Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for nanoparticle albumin-bound paclitaxel

Proprietary Product Name: Abraxane

Sponsor: Abraxis Bioscience Australia Pty Ltd

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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.
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- 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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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1. Clinical rationale

Abraxane is an albumin nanoparticle form of paclitaxel with a mean particle size of approximately 130 nanometres. paclitaxel exists in the nanoparticles in a non-crystalline amorphous state. paclitaxel is contained within nanoparticles that are consistent with an average 76% paclitaxel bound to 24% human albumin. Following administration the nanoparticle rapidly disassociates to form albumin-bound paclitaxel and free paclitaxel with a ratio of 94:6. Abraxane was designed to improve the chemotherapeutic effects of paclitaxel by exploiting endogenous transport pathways to deliver high doses of paclitaxel to the tumour and to reduce the solvent-related hypersensitivity and other toxicities associated with paclitaxel injections and Cremaphor EL vehicle. Abraxane provides unique tumour selective localisation through albumin-receptor-mediated transport across the endothelium, albumin-binding proteins in the interstitium, potential tumour uptakes through macropinocytosis and overall improved pharmacokinetics compared with solvent-based paclitaxel. 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 intra-tumoral gemcitabine levels compared to gemcitabine monotherapy.

Abraxane is currently approved for the treatment of metastatic carcinoma of the breast after failure to anthracyclines therapy and for non-small cell lung cancer in combination with carboplatin.

The proposed new indication is for the use of Abraxane in combination with gemcitabine for the first line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas.

2. Clinical rationale

The albumin nanoparticle formulation of Abraxane may provide unique tumour selective localisation through albumin receptor mediated transport across the endothelium, albumin-binding proteins in interstitium, potential tumour cell uptake through macropinocytosis and overall improved pharmacokinetics compared with solvent based paclitaxel. Molecular profiling of patients' pancreatic cancers demonstrated that the albumin-binding protein, secreted protein acidic and rich in cysteine was present in particular in the tumour stroma. This finding suggests that the albumin-bound paclitaxel may bind to this protein and be useful for treatment of pancreatic cancer. It is also indicated that Abraxane has shown single agent activity in mouse models of pancreatic cancer and to be synergistic with gemcitabine in pre-clinical models by increasing intra-tumoral gemcitabine levels compared to gemcitabine monotherapy. These pre-clinical data led to the Phase I/II dose escalation study of Abraxane combined with gemcitabine in patients with advanced metastatic adenocarcinoma, that is Study CA040. The results of this study determined the design of the pivotal Study CA046.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contains full clinical reports of the two clinical efficacy and safety studies CA046 and CA040 including final clinical reports together with relevant tables and figures. Various non-clinical pharmacology reports are also provided including pharmacodynamics, pharmacokinetics and toxicology. No clinical pharmacology data is provided in this submission.

3.2. Paediatric data

This submission does not include paediatric data.

3.3. Good clinical practice

All aspects of good clinical practice were observed in the two studies CA046 and CA040.

4. Pharmacokinetics

No new clinical pharmacology data was provided in this submission. It is appropriate to indicate that paclitaxel and gemcitabine do not share a common metabolic pathway. paclitaxel clearance is primarily determined by cytochrome P450 and 2C8 and 3A4 mediated metabolism followed by biliary excretion, while gemcitabine is activated by cytidine deaminise 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 including clearance and half-life of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine.

A non-clinical pharmacokinetic study evaluated the pharmacokinetics of Abraxane and gemcitabine administered concurrently compared to a single agent. The results showed that concurrent administration of Abraxane and gemcitabine had no significant impact on the pharmacokinetic profiles of either drug. There were no statistically significant differences in plasma paclitaxel and gemcitabine C_{max} and AUC_{last} between Abraxane plus gemcitabine concurrent administration and single agent treatment groups.

5. Pharmacodynamics

This submission does not include pharmacodynamic data.

