Pneumonitis Sepsis Gastrointestinal events* Myalgia and arthralgia Cardiotoxicity Cystoid macular edema Stevens-Johnson syndrome/toxic epidermal necrolysis Infusion site reactions/extravasation	Routine Pharmacovigilance as per EU RMP: Reports of these important identified risks will be closely monitored in ongoing clinical trials and in postmarketing surveillance, and will be the subject of special review in future PSURs. *Additional pharmacovigilance activity specific to Australia: Australian Abraxane Drug Utilisation Study to determine the requirement for pre-medication for gastro-intestinal events.	To monitor the frequency and severity of these important identified risks in a larger population of patients, and to be vigilant regarding any change of event characteristics. * Drug utilization study to assess the requirement for pre-medication for gastrointestinal events in Australia.
Important Potential Risks:		
Hepatic toxicity (drug-induced liver injury) Acute renal failure and hemolytic-uremic syndrome	Routine Pharmacovigilance as per EU RMP: Reports of important potential risks will be closely monitored in ongoing clinical trials and in postmarketing surveillance, and will be reviewed in future PSURs.	To monitor the frequency and severity of the important potential risks in a larger population of patients, and to be vigilant regarding any change of evidence of causal relationship.
Important Missing Information:		
Special Populations Patients with hepatic impairment Patients with impaired renal function Patients with central nervous system metastases Children **Other Missing Information** Concomitant therapy and interactions requiring dose adjustments** Off-label use** Reproductive toxicity Genotoxicity long-term effect	Routine Pharmacovigilance as per EU RMP: Use of ABRAXANE in these patient groups and in these situations will be monitored by review of AEs reported during postmarketing surveillance. **Additional Pharmacovigilance Activity Specific to Australia: Abraxane Drug Utilisation Study to determine off label usage and the use in combination therapies and as a concomitant medication.	To monitor the use in these patient groups and in these situations and to be vigilant regarding any change in risk/benefit in these situations. ** Drug utilization study to determine off label use of ABRAXANE in Australia and to determine the use of ABRAXANE in combination therapies and as a concomitant medication in Australia.

Evaluation of the Need for Risk Minimisation Activities		
Safety Concern	**Routine Risk Minimisation Activities Sufficient?**	**If Yes, Provide Description of Routine Activity and Justification**
Important Identified Risks		
Myelosuppression	Yes	Under CONTRAINDICATIONS, the PI contains the following: ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1.5 x 10^9/L. Under **PRECAUTIONS**, the PI contains the following with reference to Haematology: Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. ABRAXANE therapy should not be administered to patients with baseline neutrophil counts of less than 1.5 x 10^9/L. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1.5 x 10^9/L and platelets recover to a level >100 x 10^9/L. In the case of severe neutropenia (<0.5 x 10^9/L for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended (see **DOSAGE and ADMINISTRATION**). and under Hepatic Impairment: 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. Labelled under **ADVERSE EFFECTS** of the PI.
Myalgia and arthralgia	Yes	Labelled under **ADVERSE EFFECTS** of the PI
Peripheral neuropathy	No (Please see the important identified risk "cranial nerve palsies" further down in this table).	Routine Risk Minimisation Activities: Under **PRECAUTIONS**, the PI contains the following: Sensory neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. For single agent use of ABRAXANE, if grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE. For combination use of ABRAXANE and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold ABRAXANE; continue treatment with gemcitabine at the same dose. Resume ABRAXANE at reduced dose when peripheral neuropathy improves to Grade 0 or 1 (see DOSAGE and ADMINISTRATION). Labelled under **ADVERSE EFFECTS** of the PI, also with the following explanatory text: Peripheral Neuropathy. For ABRAXANE and gemcitabine, the median time to first occurrence of Grade 3 peripheral neuropathy was 140 days, and the median time to improvement from Grade 3 peripheral neuropathy to Grade 0 or 1 was 29 days. Of the patients with treatment interrupted due to peripheral neuropathy, 44% (31/70 patients) were able to resume ABRAXANE at a reduced dose. No patients treated with ABRAXANE/gemcitabine had Grade 4 peripheral neuropathy. The **DOSAGE and ADMINISTRATION** section of the PI provides details on recommended dose adjustments for severe (grade 3 or 4) peripheral neuropathy. Sensory neurotoxicity is labelled in the **OVERDOSAGE** section of the PI. Additional Risk Minimisation Activities specific to Australia: Cranial Nerve Palsies has additional risk minimisation activities in place. See "Cranial Nerve Palsies"

Gastrointestinal events	Yes	Labelled under **ADVERSE EFFECTS** of the PI. The **DOSAGE and ADMINISTRATION** section of the PI provides details on recommended dose adjustments for grade mucositis or diarrhoea. Mucositis is labelled in the **OVERDOSAGE** section of the PI. Under **PRECAUTIONS**, the PI contains the following with reference to GI events: Use in the Elderly: In the randomised study, amongst patients who
		received ABRAXANE and gemcitabine, diarrhoea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old.
Hypersensitivity reactions	Yes	Under **CONTRAINDICATIONS**, the PI contains the following: In patients who have exhibited hypersensitivity reactions to paclitaxel or human albumin, patients should not be treated with ABRAXANE. Under **PRECAUTIONS**, the PI contains the following with reference to Hypersensitivity: Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with the drug. Labelled under the **ADVERSE EFFECTS** section of the PI.
Cranial nerve palsies	No	Routine Risk Minimisation Activities: Cranial Nerve Palsies is labelled under Post-marketing experience in the **ADVERSE EFFECTS** section of the PI. Please also see "Peripheral neuropathy" for details of routine risk minimisation activities for peripheral neuropathy. Additional Risk Minimisation Activities specific to Australia: A healthcare professional (HCP) brochure has been prepared for the education of HCPs about the post marketing identified risk of cranial nerve palsies (see appendix 3). More details on this risk minimisation activity are provided in section 3.3 of this document.
Cardiotoxicity	No	Routine Risk Minimisation Activities: Cardiac Disorders are labelled under the **ADVERSE EFFECTS** section of the PI. Under **PRECAUTIONS**, the PI contains the following: Rare events of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving ABRAXANE. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history. Thus patients receiving ABRAXANE should be vigilantly monitored by physicians for the occurrence of cardiac events. Additional Risk Minimisation Activities specific to Australia: A healthcare professional (HCP) brochure has been prepared for the education of HCPs about the post marketing identified risk of cardiotoxicity in patients post anthracycline exposure (see appendix 3). More details on this risk minimisation activity are provided in section 3.3 of this document.
Stevens-Johnson syndrome/toxic epidermal necrolysis	No	Routine Risk Minimisation Activities: Labelled under Post-marketing experience in the **ADVERSE EFFECTS** section of the PI. Additional Risk Minimisation Activities specific to Australia: A healthcare professional (HCP) brochure has been prepared for the education of HCPs about the post marketing identified risk of Stevens-Johnson Syndrome/Toxic epidermal necrolysis (see appendix 3). More details on this risk minimisation activity are provided in section 3.3 of this document.

Pneumonitis	Yes	Pneumonitis is labelled in the **ADVERSE EFFECTS** section of the PI. Pneumonitis was reported with ABRAXANE as monotherapy (Table 6), and in combination with gemcitabine (Table 7). The following additional explanatory text is also included underneath Table 7: **Pneumonitis** Pneumonitis has been reported at a rate of 4% with the use of ABRAXANE in combination with gemcitabine. Of the 17 pneumonitis ADRs in the ABRAXANE/gemcitabine arm, 2 had a fatal outcome. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE and gemcitabine and promptly initiate appropriate treatment and supportive measures. Under **PRECAUTIONS**, the PI contains the following: Pneumonitis has been reported at a rate of 4% with the use of ABRAXANE in combination with gemcitabine. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE and gemcitabine and promptly initiate appropriate treatment and supportive measures. Justification: Of the 17 pneumonitis ADRs in the ABRAXANE/gemcitabine arm, 2 had a fatal outcome. Pneumonitis is a well-described toxicity in the literature when paclitaxel is combined with gemcitabine, and the rates seen in patients receiving ABRAXANE plus gemcitabine appear to be consistent with those described in the literature seen with paclitaxel and gemcitabine combination therapy.
Infusion site reactions/ extravasation	Yes	Extravasation is labelled in the **ADVERSE EFFECTS** section of the PI. The following text is included in the "preparation and administration precautions" of the **DOSAGE AND ADMINISTRATION** section of the PI: Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.
Sepsis	Yes	Under **PRECAUTIONS**, the PI contains the following: Sepsis was reported at a rate of 5% in patients with or without neutropenia who received ABRAXANE in combination with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold ABRAXANE and gemcitabine until fever resolves and ANC ≥1.5 x109/L, then resume treatment at reduced dose levels (see **DOSAGE and ADMINISTRATION**). Neutropenic sepsis is labelled under the **ADVERSE EFFECTS** section of the PI with additional explanatory text similar to the text included in the **PRECAUTIONS** section.
Cystoid Macular Oedema	Yes	Cystoid Macular Oedema is labelled under the **ADVERSE EFFECTS** section of the PI, and also includes the following additional explanatory text: There have been rare reports (<1/1000 patients) of reduced visual acuity due to cystoid macular oedema (CME) during treatment with ABRAXANE as well as with other taxanes. CME can be expected to resolve after cessation of treatment.
Important Potential Risks		
Hepatic Toxicity (Drug-induced Liver Injury)	Yes	Increased liver function tests are labeled under the **ADVERSE EFFECTS** section of the PI.
Acute Renal Failure and Haemolytic Uraemic syndrome	Yes	Acute Renal Failure and Haemolytic Uraemic syndrome are labeled under the **ADVERSE EFFECTS** section of the PI (in combination with Gemcitabine).