6. Dosage selection for the pivotal studies

In the Phase I/II Study CA040 involving the combination of Abraxane plus gemcitabine, the dose of Abraxane commenced at 100mg/m^2 based on previous safety efficacy data for Abraxane from advanced solid tumours, metastatic breast cancer and taxane refractory metastatic breast cancer. Based on this data a Phase I/II dose escalation study, that is CA040 was conducted in 67 patients with an initial dose level of Abraxane 100mg/m^2 followed by gemcitabine at the recommended dose of 1000 mg/m^2 given on days 1, 8 and 15 of a 28 day cycle. Dosage escalation during the Phase I portion of study was conducted through two additional dose levels of Abraxane namely 125 and 150mg/m^2 . The 125mg/m^2 dose was selected as the MTD based on tolerability and this cohort was expanded in the Phase II portion of Study CA040 to include a total of 44 patients.

Based on the results from this Phase I/II study the dose and treatment schedule of Abraxane for the pivotal Phase III trial CA046 was 125mg/m^2 of Abraxane followed by 1000mg/m^2 gemcitabine given on days 1, 8 and 15 of a 28 day cycle.

7. Clinical efficacy

A single pivotal study was provided in this submission CA046 with a single supportive study CA040. The pivotal study was a randomised active-controlled, open labelled, multicentre,

international Phase III study designed to compare Abraxane in combination with gemcitabine to standard treatment (gemcitabine) in patients with metastatic adenocarcinoma of the pancreas.

Eligibility criteria were standard for advanced pancreatic cancer trials and it is appropriate to note that the definitive diagnosis of metastatic clinical pancreatic adenocarcinoma was made by integrating the histopathological data within the context of the clinical and radiographic data. Initial diagnosis of metastatic disease had to have occurred no more than six weeks prior to randomisation. The study was conducted at both community and academic centres in multiple geographic regions allowing results to be easily applicable to the broader population of patients with advanced adenocarcinoma of the pancreas.

Screening procedures and study eligibility were conducted within 14 days of randomisation including medication history, physical examination, performance status evaluation, clinical laboratory tests, vital signs, ECG and radiographic assessments to determine baseline extent of disease.

Patients who met the entry criteria were randomised on a 1:1 basis to receive either Abraxane 125mg/m^2 followed by gemcitabine 1000mg/m^2 administered on days 1, 8, 15 and 29, 36, 43 of a 56 day cycle in cycle 1 only, that is weekly for three weeks with a one week rest by two and subsequent administration on days 1, 8 and 15 of a 28 day cycle in cycle 2 and onwards. gemcitabine was administered in a dose of 1000mg/m^2 on days 1, 8, 15, 22, 29, 36, 43 of a 56 day cycle in cycle 1, that is weekly for seven weeks and a one week rest period and then subsequently administered on days 1, 8 and 15 of a 28 day cycle in cycle 2 and onwards.

It is worth noting at this point that gemcitabine was chosen as the active comparator in this study and is considered standard therapy for metastatic pancreatic cancer in a number of countries including Australia. It is also the recommended treatment of choice in global treatment guidelines and the dosage schedule of gemcitabine follows the approved gemcitabine recommendation for dosing treatment.

This study had an open label design and during the study patients were evaluated during treatment for both efficacy and safety with visits weekly for the first eight weeks and then on days 1, 8 15 and 22 of each subsequent 28 day cycle. Radiographic evaluation for determinations of response was performed every eight weeks.

The assessment of tumour burden and response to treatment in study was based on RECIST guidelines. All radiology undertaken for assessment was reviewed independently by an independent review committee at a central imaging facility.

Treatment continued until patients experienced either disease progression or unacceptable toxicity. Accordingly responding patients and those with stable disease continued on treatment. At the time of discontinuation laboratory and clinical evaluations were performed. Radiologic studies for response evaluation were repeated only if required per the defined study imaging schedule. Patients who discontinued treatment in the absence of disease progression had repeat imaging and tumour response assessments every eight weeks until disease progression was documented. Survival status was monitored on a monthly basis for six months and then every three months thereafter until death, study closure or three years had elapsed since patient discontinuation from treatment.

The primary efficacy endpoint of the pivotal study was overall survival. This is chosen as an easy measured objective endpoint and clinically meaningful direct measure of patient benefit. The planned sample size was 842 patients with approximately 421 patients randomised to each treatment arm. There were at least 608 events and this would have provided a 90% power with a two-sided type 1 error of 0.049 to reject the primary efficacy null hypothesis that the Abraxane in combination with gemcitabine/gemcitabine hazard ratio for overall survival is = 1.

The primary population for analysis of efficacy in the Phase III study was the intent to treat population which included all randomised patients. Two additional patient populations were

defined, including the treated population which included all those patients who received at least one dose of study drug and the per protocol population of all treated patients who met all the eligibility criteria and received the same treatment as assigned by randomisation.

Overall survival was defined as the time from the date of randomisation to the date of death from any cause. Patients who were alive at the time of the analysis were censored at the last known date alive or the clinical cut-off date of the 17th September 2012 whichever was earliest. The survival distribution was estimated using Kaplan-Meier (KM) methods which are standard methodology for time to event endpoints. Differences in the curves were tested using the log rank test stratified by the randomisation strata which included geographic region, baseline performance status and presence of liver metastases. The associated hazard ratio of 95% CI was estimated using a stratified Cox proportional hazard model.

A planned interim analysis for the assessment of futility was conducted after 200 patients had been followed for at least six months from the date of randomisation. The independent monitoring committee reviewed the data from the interim analysis and recommended continuation of the study. The final analysis for overall survival was conducted as planned when a total of at least 608 deaths had occurred. All the deaths that occurred on or prior to the clinical cut-off date of the 17 September 2012 were included.

Sub-group multivariate analyses were performed to assess the potential influence of a number of prognostic factors on the primary efficacy endpoint of overall survival. Again the multivariate analysis on overall survival was conducted using a Cox proportional hazard model to evaluate the treatment effect adjusted for the stratification factors.

The secondary efficacy endpoints for this study were progression free survival and overall response rate which again are considered direct measures of the impact of the study treatment on tumour control and are not affected by crossover or subsequent anti-cancer therapy. Progression free survival and overall response rates were evaluated based on the independent radiology review of blinded data from CT or MRI scans using standard response RECIST criteria.

Other efficacy endpoints included disease control rate, time to treatment failure, time to response and duration of response.

Absolute CA19-9 levels and change from cycle 1, day 1 in these levels were summarised for each treatment arm using descriptive statistics.

Several correlation analyses were undertaken including correlation between CA19-9 levels and tumour response by scanning with overall survival and progression free survival, correlation between tumour response by radiology and overall response rate.

7.1. Results

7.1.1. Disposition and exposure to treatment

This pivotal study was initiated on 8 May 2009 when the first patient was enrolled and the last patient was randomised on the 17 April 2012. The study was conducted at 151 sites in 11 countries. The data cut-off date for the study based on the planned final analysis of overall survival after a total of at least 608 deaths had occurred was the 17 September 2012.

A total of 861 patients were enrolled and randomised to the study including 431 patients randomised to Abraxane followed by gemcitabine and 430 patients randomised to receive gemcitabine alone. All 861 patients were included in the intent to treat population for the analysis of efficacy results.

A total of 38 or 4% of patients were randomised but not treated including 11 or 3% of patients in the combination arm and 27 or 6% of patients in the gemcitabine arm. The most common reason was withdrawal by the patient after the randomisation results became known being three in the combination arm and 21 in the gemcitabine arm. A total of 823 patients received at

least one dose of study treatment. The proportion of treated patients in the intent to treat population was comparable in each treatment arm being 97% for the combination and 94% for the gemcitabine arm. The per protocol population included a total of 771 patients, 394 in the combination arm and 377 in the control arm.

At the time of data cut-off the majority of patients had discontinued treatment, that is 785 or 91%. The most common reason for treatment discontinuation was progressive disease in 51% being less common in the combination arm at 45% compared to the control at 57%. More patients in the combination arm, that is 20% discontinued treatment due to adverse events on the study drug than the control arm at 7%.

The survival follow up data is mature and at the time of the final analysis 692 or 80% of the randomised patients had died including 333 or 77% in the combination arm and 359 or 83% in the control arm.

Treatment and exposure to the combination and control arm of treatments including number of cycles administered and dose intensity is given in Part B, Section B, Tables IV and V. The median number of cycles administered was three for the combination arm and two for the gemcitabine arm and the median duration of treatment was 119 days for the combination and 86 days for the control. In the gemcitabine alone arm 44% of patients received only one cycle of treatment compared to 30% in the combination arm. Twice as many patients in the combination arm compared with the control arm received six or more cycles of treatment being 33% versus 16%.