Important Missing Information		
Use in patients with hepatic impairment	Yes	Under **PRECAUTIONS**, the PI contains the following: 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. The use of ABRAXANE has not been formally studied in patients specifically with hepatic impairment. Patients with severe hepatic impairment should not be treated with ABRAXANE. The appropriate dose regimen in patients with mild to moderate hepatic impairment is unknown. Under **DOSAGE AND ADMINISTRATION** the PI contains the following with reference to Hepatic Insufficiency: No data are currently available to recommend dosage alterations in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should not be treated with ABRAXANE.
Off-label use	Yes	The **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections of the PI sufficiently advise on the approved indications, populations and dosages for ABRAXANE.
Concomitant therapy and interactions requiring dose adjustments	Yes	Under **PRECAUTIONS** the PI contains the following with respect to Drugs Metabolised in the Liver: The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g. erythromycin, ketoconazole, fluoxetine,, imidazole antifungals, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4. Paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is primarily determined by CYP 2C8 and 3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidine deaminase followed by urinary excretion. PK interactions between ABRAXANE and gemcitabine have not been evaluated in humans.
Patients with impaired renal function	Yes	The potential for use in patients with impaired renal function is subject to routine pharmacovigilance. Under **DOSAGE AND ADMINISTRATION** the PI contains the following with respect to Patients with Impaired Renal Function: Studies in patients with impaired renal function have not been performed and there is insufficient data to permit dosage modifications in this patient population.
Use in children	Yes	There is no relevant use of ABRAXANE in the paediatric population in the indication of metastatic breast cancer or pancreatic cancer. Under **PRECAUTIONS** the PI contains the following with respect to Paediatric Use: The safety and effectiveness of ABRAXANE in paediatric patients have not been evaluated.
CNS metastases	Yes	CNS metastases are typically not well controlled by systemic chemotherapy. Even though these subjects were excluded from clinical trials, and there is no data on the safety and efficacy of ABRAXANE in this patient population, 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.
Reproductive Toxicity	Yes	Under **CONTRAINDICATIONS**, the PI contains the following: ABRAXANE is contraindicated during pregnancy and lactation. Under **PRECAUTIONS**, the PI contains the following: Effects on Fertility Administration of ABRAXANE to male rats on a weekly basis for 11 weeks prior to mating with untreated female rats was associated with testicular atrophy/degeneration and reduced fertility accompanied by

Evaluation of the Need for Risk Minimisation Activities		
Safety Concern	**Routine Risk Minimisation Activities Sufficient?**	**If Yes, Provide Description of Routine Activity and Justification**
		decreased pregnancy rates and increased loss of embryos in mated females. Testicular atrophy/degeneration has also been observed in single dose toxicology studies in rodents administered ABRAXANE at 6 mg/kg (54 mg/m2) and dogs administered 8.75 mg/kg (175 mg/m2). Use in Pregnancy Category D ABRAXANE is suspected to cause serious birth defects when administered to a pregnant woman. Administration of ABRAXANE to female rats on gestation days 7 to 17 daily at doses of 6 mg/m2 (approximately 2% of the daily maximum recommended human dose on a mg/m2 basis) caused embryo- and foetotoxicity, as indicated by intrauterine mortality, increased resorptions, reduced numbers of live foetuses, reduction in foetal body weight and increase in foetal abnormalities. Foetal abnormalities included skeletal and soft tissue malformations, such as eye bulge, folded retina, and dilation of brain ventricles. There are no adequate and well-controlled studies in pregnant women using ABRAXANE. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE. Like other genotoxic cytostatics, ABRAXANE can have genotoxic effects. Male patients treated with ABRAXANE are advised not to father a child during and up to six months after treatment.
Genotoxicity Long term effect	Yes	Under **PRECAUTIONS**, the PI contains the following: Carcinogenicity The carcinogenic potential of ABRAXANE has not been studied. Genotoxicity Paclitaxel has been shown to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice).

Reconciliation of issues outlined in the RMP report

Table 2 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised and the TGA's evaluation of the sponsor's responses.

Table 2. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information	The sponsor states that the clinical and nonclinical evaluation reports were received at the Milestone 3 stage and no questions were raised by the clinical and nonclinical evaluators. Therefore, as there have been no additional safety considerations raised, there is no additional information	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	required to be included in the RMP, other than that recommended by the RMP evaluator.	
In regard to the draft protocol for the Abraxane Drug Utilisation study (ADUS), the sponsor should provide justification for proposing a sample size of approximately 200 patients, rather than say 400 patients. The sponsor should also advise if data collection has indeed commenced as of 30 September 2013 and provide an assurance that the final protocol, including a detailed analysis plan giving consideration to the handling of missing data, will be provide to the TGA for review once it becomes available.	The sponsor has provided justification for the proposed sample size of 200 patients (approximately 8% to 10% of the annual number of patients prescribed Abraxane in Australia), which will provide a meaningful assessment of the objectives for this descriptive post market non-interventional study. In addition the sponsor has advised that the study has not yet commenced and these details have been revised in an updated draft protocol for the ADUS provided in Appendix 2 of the ASA.	This is acceptable.
Given that the NSCLC extension of indication application was approved as at 6 August 2013, the sponsor should now revise Section 3.1: 'Summary of risk minimisation activities (routine and additional) in Australia'	The sponsor has revised Section 3.1 of ASA, and any differences to section 3.1 of the since ASA version 2.1 have been identified using tracked changes. In addition the reasons for the changes are justified/explained using comments. Updates to all other sections reflect changes	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
of the ASA accordingly. Any differences to Section 3.1: 'Planned Actions' of the ASA Version: 2.1 (previously accepted for Abraxane) should be identified, justified or explained in detail. Upon receipt of such information recommendations to the Delegate in regard to the proposed routine risk minimisation activities can then be made.	from ASA v3.0, since all other sections have been evaluated in ASA v3.0 during the current application (PM-2013-01523-1-4). Changes from v3.0 in these sections are also explained using comments. Minor changes (formatting, spelling or re-structuring of sentences) were not tracked, unless it involved a change in the data.	
In regard to the proposed prospective, non-interventional, cross-sectional survey to HCPs, the sponsor should justify the 30% response rate as an element of validity.	The sponsor reports that based on the evidence provided in the published literature, a 10% response rate is considered to be more realistic and in line with response rates reported for an HCP brochure effectiveness survey. Nevertheless, the sponsor states that it will strive for a greater than 10% response rate for this educational HCP brochure. The sponsor will attempt to increase response rates through presenting HCPs with an online survey, sending repeat reminders to HCPs to complete the survey, by keeping the survey brief to encourage completion, and providing a small incentive such as a small monetary donation to the Australian Cancer Research Foundation (or similar body) for every completed survey. The sponsor reports that the results of such a survey will serve to provide a baseline measurement on the success of such a risk minimisation communication tool on rare and important side effects for	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	Abraxane. If found to be an ineffective method, alternative methods of educating and assessing the information transfer will be investigated. The latest draft protocol for this survey has been provided as Appendix 4 of the ASA.	
There is an expectation that periodic market research of the Australian target audiences of the educational materials should be planned for the post-market period for as long as these additional risk minimisation activities are considered necessary and are implemented. Consequently the draft protocol for the proposed prospective, non-interventional, cross-sectional survey to HCPs should be amended to state repeat distribution or content revision of the Educational Brochure will be determined based on the results of the survey and as agreed by the TGA.	The sponsor states that it is committed to obtaining baseline information from this prospective, non-interventional, cross-sectional survey to HCPs, and providing proposals based on the findings to ensure appropriate risk minimisation implementation activities are being addressed in the most efficient and effective manner, as agreed by the TGA. The draft HCP brochure survey protocol has been amended to add the language "and as agreed by the TGA" as requested with the addition of a qualifying paragraph to Section 10 of the HCP Survey Protocol.	This is acceptable.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The non-clinical evaluator noted that dose/dosing regimen for the proposed indication differs from that currently approved and that the tolerability of the proposed doses and dosage regimen with Abraxane and gemcitabine needed to rely solely on the clinical data.

Data submitted consisted of pharmacology studies to support the proposed indication, a study assessing potential pharmacokinetic drug interactions between the two drugs, and toxicity studies with Abraxane alone. No major deficiencies were identified.

In vitro, both Abraxane and gemcitabine had inhibitory activity on pancreatic ductal adenocarcinoma cell lines. The IC_{50} values for gemcitabine were significantly lower in the presence of Abraxane. In mouse models of pancreatic ductal adenocarcinoma, reduced tumour growth and greater animal survival were observed with the gemcitabine/Abraxane combination compared with either agent alone. Overall, the pharmacology data support the proposed clinical use of Abraxane and gemcitabine for the treatment of patients with adenocarcinoma of the pancreas.

No PK interactions were evident in rats.

Attention was drawn to concerns regarding the potential for significant toxicity given the cumulative dose is higher than the current approved dose for Abraxane (for either non-small cell lung cancer (NSCLC) or metastatic breast cancer), and the potential overlap of toxicities between Abraxane and gemcitabine: myelosuppression, gastrointestinal toxicity, dermal toxicity and reproductive toxicity.

The Delegate notes the previously identified increased risk of pneumonitis when using taxanes (including Abraxane) in combination with gemcitabine, compared with either as a single agent (which is included in the PI).

Clinical

The EMA Guidelines adopted by the TGA used for the evaluation of this submission were:

- Points to consider on application with 1. Meta-analyses; 2; One pivotal study.
- Guideline on the evaluation of anticancer medicinal products in man.

Overview of data

Two clinical studies

- CA046 A pivotal Phase III, multicentre, international, randomized, controlled, open-label study of Abraxane followed by gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas.
- CA040 A supportive Phase I/II, multicentre, open-label, dose level escalation study of Abraxane followed by gemcitabine in patients with metastatic adenocarcinoma of the pancreas which determined the MTD, DLTs and initial anti-tumour activity and supported the dose selection for the Phase III trial.

Pharmacology

No new clinical PK/PD data was submitted. The clinical evaluator noted that paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is primarily

determined by cytochrome P4502C8 and 3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidine deaminase followed by urinary excretion. Analysis of data from metastatic breast cancer patients showed that, on average, gemcitabine has little or no effect on the pharmacokinetics (clearance and half-life) of

paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine (note this information is in the US Gemzar PI, Gemzar SmPC). The extrapolation of these findings to Abraxane is acceptable, and supported by the preclinical data submitted (see above).

Efficacy

The Overview and Key Designs of the two Trials, CA046 and CA040 appear in the CER. The key inclusion criteria were:

- histological or cytological confirmation of metastatic adenocarcinoma of the pancreas, and
- CT or MRI demonstrable metastatic disease (that is patients with locally advanced pancreatic adenocarcinoma were excluded).

Phase I/II trial, CA040

67 patients (30 in Phase I, 37 in Phase II), median age 62 (range 28-86) received Abraxane followed by gemcitabine until disease progression or unacceptable toxicity to determine MTD or DLTs. Patients had to have an ECOG PS 0 or 1, and prior gemcitabine chemotherapy was permitted in adjuvant setting if relapse occurred greater than or equal to 6 months after completion of last dose.

> Comment: the first inclusion criterion required subjects to have metastatic adenocarcinoma of the pancreas confirmed by cytology or histology. The median time to relapse from initial diagnosis ranged from 0-13 months. For those who relapsed after an initial diagnosis of pancreatic carcinoma (that is no metastatic disease at initial presentation), the sponsor is requested to clarify whether histological or cytological confirmation was from a biopsy/fine needle aspirate of a metastatic site in all these patients. If some did not have this histological confirmation, the sponsor is requested to provide the 25th quartile, median and 75th quartile for such patients for time to relapse from the initial diagnosis of pancreatic carcinoma (See Questions for sponsor).

Phase I: 3 arms assigned to receive Abraxane either 100 mg/m^2 or 125 mg/m^2 or 150 mg/m^2 IV, each followed by 1000 mg/m^2 IV on days 1, 8, 15 of a 28 day cycle.

After determining the maximum tolerated dose (MTD), Phase H cohort expanded to a total of 44 patients who received Abraxane 125 mg/m^2 IV followed by gemcitabine 1000 mg/m^2 on days 1, 8, 15 of a 28-day cycle until progression, unacceptable toxicity or withdrawal of consent.

- Primary efficacy endpoint: overall response rate (ORR).
- Secondary efficacy endpoints: disease control rate, duration of response, progression free survival (PFS), overall survival (OS).

Other endpoints of interest: positron emission tomography/computed tomography (PET/CT) evaluation of antitumor activity, changes in Carbohydrate Antigen 19-9 (CAI9-9) levels, Secreted Protein Acidic and Rich in Cysteine (SPARC) expression.

Following the death of a patient receiving the 150 mg/m^2 dose level of Abraxane, the MTD was determined at Abraxane 125 mg/m^2/gemcitabine.

Results:

At the MTD, the ORR was 39% (defined as CR or PR, determined by independent radiologic review (IRR)). The Median PFS of 6.9 months (95% CI 4.8,9.2) and median overall survival (OS) of 12.2 months (95% CI 8.9,17.9) were supportive of those results seen in CA046.

Safety findings at the MTD level were included in the pooled analysis together with those from the CA046 Abraxane/gemcitabine group.

CA046

Phase III randomised, ongoing multicentre (151 sites in Australia, Austria, Belgium, Canada, France, Germany, Italy, Spain, Russian Federation, Ukraine, United States from 8 May 2009- cut-off 17 September 2012) open label pivotal trial, to evaluate the efficacy, safety and tolerability of Abraxane followed by Gemcitabine versus Gemcitabine alone. Data cut-off for the primary endpoint was 17 Sept 2012.

Eligible patients were adults with metastatic adenocarcinoma of the pancreas, with a Karnofsky performance status scale (KPS) greater than or equal to 70 (equivalent to Eastern Cooperative Oncology Group (ECOG) PS 2, thus lower PS permitted than for CA040), and there was no age restriction. Key exclusion criteria were having only locally advanced pancreatic adenocarcinoma, any prior treatment for metastatic disease (chemotherapy, surgery, radiotherapy). Chemotherapy was only permitted in the adjuvant setting when used at a dose level for radiation sensitisation > 6 months earlier, that is cytotoxic doses of gemcitabine or other agents in the adjuvant setting were not permitted. The inclusion/exclusion criteria were the same as for CA040 except warfarin use was not permitted and the performance status could be slightly lower for the Phase III trial.

861 patients were enrolled, 58% male/42% female, median age 63 (range 27-88) with 10% and 11% greater than or equal to 75 years of age in combination and gemcitabine arm respectively. These subjects were randomised 1:1 to receive Abraxane followed by gemcitabine (431 patients) or gemcitabine alone (430 patients) until disease progression, unacceptable toxicity or withdrawal of consent:

- Abraxane and gemcitabine (n = 431); Abraxane 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 administered on days 1, 8, 15 and 29, 36, 43 of 56-day cycle in cycle 1, thereafter days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onwards, or
- Gemcitabine alone (n = 430); gemcitabine 1000 mg/m^2 on Days 1, 8, 15, 22, 29, 36 and 43 of a 56-day cycle in Cycle 1; thereafter Days 1, 8 and 15 of a 28 day cycle in Cycle 2 and onwards.

The median number of cycles was 3 (range 1-23) for the Abraxane/gemcitabine arm and 2 (range 1-23) for the gemcitabine alone arm.

Median age in the combination arm was 62 years (range 27-86), and 63 years (range 32-88) in the gemcitabine arm, with 10 and 11% greater than or equal to 75 years in the combination and single arm respectively. The remainder of the baseline demographics were similar between the arms, and representative of those presenting with this disease. The baseline disease characteristics such as stage at primary diagnosis, location of primary lesion were similar across both arms. The median time to first documented metastasis was similar in both arms, but there was a much wider range in the gemcitabine alone arm. It was not stated explicitly (unlike CA040) that there was histological confirmation from a metastatic site that the disease was metastatic adenocarcinoma of the pancreas. This becomes particularly important when distant disease developed relatively late (109 months) See Comment below. 78% in the in the Abraxane/gemcitabine arm and 82% in the gemcitabine arm had metastatic disease at presentation, and with most patients greater than or equal to 2 metastatic sites of which abdominal/peritoneal (90%) and liver metastases (84%) were most common.

Patient disposition was similar across both treatment arms, and for the same dose level in the Phase I/II study.

> Comment: the inclusion criteria state eligibility were met if the '*patient had definitive histologically or cytologically confirmed metastatic adenocarcinoma of the*

pancreas. The definitive diagnosis of metastatic pancreatic adenocarcinoma was made by integrating the histopathological data within the context of the clinical and radiographic data'". The sponsor was asked whether the 14% and 10% in the combination and gemcitabine alone arms respectively, who did not have metastatic disease at initial presentation, underwent a biopsy of a metastasis to confirm the origin of the metastatic disease. In response, the sponsor has stated, '*all patients had at least one biopsy to confirm the diagnosis of adenocarcinoma of the pancreas; however, no biopsy information was collected in the CRF. All of the patients who initially had Stage I, II or III pancreatic adenocarcinoma had histological confirmation of their disease. The information regarding whether the biopsy was taken from the primary tumour site or a metastatic site was not collected in the CRF*.'