Dose delays, doses not given and dose reductions were more frequent in the combination arm with dose reductions for this arm being reported for 41% of patients involving Abraxane dose reduction. The incidence of gemcitabine dose reductions was greater in the combination arm compared with the gemcitabine alone arm being 47% versus 33%.

7.1.2. Demographic and baseline characteristics

Patient demographics were balanced between the two treatment arms with the majority of patients in both treatment arms being < 65 years of age, that is 59% for the combination and 56% for the control. Overall 39% of patients had performance statuses of 70-80.

Baseline disease characteristics were also well balanced between the two treatment arms and consistent with a patient population with metastatic pancreatic cancer on chemotherapy. It is noted that 80% of patients were diagnosed with stage IV disease and only 7% of patients in both treatment arms had a prior Whipple procedure. Over 80% of patients in both treatment arms had liver metastases. Baseline CA19-9 values were markedly elevated in the study but balanced between treatment arms.

The treatment arms were well balanced with respect to the extent of disease and in both treatment arms 76% of patients had greater than 5 lesions and 76% of patients had liver lesions.

Only 4% of patients had received prior chemotherapy with 3% as adjuvant therapy and 1% as neo-adjuvant therapy with the types of therapy being well balanced between the treatment arms.

7.1.3. Efficacy results

7.1.3.1. Primary efficacy endpoint

The median follow up time for censored (surviving) patients being 20% of those patients entered with 9.1 months per combination and 7.4 months for the gemcitabine arm. There was a statistically significant improvement in median overall survival for the combination arm for the ITT population being 8.5 months with a 95% CI 7.89, 9.53 per combination arm versus 6.7 months with a 95% CI 6.01, 7.23 for the gemcitabine arm. The hazard ratio was 0.72 indicating a 28% overall reduction in the risk of death for patients receiving the combination with a P < 0.0001 stratified log rank test. One year survival is improved by 59% from 22% in the

gemcitabine arm and 35% in the combination arm and two year survival rates were improved by 125% for the combination arm.

As indicated in Part B, Section B, Figure 1 survival curves separated early and continued to separate as long as survival.

A multivariate analysis of overall survival was conducted using a Cox proportional hazard model to evaluate the treatment effect adjusted for the stratification. The model indicated that the presence of liver metastases and baseline performance status were significant predictors of overall survival. After adjustment of these factors the assessment of the treatment effect for the combination and overall survival are similar to the effects seen in the primary analysis and remains statistically significant with an HR of 0.71 P < 0.0001.

Stepwise multivariate analysis was performed to evaluate the treatment effect and identify possible predictors for overall survival by including all prognostic factors in the model. Those factors which were predictors of an increased risk of death regardless of treatment included region, that is Eastern Europe, ages greater than 65 years, poor performance status, presence of liver metastases and greater number of metastatic sites. Again after adjustments of these factors the estimate of treatment effect was similar to that of the primary analysis and remains statistically significant with an HR 0.72, P < 0.0001. Addition of the CA19-9 values to the multivariate analysis maintained the influence of the treatment effect. Overall the reduction in the risk of death for the combination with adjustment for the effect of the identified prognostic factors ranged from 28% to 33%.

A number of pre-specified sensitivity analyses were conducted on overall survival and were consistent with the primary analysis revealing a statistically significant improvement in overall survival with a 26% - 32% reduction in the risk of death for the combination arm.

To assess the influence of subsequent anti-cancer therapy on those patients who progressed, evaluation revealed that the proportion of patients who received subsequent anti-cancer therapy was balanced between the treatment arms being 38% for the combination and 42% for the gemcitabine arm. As well the types of subsequent therapy were similar being 26% and 30% for the combination and gemcitabine arms respectively. Sensitivity analysis was consistent with the primary analysis with an HR 0.68 and P < 0.0001 indicating the survival benefits seen in the primary analysis was independent of subsequent anti-cancer therapy.

Analysis of survival for the various clinical sub-groups defined by stratification factors revealed the median overall survival was higher in the combination arm compared with the gemcitabine arm for each of these.