According to the inclusion criteria above, it may be somewhat open to interpretation as to whether those without histologically confirmed metastatic adenocarcinoma from a biopsy of a metastatic site were eligible for entry into the trial, that is whether it was acceptable that the presence of newly diagnosed metastatic disease was presumed to be secondary to the previously diagnosed pancreatic adenocarcinoma. For those with metastatic disease at the initial diagnosis, this is acceptable. However, for those who developed disease after their initial diagnosis, the absence of such histological confirmation raises uncertainty about whether the metastatic disease is related to the primary diagnosis of pancreatic adenocarcinoma or potentially from an unrelated primary cancer at a different site. Factors influencing the level of uncertainty include a longer time to relapse (the longest time to relapse was 40 months in the Abraxane/gemcitabine arm and 109 months in the gemcitabine arm), whether any prior treatment of the primary lesion was undertaken with curative intent, and also other personal risk factors (for example smoking history) or family history of other cancers (that might suggest a predisposition to other cancers for example Lynch syndrome).

The median time to relapse presented (0.03 months) incorporates all patients in the ITT population and reflects that the vast majority presented initially with metastatic disease.

The sponsor is asked to provide a breakdown for all patients presenting initially with Stage I, II or III disease, of the median time (plus 25th and 75th quartiles) from initial diagnosis to relapse (as a proxy indicator of likelihood of metastatic disease being related to their primary lesion) and to perform a per protocol analysis of the primary and secondary efficacy (OS, PFS and ORR) endpoints with these patients excluded (See Questions for sponsor).

Efficacy endpoints

- Primary efficacy endpoint: OS (ITT population).
- Secondary Efficacy endpoints PFS, ORR (tested only when OS difference statistically significant) and determined by CT or MRI imaging performed every 8 weeks, assessed centrally by IRR blinded to the treatment arm assignment.

Other efficacy endpoints of interest to the Delegate: time to response and disease duration (RECIST guidelines by IRR); disease-control rate (objective tumour response or stable disease for greater than or equal to 16 weeks) by IRR; Time to treatment failure by IRR; PFS, ORR by investigator; PET/CT evaluation of antitumor activity; changes in CA19-9 levels; SPARC expression.

Statistical analysis

This study had 90% power to detect a hazard ratio (HR) of 0.769 at the significance level of 0.049, and all analyses were carried out on the ITT population. The survival distribution of OS was estimated using Kaplan-Meier method for each arm, and compared between two

treatment arms by using stratified log-rank test. The associated HR and two-sided 95% confidence interval (CI) were estimated using stratified Cox proportional hazard model. No pooled efficacy analysis was conducted across Studies CA040 and CA046.

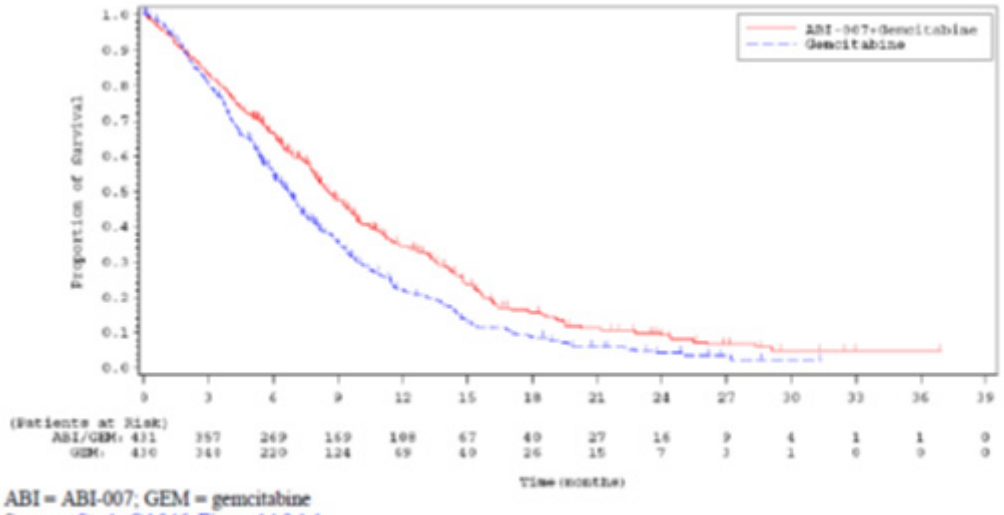
Analysis populations included the Intention-to-Treat population (ITT, all randomised patients), the Treated population (assignment according to drug actually received) and Per-Protocol population (PP, eligibility criteria met, same treatment as randomised).

Primary efficacy endpoint - overall survival

At cut-off, 80% had died (77% in the Abraxane/gemcitabine arm, and 83% in the gemcitabine arm), indicating the survival data is mature. Results for OS are for the ITT population are presented below.

The median OS (ITT) for the combination arm was 8.5 months (95% CI 7.89-9.53) compared with 6.7 months (6.01-7.23) for the gemcitabine alone arm, yielding a HR of 0.72 (0.617-0.835), p<0.0001 in favour of the combination treatment. The 1-year survival rate in the combination arm was 35% (95% CI 29.7-39.5) compared with 22% (95% CI 18.1-26.7) in the gemcitabine alone arm. In the per protocol population the median OS and HR were very similar at 8.6 months (95% CI 7.89-9.59) compared with 6.8 months (6.01-7.29) with an HR 0.72 (95% CI 0.613-0.844), p<0.0001 (Table 16, CER p48). The 75th percentile survival was 14.8 months (13.6-15.67) compared with 11.4 months (95% CI 10.05-12.55) in the gemcitabine arm, and better survival rates with the Abraxane/gemcitabine combination continued over the 24-month assessment period reported.

Figure 1. Kaplan-Meier Curve of Overall Survival, randomized Phase III study CA046 (Intent to Treat population).



ABI = ABI-007; GEM = gemcitabine
Source: Study CA046, Figure 14.2.1.1

Table 3: Overall Survival: Stratified Analysis by Randomization Strata (Intent-to-treat Population)

Variable	Abraxane/Gemcitabine (N = 431)	Gemcitabine (N = 430)	Hazard Ratio $HR_{A+G/G}$ [a]	P-value [b]
Deaths	333 (77%)	359 (83%)		
Censored	98 (23%)	71 (17%)		
Median (months)	8.5	6.7	0.72	< 0.0001
95% Confidence Interval	(7.89, 9.53)	(6.01, 7.23)	(0.617, 0.835)	
Survival Rate (%) (95% CI) at				
3 month	83 (79.1, 86.3)	80 (76.1, 83.7)		
6 month	67 (61.8, 70.8)	55 (50.4, 59.9)		
9 month	48 (42.8, 52.6)	36 (31.1, 40.6)		
12 month	35 (29.7, 39.5)	22 (18.1, 26.7)		
15 month	24 (19.3, 28.4)	13 (9.9, 17.2)		
18 month	16 (11.7, 19.9)	9 (5.9, 12.1)		
21 month	11 (7.8, 15.1)	6 (3.8, 9.2)		
24 month	9 (6.2, 13.1)	4 (2.3, 7.2)		

CI = confidence interval, $HR_{A+G/G}$ = hazard ratio of ABI-007 followed by gemcitabine/gemcitabine alone,
a The associated hazard ratio and two-sided 95% confidence interval were estimated using a stratified Cox proportional hazard model.
b P-value was based on a stratified log-rank test stratified by randomization strata of geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).

Sub-group analyses[6]

The data forest plot for the subgroup analysis of the ITT population demonstrated those with the following did not receive a statistically significant benefit (CI for HR crossed 1):

- age greater than or equal to 75 years (See Efficacy Discussion),
- those from Europe (compared with USA),
- baseline CA19-9 within normal limit or up to 59 x ULN (see Efficacy Discussion),
- no liver metastases (see Issues, Efficacy Discussion),
- Peritoneal carcinomatosis,
- previous Whipple procedure (see Efficacy Discussion),
- Presence of biliary stent at baseline,
- Stage I, II or III initial presentation (see Issues).

The results for the number of metastatic sites were inconsistent. Potential explanations for these findings are in the Issues Section and the Efficacy Discussion below.

[6] Detailed discussion of the sub-group analyses can be found in the CER extract (Attachment 2).

The sponsor paid special attention to and listed potential reasons why there was no benefit seen in the greater than or equal to 75 year-old population and those with normal CA19-9 (CER p16). In the Clinical Evaluation report, there appears to have been an error, recording the median OS after Abraxane/gemcitabine of the whole ITT population as the median OS for the greater than or equal to 75 year-olds, and the actual median OS for the Abraxane/gemcitabine group for this group as the gemcitabine median OS in this group. Accordingly, the ensuing discussion of benefit in the Clinical Evaluation Report should be disregarded. The actual median OS for the greater than or equal to 75 year-old sub-group of 7.6 months (95% CI 3.81, 11.24) was lower but not statistically significantly different from that seen in the gemcitabine arm 8.0 (95% CI 4.7, 11.14), demonstrating there was no survival benefit with the combination treatment, and raising the possibility of there being some harm (although the numbers are too small to draw meaningful conclusions regarding this last aspect - see Efficacy Discussion and Risk-Benefit Discussion below).

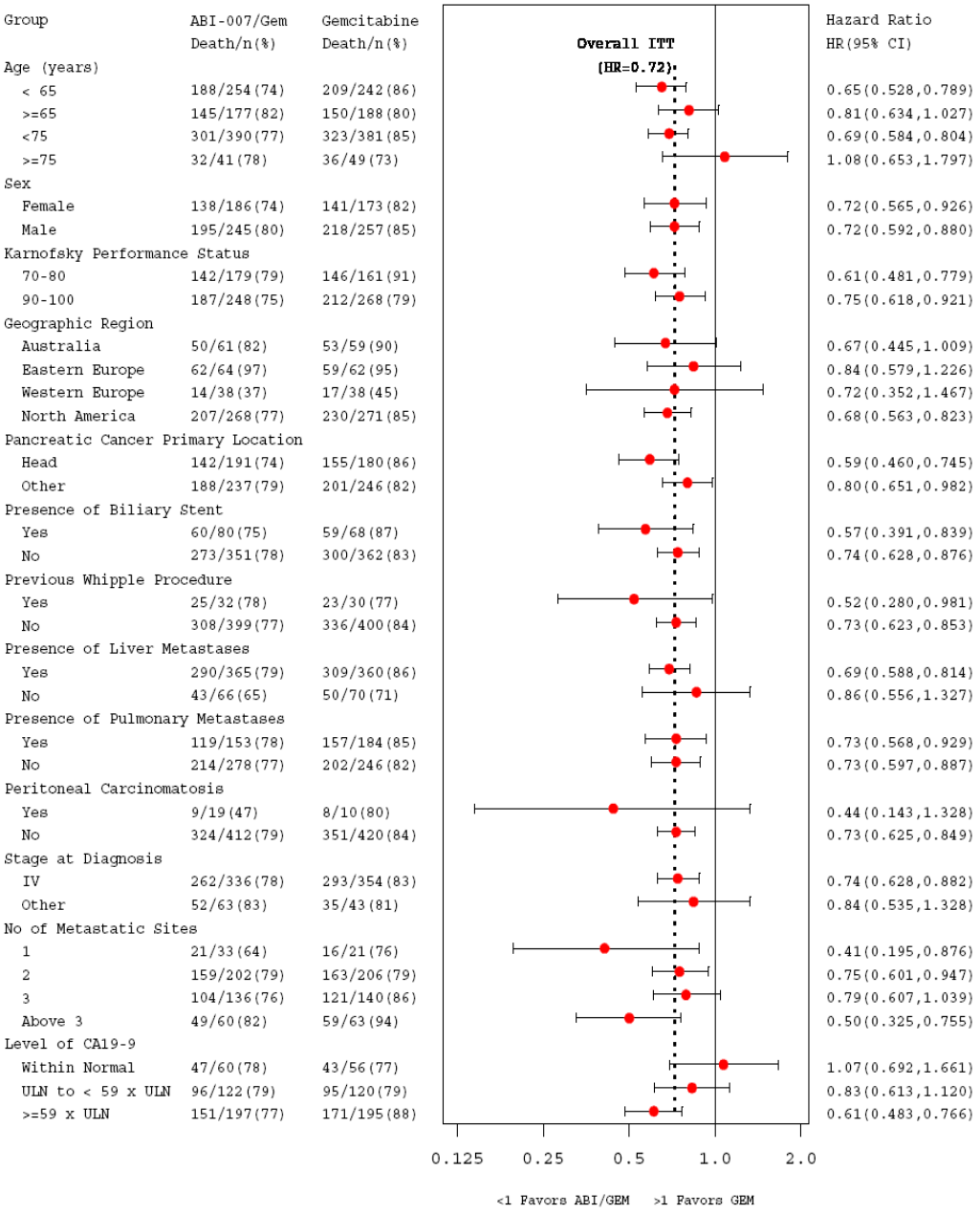
The median OS and PFS for those with normal baseline levels of CA19-9 (the latter excludes the effect of subsequent treatment in this subgroup) indicated there was no significant improvement in either parameter for this sub-group with combination treatment versus gemcitabine alone, and this is discussed below in the Efficacy Discussion.

There was a significant improvement for those presenting with Stage IV disease in the combination arm 8.1(7.56, 8.84) compared with gemcitabine alone 6.6 (5.72, 7.26), HR 0.74(95% CI 0.628, 0.882), $p < 0.0006$. Of note, there was no significant benefit demonstrated of combination therapy over gemcitabine alone for patients with disease other than metastatic at presentation (Stage I, II, III) where the diagnosis of metastatic pancreatic adenocarcinoma was not histologically confirmed.

OS with stratified factors as covariates identified a higher risk of death with the presence of liver metastases and lower performance status. Favourable prognostic factors identified by stepwise selection included being treated with the combination therapy, being <65 years of age, while a lower Karnofsky score (70-80 compared with 90-100), or having liver metastases were significantly associated with a poorer OS.

Subsequent anticancer therapy was balanced between treatment arms: 38% in the Abraxane/gemcitabine arm and 42% in the gemcitabine arm received subsequent anticancer therapy. Twenty-seven patients from the gemcitabine arm received a subsequent Abraxane-containing regimen. A third sensitivity analysis censoring for OS on the initiation date of subsequent anticancer therapy shows a statistically significant improvement in the Abraxane/gemcitabine arm compared with the gemcitabine arm with similar estimates of the reduction in the risk of death ($HR_{A+G/G} = 0.68$ [95% CI = 0.559, 0.823], $p < 0.0001$). The median OS in the Per-protocol population was consistent with the ITT and Treated populations. In the Per-protocol population, the median survival for patients in the Abraxane/gemcitabine arm was 8.6 months (95% CI = 7.89, 9.59) compared with 6.8 months (95% CI = 6.01, 7.29) in the gemcitabine arm, $p < 0.0001$; $HR_{A+G/G} = 0.72$ (95% CI =0.613, 0.844). The median OS in the Treated population was Abraxane/gemcitabine: 8.6 months (95% CI = 7.89, 9.66) compared with 6.8 months in the gemcitabine arm (95% CI = 6.01, 7.26), $p < 0.0001$; $HR_{A+G/G} = 0.70$ (95% CI = 0.604, 0.823).

Figure 2: Forest Plot of Overall Survival (Intent-to-treat Population)



CA19-9 = Carbohydrate Antigen 19-9; CI = confidence interval; GEM = gemcitabine; HR = hazard ratio; ULN = upper limit of normal. Note: The confidence intervals were truncated between 0.125 and 2 where applicable.

Secondary efficacy endpoints PFS, ORR

The median PFS (ITT) in the Abraxane/gemcitabine arm was 5.5 months (95% CI = 4.47, 5.95) compared with 3.7 months (95% CI = 3.61, 4.04), in the gemcitabine arm $p < 0.0001$; HR = 0.69 (95% CI = 0.581, 0.821).

The ORR (ITT) in the Abraxane/gemcitabine arm was significantly higher compared with the gemcitabine arm (23% versus 7%, $p < 0.0001$); response rate ratio [p_{A+G}/p_G] = 3.19 [95% CI = 2.178, 4.662]). This was confirmed in the treatment and per protocol population analyses. Only one patient achieved a CR in the study (combination treatment arm). Although not a formal endpoint, the median decrease in diameter by IRR of the target lesions (pancreatic and non-pancreatic metastases) was greater in the combination arm.

There was 67% concordance for the ORR assessment between investigator and IRR for the combination treatment arm and 64% for the gemcitabine alone arm.

Other efficacy endpoints (ITT)

The median time to response was similar in both arms (3.5 months), the duration of response was comparable between the arms (11.1 months (95% CI 9.23,13.11) in the combination arm compared with 11.4 months (95% CI 9.03, NE months) in the gemcitabine arm), and the disease control rate (CR/PR/SD > 16 weeks) was higher in the combination arm (48% versus 33%; $p_{A+G}/p_G = 1.46$ [95% CI 1.233, 1.723]; $p < 0.0001$. The median TTF was longer in the combination arm (5.1 months compared with 3.6 months, ($HR_{A+G/G} = 0.70$ [95% CI = 0.604, 0.803]; $p < 0.0001$). The median maximum percentage decrease in CA19-9 from baseline was 89% for the combination arm compared with 74% for the gemcitabine arm, and a greater percentage experienced a decrease in their CA19-9>90% in the combination arm from baseline recording (42% compared with 22%). There was a correlation between maximum decrease in CA19-9 from baseline for both OS and PFS, but as previously noted, there was no benefit demonstrated for those with a normal baseline for CA19-9.