Similarly stratified analysis of overall survival according to the per protocol population revealed results similar to those in the intent to treat population with a median overall survival of 8.6 months in the combination versus 6.8 months for gemcitabine arm with an HR 0.72, P < 0.0001.

7.1.3.2. Sub-group analyses

Sub-group analyses were performed on the pivotal study to assess the possible influence of demographic and baseline characteristics. As indicated in Part B, Section B, Figure 2 the treatment effect on overall survival consistently favoured the combination arm across the majority of patient sub-groups and the patients with the most advanced disease generally had the greatest reduction in the risk of death.

7.1.4. Secondary efficacy endpoints

7.1.4.1. Progression free survival

The results of the stratified analysis progression free survival for the ITT population indicated that 64% and 62% of patients in the combination arm and gemcitabine arm respectively died of progression of disease. There was a statistically significant increase in progression free survival in the combination arm compared with the gemcitabine arm with a median progression free

survival based on independent review being 5.5 months per combination compared to 3.7 months for the gemcitabine arm P < 0.0001 and HR 0.69 corresponding to a 31% reduction in the risk of progression or death for patients who received the combination. A progression free rate at nine and 12 months had approximately doubled in the combination arm compared with the gemcitabine arm. Progression free survival according to sub-group analyses based on demographic and baseline characteristics and again the treatment effect consistently favoured the combination arm across the various sub-groups. Similarly multivariate analysis of PFS with adjustments for potential prognostic factors revealed a consistently significant treatment effect in reduction in risk of PD or death for the combination arm with HR in the range of 0.66 – 0.69.

A median progression free survival of 5.5 months for the combination arm and 3.7 months for the gemcitabine arm were noted in the intent to treat population, for the per protocol and treated populations as well. The HR was 0.69 for the per protocol population and 0.68 for the treated population with a P < 0.0001.

7.1.4.2. Overall response rate

The percentage of patients in the ITT population with a confirmed CR or PR was three-fold higher in the combination arm compared with the gemcitabine arm at 23% versus 7% and the difference was highly significant P < 0.0001 by Chi2 test. It is noted that only one patient in the combination arm actually had a confirmed CR. Again sub-group analysis for overall response rate based on demographic and baseline characteristics consistently favoured the combination arm across the sub-groups and is indicated in Part B, Section B, Figure 5. Similarly the results for the overall response rate based on the per protocol treated population was consistent with those observed for the ITT population. For the per protocol population the overall response rate was 24% for the combination versus 8% for the gemcitabine arm with P < 0.0001.

7.1.4.3. Review of data from the sub-group of patients 75 years of age or older

It is noted that in patients who are at least 75 years of age for both treatment arms, there was a similar overall survival for the combination versus the gemcitabine arms with survival HR 1.08. It is noted however that there was a small sample size involved being 41 patients for the combination and 49 for the gemcitabine arm. There was also a high rate of early withdrawal prior to treatment in the gemcitabine arm. It is of note however that in relation to median overall survival there was a superior survival in the combination arm at 8.5 months for these patients compared to the gemcitabine arm at 6.7 months and also in relation to one year overall survival rates.

It is also noted in the sub-group of patients with normal baseline CA19-9 levels, that is 60 patients in the combination and 56 for the gemcitabine arm the survival HR was 1.07 but the median overall survival was 9.2 months compared with 6.9 months respectively. It is also noted that in the reviews of subsequent anti-cancer therapy there was an imbalance across the treatment arms which may well have affected the results.

7.1.4.4. Additional efficacy endpoints

Other efficacy endpoints including time to response, duration of response, disease control rate and overall response rate based on PET scans, time to treatment failure and percentage of patients with at least a 90% reduction from baseline and CA19-9 revealed that the PET and CA19-9 response rates were nearly doubled in the combination arm. Comparable results were noted between the treatment arms for time to response and duration of response.

Comment: This data from the pivotal study involving a total patient population of 861 patients resulted in a significant and clinically meaningful 28% overall reduction in the risk of death for the combination of Abraxane and gemcitabine compared to standard therapy with gemcitabine alone. It is pertinent that this significant result related to differences in overall survival and various analyses including sub-group analyses and multivariate analyses confirmed this data. Similarly results from secondary efficacy parameters such as progression free survival and

overall response rate again confirmed the clear-cut benefit for the combination compared to standard control. This represents impressive evidence for improved outcomes with the combination of Abraxane with gemcitabine in patients with metastatic adenocarcinoma of the pancreas.