> Comment: the CA19-9 observations, together with the benefit seen in those with liver metastases compared with those without, suggests the population benefiting most are those with either very advanced and/or bulky disease who also have the highest risk of death from a relatively small incremental increase in their disease burden.

SPARC level measurements were not available, and the sponsor is requested to submit these data when they become available if they have clinical utility as a Category 1 submission.

No quality of life data were collected. Change in KPS score to the worst recorded was presented from baseline but it is not clear at what point the measurements were done (that is median number of treatments received). 10-point decrements from 100 to 70, thereafter a cut-off grouping of <60 were used. It was not possible to track the median change in KS for cohorts of patients according to, and subsequently from, their baseline measurement.

The PET scan response rate compared with baseline by IRR was significantly higher in the Abraxane/gemcitabine arm (82/130 patients, 63%) compared with the gemcitabine arm (48/127 patients,38%), $p < 0.0001$. Amongst responders (CR or PR by PET scan), there was no difference between median time to response in the Abraxane/gemcitabine arm (1.92) compared with the gemcitabine arm (1.87 months).

The median OS for PET scan responders was 13.1 months (95% CI = 10.51, 14.26) compared with 6.9 months (95% CI = 6.05, 8.15) in non-responders (patients with SD, PD, or was not-evaluable), $p<0.0001$. The median time of PFS for responders by PET scan was 7.4 month (95% CI = 6.05, 9.23) compared with 3.8 months (95% CI = 3.65, 4.96) in non-responders, $p<0.0001$. The CT and PET scan-based concordance rate for disease response was 55% in Abraxane/gemcitabine arm and 67% in gemcitabine arm.

Safety

Exposure

Safety data for Abraxane in combination with gemcitabine, were collected from the two studies: Phase I/II CA040 and Phase III CA046 (see regimens for each in Efficacy section above). 465 patients received at least one dose of Abraxane/gemcitabine at the MTD, and for comparison 402 patients in the gemcitabine arm, received at least 1 dose of study drug and were included in the Treated population. Results from an additional 23 Phase I patients from the other 2 dose cohorts provided safety data. The MTD was determined

after the highest Abraxane dose level (150 mg/m^2) in the Phase I trial resulted in Grade IV leukopenia and fatal sepsis in on e patient.

Table 4: Number of Patients Exposed to Abraxane/Gemcitabine by Dose and Study - Treated Population

Study	Abraxane 100 mg/m^2 Gemcitabine	Abraxane 125 mg/m^2 Gemcitabine	Abraxane 150 mg/m^2 Gemcitabine
CA046	0	421	0
CA040	20	44	3
Total	20	465	3

The median treatment duration was longer in the Abraxane/gemcitabine arm (3.9 months; 3 cycles (range 1-23)) than in the gemcitabine arm (2.8 months; 2 cycles (1-23)); this resulted in an increased cumulative delivery of gemcitabine in the combination arm compared with the control arm (11,400 mg/m^2, compared with 9,000 mg/m^2). Notably, there was a higher discontinuation after just 1 cycle (8 weeks of treatment) in the gemcitabine alone arm compared with the combination arm (44% versus 30%); similar numbers received cycles 2-5 of therapy, but fewer continued for greater than or equal to 6 cycles in the gemcitabine arm (16% compared with 33.3% respectively).

Dose reduction/intensity

The effect of the addition of Abraxane to gemcitabine resulted in a predictable rise in toxicity and consequently more dose reductions for the combination arm compared with the gemcitabine alone arm. In the combination arm, 71% of all Abraxane doses were administered at the full 125 mg/m^2; and overall, 41% had reductions of Abraxane, 47% had reductions in gemcitabine dose. In the gemcitabine arm, 33% of patients had gemcitabine dose reductions, resulting in a median relative dose intensity of 85%. The higher dose reduction rate in the combination arm resulted in a lower gemcitabine median relative dose intensity for this arm (75%), and 74% for Abraxane.

Treatment AE, SAE, discontinuations

In the Abraxane/gemcitabine arms, 20% discontinued due to a study drug-related AE (compared with 7% gemcitabine arm) but only 47% compared with 61% withdrew due to progressive disease. Thus the proportion who withdrew due to either progressive disease or an adverse drug-related event were similar between the arms (67% for Abraxane/gemcitabine versus 68% for gemcitabine).

Treatment adverse event tables show the combination arm experienced a higher rate of Treatment-related events: greater than or equal to 1 AE greater than or equal to grade 3 severity (77% versus 50%), greater than or equal to 1 SAE (29% versus 13%) and TEAEs that resulted in discontinuation. The most common TEAE leading to drug discontinuation in the combination arm was peripheral neuropathy SMQ (8%), fatigue (4%) and thrombocytopenia (2%). The percentage of patients who had a TEAE with an outcome of death was identical in the 2 treatment arms at 4%.

Grade 3 or higher treatment-related TEAEs occurred more commonly in the combination arm (77% versus 50%) and those reported with greater than or equal to 5% difference in the Abraxane/gemcitabine arm compared with the gemcitabine arm in decreasing order were: neutropenia, fatigue, leukopenia, peripheral sensory neuropathy, and peripheral neuropathy.

Haematological

Grade 3/4 neutropenia occurred in 38% subjects in the Abraxane/gemcitabine arm and 27% in the gemcitabine arm. Grade 3/4 anaemia and thrombocytopenia rates in the combination arm were both 13%, compared with 12% and 9% respectively for the gemcitabine arm. WBC growth factors were administered in 26% of patients in the Abraxane/gemcitabine arm and 16% in the gemcitabine arm. Febrile neutropenia rates were 3% in Abraxane/gemcitabine arm and 1% in the gemcitabine arm, and did not results in any deaths. In the combination arm, 16% of patients had a dose delay in their Abraxane (16%) and gemcitabine (18%) compared with 11% of patients in the gemcitabine alone arm. Thrombocytopenia was the 3rd most common cause of treatment-related discontinuation in the combination arm, reflecting that it is a component of treatment-induced myelosuppression for which there are no long lasting supportive therapies.

Although the rates of Grade 3/4 anaemia were similar were higher in the combination arm (13% versus 9%) and as were the use of erythropoietins (16% versus 11%) and blood transfusions (12% versus 7%).

Peripheral neuropathy

54% of patients developed peripheral neuropathy (17% Grade 3, no Grade 4) in the Abraxane/gemcitabine arm compared with 13% (1% Grade 3) in the gemcitabine arm. Discontinuation due to peripheral neuropathy was a significant problem: 8% for Abraxane and 4% for gemcitabine in the Abraxane/gemcitabine arm while no patients stopped in the gemcitabine alone arm. The Grade 3 peripheral neuropathy persisted in 37%, with 63% improving by greater than or equal to 1 Grade and 43% returning to Grade 0 or 1. 56% who experienced a Grade 3 did not resume Abraxane treatment after a delay. The development rate of Grade 3 peripheral neuropathy increased with exposure to Abraxane from 7% to 12% between cycles 3 and 6, and 17% beyond 6 cycles.

> Comment: an appropriate recommendation for stopping Abraxane and dose adjustment when Grade 3 peripheral neuropathy occurs is included in the PI but as this is a dose-dependent and dose-limiting effect seen across all indications for Abraxane, this should be stated under the heading “Peripheral Neuropathy”.

Pneumonitis

24 cases of pneumonitis (2 in CA040: Abraxane dose level 100mg/m^2 and 125mg/m^2, both in combination with gemcitabine; 22 in CA046: 17 Abraxane/gemcitabine arm, 5 gemcitabine arm) resulted in 2 deaths in the Abraxane/gemcitabine arm (CA046 trial) and a 3rd patient who died with pneumonitis is reported to have had progressive disease as the cause of death. There is a discrepancy between the CSR and the Pneumonitis Directive Letter sent to physicians 05 October 2011, which states 3 deaths from pneumonitis occurred. Following that directive, a further 8 cases were identified in the combination arm (0 in the gemcitabine arm) with no further deaths.

Sepsis

37 patients developed sepsis, including 32 patients in Study CA046 (22 patients in the Abraxane/gemcitabine arm; 10 in the gemcitabine arm) and 5 patients in Study CA040 (3 patients treated with Abraxane 125 mg/m^2/gemcitabine; 1 patient each treated with Abraxane 100 mg/m^2/gemcitabine and Abraxane 150 mg/m^2/gemcitabine).

In Study CA046, Sepsis occurred in 22 (5%) patients receiving combination therapy and 10 (2%) patients in the gemcitabine arm. Most infections were Gram negative bacilli, and occurred more commonly when there was biliary obstruction (52% of cases of sepsis in the combination arm occurred in patients with a biliary stent resulting in 1 death from sepsis in this sub-group). In Study CA046, 7 deaths occurred: 5 in the combination arm (3 were also neutropenic) and 2 in the gemcitabine arm (none was neutropenic). There was

an increased risk of death from sepsis was associated with increasing age (median age 70) and this needs to be indicated in the PI (see PI changes).

5 cases of sepsis were recorded in Study CA040, with one patient dying in the 150 mg/m^2 Abraxane/gemcitabine.

A protocol amendment recommended commencing immediate prophylaxis with ciprofloxacin and the use of GCSF, following which there were a further 3 deaths from infection. Pharmacovigilance will help determine whether this is an effective strategy.

Deaths

18 (4%) of patients in each of the arms of Study CA046 had a TEAE and died, and 2 patients from Study CA040 (1 on 125mg/m^2 Abraxane/gemcitabine and 1 on 150mg/m^2 Abraxane/gemcitabine). Treatment-related fatal AEs occurred in 8 (2%) patients receiving the combination treatment from infection or pneumonitis (7 in CA046, 1 in CA040)(Infection and Pneumonitis) and 2 (<1%) patients receiving gemcitabine arm (infection). These deaths have been discussed above under Infection or Pneumonitis sections above.

Special Populations

Greater than or equal to 65 years of age

In Study CA046, there were 175 patients greater than or equal to 65 years. With combination treatment, those greater than or equal to 65 years of age this group experienced increased rates of diarrhoea (51 versus 38%) and epistaxis (22 versus 11%) compared with those < 65 years of age. Grade 3 or higher TEAEs reported with a greater than or equal to 5% difference in the Abraxane/gemcitabine arm compared with gemcitabine arm were neutropenia (35% versus 21%, respectively), fatigue (22% versus 11%, respectively), dehydration (12% versus 3%, respectively), decreased appetite (10% versus 2%, respectively), diarrhoea (9% versus 1%, respectively), and peripheral neuropathy (7% versus 0, respectively, each). SAEs occurred in 59% compared with 44% <65 years of age but there was no clear pattern of individual SAEs.

G*reater than or equal* ***to 75*** *years of age*

The overall incidences of SAEs and TEAEs with an outcome of death were 75% (30/40) and 13% (5/40), respectively, in patients greater than or equal to 75 years of age and 48% (182/381) and 3% (13/381), respectively, in patients < 75 years of age in the Abraxane/gemcitabine arm.

In the combination arm, Grade 3 or higher TEAEs reported with a greater than or equal to 5% difference in patients greater than or equal to 75 years of age than in patients < 75 years of age were decreased appetite (18% versus 4%, respectively) and dehydration (18% versus 6%, respectively). SAEs reported with a greater than or equal to 5% difference in patients greater than or equal to 75 years of age than in patients < 75 years of age were dehydration (13% versus 4%, respectively) and hypernatremia (5% versus 0, respectively) and there were 2 deaths from sepsis in patients greater than or equal to 75 years of age in the Abraxane/gemcitabine arm.

Warnings about the potentially increased side effects are included in the PI.

Other AEs of Special Interest

Cranial nerve palsy (VIIth): One patient in combination arm who did not discontinue treatment, none in gemcitabine arm.

A single case of cystoid macular oedema occurred in the Abraxane/gemcitabine arm resulting in treatment discontinuation.

Arthralgias and myalgias were more common in the combination arm but <1% were greater than or equal to Grade 3.

Clinical evaluator's recommendation

The Clinical evaluator recommended approval of the sponsor's proposed new indication.

Risk management plan

There were no outstanding issues identified by the RMP evaluator who has recommended the following as a condition of registration;

- The European Risk Management Plan Version 13.0 (dated 16 August 2013), with an Australian Specific Annex (ASA) Version: 4.0 (dated 20 December 2013) must be implemented.

Risk-benefit analysis

Delegate's considerations

Trial design and single pivotal study

Gemcitabine as comparator was appropriate. The dose and regimen was consistent with that used in other trials of gemcitabine in pancreatic adenocarcinoma including those trials which combined experimental therapies with gemcitabine (for example erlotinib) versus gemcitabine alone. Trial CA046 could not be blinded as the addition of Abraxane resulted in identifiable toxicities, as well as there being a slight difference in the gemcitabine treatments for the first cycle (see Phase III trial regimen in Efficacy section) 1 less treatment of gemcitabine in the combination arm.

The single pivotal trial is considered acceptable for consideration of registration as it provides strong statistical evidence of a clinically relevant benefit on survival, supported by the earlier ORR findings in the Phase I/ II Study. There was a sound rationale in the choice of combination therapy, and the pharmacological action of Abraxane is understood; there have been studies of gemcitabine in combination with paclitaxel in the treatment of other malignancies, and efficacy and safety have been approved for Abraxane in combination with another cytotoxic agent (carboplatin) in NSCLC in Australia. The slight difference in the number of gemcitabine treatments in the first cycle is unlikely to alter significantly the total dose of gemcitabine received by the majority of patients in this arm compared with the combination arm and therefore does not compromise the internal validity of the study. The study was conducted at both community and academic centres in multiple geographic regions, allowing the results to be generalizable to the broader population of patients with metastatic adenocarcinoma of the pancreas. Confirmatory studies are not required and would be unethical, especially given orphan status was granted for Abraxane for this indication and the time it would take to recruit sufficient numbers to replicate the study.

Absence of recorded histological confirmation from metastatic disease site

For those in Study CA046 who initially presented with Stage I, II or III disease, there was no recorded information about whether they underwent a biopsy of a metastatic site to provide histological confirmation of their metastatic disease being from adenocarcinoma of the pancreas. This information should be able to be obtained from the pathology records. So there is uncertainty as to whether their metastatic disease was from their initial primary lesion in the pancreas, or possibly a second malignancy, especially for patients with a longer time between primary diagnosis and relapse for example up to 40

months in the combination treatment arm and 109 months in the gemcitabine arm - it is very distinct possibility that these patients had a second primary cancer. Pancreatic cancer is associated with a number of inherited cancer syndromes such as (breast cancer) BRCA mutations, Lynch syndrome, familial adenomatous polyposis (FAP) with an increased risk of further unrelated primary cancers. The numbers were not dissimilar across the two arms (14% for the combination arm, 10% for the gemcitabine arm) but within those groups it is not possible to determine who actually did have a metastasis biopsied and therefore, what bias might be introduced in terms of the key outcomes.

As this was not considered as a protocol violation, such patients were not excluded from the per protocol analyses. A subgroup analysis of those presenting with Stage IV disease in the ITT (that is excluding this population with a protocol violation) indicated that there was still a significantly improved survival for those with Stage IV disease at presentation, but not for those presenting initially with Stage I, II and III disease. Potential explanations for this include the possibility that they 1) did not have metastatic adenocarcinoma of the pancreas, 2) had lower disease burden through earlier detection of relapse through regular follow-up (demonstrated in this study to be associated with a poorer response).

Thus, as there was no benefit of Abraxane/gemcitabine demonstrated in the subgroup analysis for those with an initial diagnosis of Stage I, II or III pancreatic adenocarcinoma together with the uncertainty regarding the diagnosis of metastatic pancreatic adenocarcinoma in this population, it needs to be stated under a special population heading in the PI, that efficacy of Abraxane/gemcitabine has not been established in this population.

It is essential that for any future studies, biopsy of the metastatic site is both undertaken and recorded especially when it is an entry criterion. In clinical practice, biopsies of metastatic sites would not necessarily be performed in patients presenting with metastatic disease, unless there is more than one primary cancer site diagnosed. Thus, for those patients presenting with metastatic disease there is not the same level of uncertainty about the likely diagnosis.

Data deficiencies

No data were submitted for evaluation of the safety or efficacy in subjects with locally advanced pancreatic cancer (that is not metastatic disease).

Quality of life measurements are an important component of assessing the potential benefit or harm of a treatment given in the metastatic setting, particularly where absolute benefits in OS and PFS are of a relatively short duration (See Data Deficiencies). Karnofsky PS assessment is an estimate by clinicians, which incorporates patient functioning and disease status (signs and symptoms) and is not designed to measure a patient's sense of wellness and level of functioning.

SPARC level measurements were not available, and the sponsor is requested to submit these data when they become available if they have clinical utility as a Category 1 submission.

Efficacy discussion

Patients presenting with metastatic pancreatic adenocarcinoma treated with Abraxane/gemcitabine had a statistically significant improvement in both overall survival and progression-free survival of 1.8 months compared with those who received gemcitabine alone. Those with the highest baseline risk of death (that is those with poorer KPS, liver metastases, >3 metastatic sites and CA19-9>59 times ULN) had the greatest reduction in that risk.

Those in whom there was not a statistically significant OS benefit with the combination treatment included subjects are summarised in the sub-group analysis in the Efficacy section above. Within those sub-groups, the sponsor identified several potential

contributing factors to the apparent lack of benefit seen in the greater than or equal to 75 year-old group with combination therapy, such as there being small numbers in each arm, uneven distribution of poor prognostic factors in favour of the control arm etc. While there are always caveats with accepting the findings of sub-group analyses, the greater than or equal to 75 year-old median OS of 7.6 months (95% CI 3.81, 11.24) was not statistically significantly different and was lower that seen in the gemcitabine arm 8.0 (95% CI 4.7, 11.14) and with the increased toxicity observed in this age group, careful consideration has to be given as to whether adding Abraxane to gemcitabine is warranted. This is reflected in the Special Populations section of the PI, detailed discussion of the PI negotiations is beyond the scope of the AusPAR.