7.1.4.5. Supportive study

The single supportive study was a Phase I/II trial of gemcitabine plus Abraxane in patients with advanced metastatic pancreatic cancer (CA040). The primary objective of the study was to determine the MTD and DLT of the combination in patients with metastatic pancreatic cancer. Secondary objectives were to obtain additional data on the antitumor activity of the combination as well as safety and tolerability.

7.1.4.6. Patient disposition and exposure to treatment

A total of 67 patients were enrolled at four sites in the USA and the study was initiated on the 14th November 2006 and completed on the 31st October 2010. The data cut-off for the study was the 31st December 2010 at which time all patients were off treatment.

All 67 patients received at least one dose of study drug including 20, 44 and three patients who received Abraxane 100mg/m^2 , 125mg/m^2 and 150mg/m^2 respectively followed by gemcitabine 1000mg/m^2 . Cohort 1 had 100mg/m^2 of Abraxane, 2/14 patients experienced a DLT being grade IV neutropenia and grade IV febrile neutropenia and grade III diarrhoea. Accordingly the dose of Abraxane was increased to 125mg/m^2 for cohort 2 after seven patients were enrolled without any protocol defined DLTs with doses escalated to 150mg/m^2 and at this dose level 1/3 patients experienced DLTs including grade IV leukopenia, thrombocytopenia and fatal sepsis. Accordingly it was considered that the MTD was 125mg/m^2 of Abraxane followed by 1000mg/m^2 of gemcitabine. A total of 37 additional patients were recruited in the Phase II portion of the study at this dose for a total of 44 patients treated.

The most common reason for discontinuation of treatment across the 67 patients was progressive disease in 49%, unacceptable toxicity in 25% and patient discretion in 16%. As for this study all cycles including cycle 1 of 28 days duration and across all 67 patients the median number of cycles administered was six.

7.1.4.7. Demographic and baseline characteristics

The demographic and baseline disease characteristics for the patients in the study, the median age of patients was 62 years with the majority, that is 61% < 65 years. Sixty-nine percent of patients had metastatic lesions of the liver and 56 patients had stage IV disease at time they entered the study.

7.1.4.8. Efficacy results

Key efficacy results based on the independent review from the supportive Phase I/II study, CA040, the highest overall response rate was observed for the 125mg/m^2 cohort at 39% with all responses being partial. In the 100mg/m^2 cohort the overall response rate was 25% again being partial responses. There were no responses among the three patients who received 150mg/m^2 and only received two cycles of therapy. It is noted that the median progression free survival for the 125mg/m^2 cohort was 6.9 months and 6.1 months in the 100mg/m^2 cohort. A total of 45% of the patients had been censored including 55% at a 100mg/m^2 cohort and 43% for the 125mg/m^2 cohort. It is noted that the investigator evaluation of overall response rates were comparable to those of the independent review.

Patients in this study were followed for a median of 13 months and the median overall survival was longest for the patients in the 125mg/m^2 group at 12.2 months and for the 100mg/m^2 group 9.3 months.

Comment: This preliminary data confirms definite activity for the combination of Abraxane and gemcitabine which appears superior to gemcitabine alone, therefore warranting the subsequent pivotal study performed.

8. Clinical safety

Safety data for this evaluation is provided from the two studies namely Phase III pivotal trial CA046 and the Phase I/II Study CA040. For both of these studies safety and tolerability were monitored through reporting of adverse events and serious adverse events together with laboratory abnormalities using a central laboratory and incidence of patients experiencing dose reduction, dose interruptions, dose delay or dose not given and/or premature discontinuation of study drug due to adverse event. Investigator reported all adverse events and adverse events were graded using the NCI grading definitions.

Adverse events were monitored on each day of administration of therapy and at end of study visit. In both studies follow up of adverse events continued until 30 days after study drug discontinuation or end of study whichever came later. During the clinical evaluation of adverse events careful note was taken in relation to potential peripheral neuropathy.