Similarly, for those with a normal CA19-9 which may reflect a lower burden of disease, more patients received subsequent anticancer therapies which may have had an impact upon survival figures. The PFS and ORR which are censored at the time of receiving a further anticancer therapy still had a HR with the CI crossing 1 that is not statistically significant demonstration of benefit of combination therapy for this CA19-9 sub-group. As previously mentioned, the smaller numbers in a sub-group analysis result in wider confidence intervals, which overlapped those for the control arm for both groups, and resulted in the HR crossing 1. Future studies may clarify this but at present, there remains no evidence to support a benefit from adding Abraxane to gemcitabine therapy in this population. This needs to be stated in the PI under Special Populations as in the EMA SmPC.

The finding of 3 sites of metastatic disease being associated with no significant benefit from combination therapy, while other numbers of sites are (see Sub-group analysis in Efficacy section above) is difficult to interpret.

The sponsor's initial proposed indication includes those with locally advanced disease as well as those with metastatic disease, but after correspondence with the TGA, the sponsor agreed to modify the indication to be for those with metastatic adenocarcinoma of the pancreas. Patients with locally advanced disease only (that is no evidence of metastatic disease) were specifically excluded from both trials presented in this submission and thus the efficacy is unknown in this population. Furthermore, the finding in the pivotal Phase III trial that those with advanced metastatic disease benefited, and that those with characteristics that indicate potentially less advanced or a lower burden of disease (normal CA19-9 levels and those presenting with Stage I, II or III disease initially) did not receive a statistically significant benefit from Abraxane/gemcitabine over gemcitabine alone indicates it is not possible to extrapolate from the findings in the metastatic setting.

The clinical trials for the two drugs approved in Australia for treatment of locally advanced adenocarcinoma of the pancreas, gemcitabine as single agent, or in combination with erlotinib, both included outcomes for patients with locally advanced and metastatic pancreatic adenocarcinoma. Registration of Abraxane for use in those with only locally advanced and/or unresectable disease would require evidence demonstrating efficacy and safety in this population specifically.

Safety discussion

The overall safety profile for the combination of Abraxane/gemcitabine was consistent with the established profiles for the individual agents and was notable for peripheral neuropathy, neutropenia, infection/sepsis, and pneumonitis.

There were markedly higher rates of peripheral neuropathy in the Abraxane/gemcitabine arm which did not necessarily resolve fully with treatment delays or discontinuation and was the leading cause of treatment discontinuation. Given the poor prognosis of these patients, the risk of developing this side effect with combination treatment is likely to be outweighed by the potential benefit.

A higher risk of neutropenia is expected when combining two myelosuppressive chemotherapy agents. The rates of sepsis were higher in the combination arm and there were more deaths with risk factors being the presence of biliary obstruction and a biliary stent (Gram negative sepsis) and advancing age. The impact of the protocol amendment recommending the immediate commencement of prophylactic antibiotics when developing a fever or routinely in patients with a biliary stent is unclear in terms of the reduction in risk of death or severity of the infection and ongoing pharmacovigilance may clarify this further.

Increased risk of pneumonitis when taxanes and gemcitabine are used in combination exceeding those seen with either agent used alone, have been reported, and the 4% incidence in the combination therapy arm (compared with 1% in the gemcitabine arm) underscores the need to monitor patients closely. An appropriate warning is included in the PI, and this needs to be an area of pharmacovigilance.

The use of Abraxane/gemcitabine in patients greater than or equal to 65 years of age requires careful assessment of performance status, and management of the increased risk of diarrhoea and dehydration. This group were more likely to develop neutropenia and peripheral neuropathy. Similar issues exist for the patients greater than or equal to 75 years of age, with the additional concern that two patients in this cohort died of sepsis. An appropriate warning is included in the PI. Detailed discussions of PI negotiations are beyond the scope of the AusPAR.

Overall, these findings support the conclusion that Abraxane/gemcitabine regimen has an acceptable safety profile for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas in comparison with gemcitabine monotherapy.

Risk-benefit discussion

Metastatic adenocarcinoma of the pancreas has a very poor outlook and considerable morbidity. The improvement in overall and progression-free survival demonstrated for Abraxane and gemcitabine combination therapy is clinically meaningful. Treatment-related toxicities were observed at higher rates than for gemcitabine alone, which is to be expected when adding in an extra chemotherapeutic agent but overall, but these were generally manageable with high levels of vigilance, and with dose delays, dose adjustments and supportive treatment. The three leading cause of treatment discontinuation reflect the toxicities for which there is no effective intervention or supportive treatment: peripheral neuropathy, fatigue and thrombocytopenia – all of these are well known side effects of Abraxane and taxanes in general.

It would have been informative to have had quality of life data, as an important objective of palliative therapies is to improve quality of life. It would be important to determine whether symptoms such as pain were improved with the treatment, as this has been an endpoint demonstrating benefit for treatment of metastatic adenocarcinoma of the pancreas with gemcitabine (Gemzar, PI). It might also have indicated whether there was any compromise in the quality of life improvements noted with gemcitabine alone with the addition of the Abraxane. It might have informed regarding benefits in those subgroups where an overall or progression-free survival benefit was not demonstrated, or treatment discontinuation due to toxicity was required.

Special caution needs to be taken in determining the risk-benefit equation for those greater than or equal to 65 years of age but in particular, those greater than or equal to 75 years of age as there was no demonstrated improvement in survival in this latter group, and they were all vulnerable to side effects including infection, loss of appetite and dehydration. Special consideration should be given regarding the patients' overall performance status, co-morbidities, and risk of infection.

No data were presented and therefore, no risk-benefit equation could be established for the safety and efficacy of Abraxane/gemcitabine in the treatment patients with locally advanced adenocarcinoma of the pancreas without evidence of metastases. Furthermore, the groups who benefited most in terms of reduction of the risk of death were those with the highest risk of death (large burden of disease, liver metastases) and there were signals that those with potentially less bulky metastatic disease (normal or lower CA19-9; those presenting initially with Stage I, II or III disease) did not benefit from the combination therapy (see Efficacy Discussion) and thus extrapolation of the benefits in overall and progression-free survival in these studies cannot be made to those with earlier stage disease.

Proposed action

The Delegate considers that the data supports the following indication (as amended by agreement between the TGA and the sponsor on 11 February 2014):

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

Request for ACPM advice

Not applicable.

Response from sponsor

Delegate's questions

Please could you confirm what percentage of patients in Study CA046 had histological confirmation of their distant disease as metastatic adenocarcinoma of the pancreas? If not 100%, please can you provide a breakdown as to the percentage for each treatment group?

Sponsor's response

In study CA046, the inclusion criteria required a patient to have had definitive histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. The definitive diagnosis of metastatic pancreatic adenocarcinoma was made by the investigator by integrating the histopathological data within the context of the clinical and radiographic data. Of the 861 patients enrolled in study CA046, 99% of patients had histological confirmation of metastatic adenocarcinoma of the pancreas. Although the number and location of metastatic sites(s) was collected, the biopsy location was not collected in the CRF. All patients had at least one metastatic site. At the time of diagnosis, 78% of patients in the Abraxane+gemcitabine treatment group and 82% of patients in the gemcitabine only treatment group presented with Stage IV metastatic disease. The remaining patients presented with earlier stage disease at the time of diagnosis and may have had histological confirmation based on the earlier disease stage or may have had another biopsy of the metastatic disease. The time from primary diagnosis to first documented metastases was a median of 0.03 months in both treatment groups. In summary, patients enrolled in study CA046 had histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas and are representative of the broader population of patients with this disease.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Abraxane nanoparticle albumin-bound paclitaxel 100 mg powder for injection

(suspension) vial for 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 on Days 1, 8, 15 repeated every 28 days; indicated for:

> *Abraxane, in combination with gemcitabine, is indicated for the first line treatment of patients with metastatic adenocarcinoma of the pancreas.*

The full indications are now:

> *Metastatic Breast Cancer; Abraxane is indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.*
>
> *Non-small Cell Lung Cancer; Abraxane, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.*

Metastatic Adenocarcinoma of the Pancreas; Abraxane, in combination with gemcitabine, is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas.

Specific conditions of registration applying to these goods

- For all injectable products the Product Information must be included with the product as a package insert.
- The Abraxane European Risk Management Plan Version 13.0 (dated 16 August 2013), with an Australian Specific Annex (ASA) Version: 4.0 (dated 20 December 2013) included with submission number PM-2013-01523-1-4 (or any updated subsequent version negotiated with the TGA) must be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for Abraxane at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au