It is noted that in the Phase I/II Study CA040 the initial Phase I component involved the determination of MTD and DLT. It is noted that three dose levels were studied with the MTD determined at 125mg/m^2 . It is also noted that of three patients entered at 150mg/m^2, one patient experienced grade IV neutropenia and sepsis which proved to be fatal.

In relation to laboratory evaluations, haematological assessment was performed weekly during courses of therapy and on day 1 of each new cycle and subsequently at the end of study visit. Similarly clinical chemistry evaluations were undertaken at baseline and then on day 1 of each cycle of therapy thereafter and at the end of study visit.

All safety data was analysed using the treated population which consisted of all randomised/enrolled patients who received at least one dose of study drug. Evaluation of safety data for the two studies was combined specifically for Study CA040 in relation to the 125mg/m^2 dose group.

8.1. Extent of exposure

A total of 465 patients received at least one dose of Abraxane/gemcitabine combination in Study CA046 and CA040 that were included in the pooled analysis.

The median time on study and treatment exposure for the two studies with a median time being 7.9 months for the combination and the median number of cycles administered being four.

In the pivotal study the median treatment duration was longer in the combination arm at 119 days compared to the gemcitabine arm at 86 days. Twice as many patients in the combination arm compared with the gemcitabine arm received six or more cycles of treatment and the median number of doses administered was greater in the combination arm than the gemcitabine arm being 12 doses of each drug for the combination and nine doses for the gemcitabine alone arm.

For the pooled analysis the median cumulative Abraxane dose administered was 1500mg/m^2 which corresponded to a median of 81% of the protocol specified Abraxane dose. The median cumulative gemcitabine dose was higher in the combination arm than the gemcitabine alone arm at 11,400mg/m^2 compared to 9000mg/m^2 while the median average gemcitabine dose intensity, percentage of the protocol specified gemcitabine dose administered was lower in the combination arm than the gemcitabine arm.

The incidence of Abraxane and/or gemcitabine dose reductions for the combination group 39% of patients had Abraxane dose reduction. gemcitabine dose reductions occurred in 43% of patients. In both studies most or at least 91% of Abraxane or gemcitabine dose reductions were due to adverse events. Sixty percent of patients with Abraxane dose reduction had one dose reduction and 33% had two dose reductions. It is noted that 10-15% patients had no Abraxane dose reduction in each of the six treatment cycles. In both arms of the pivotal study a higher percentage of patients had gemcitabine dose reductions in cycle one, being 27% for the combination and 23% for the control followed by 8-16% of patients in each of cycles 2-6.

In the pivotal study Abraxane dose delay and/or dose not given was reported for 71% of patients. The vast majority of these, that is 93% were due to treatment emergent adverse events. gemcitabine dose delay or not given occurred in 70% of patients in the combination arm and 57% of patients in the gemcitabine arm. Again adverse events were the most common reason for this.

8.2. Patient disposition

In the pivotal study as of the data cut-off on 17th September 2012 the majority of patients had discontinued treatment, that is 91% although 26 patients remained on treatment in the combination arm compared to 12 or 3% on the gemcitabine arm. The most common reason for treatment discontinuation was progressive disease and it is noted that more patients discontinued treatment due to adverse events on the combination arm at 20% compared to gemcitabine arm at 7%.

It is noted that patient demographics and pre-treatment disease characteristics have been outlined in the Efficacy section.

8.3. Adverse events

An overview of adverse events in the two studies and pooled analysis. Virtually all, that is 99% of patients in the pooled analysis reported at least one treatment emergent adverse event (TEAE) and 96% of these were considered by the investigator to be treatment related. Grade III or higher events were frequently reported at 89% and again most were treatment related at 78%. Serious adverse events were reported for 51% of patients in the pooled combination group and fatal serious adverse events were reported in 4% of patients in the pooled combination group. Treatment emergent adverse events leading to discontinuation were reported in 35% of patients in the pooled combination group. In the pivotal study the overall percentages of patients who experienced a treatment related TEAE or serious adverse event (SAE) were comparable for the two arms of therapy. There was however a greater proportion of grade III adverse events and adverse events leading to treatment discontinuation for the combination arm. The incidence of adverse events leading to death was identical in the two treatment arms at 4% each.

Treatment emergent adverse events for the two studies and pooled analysis in at least 10% of patients. The most common adverse events in the combination included fatigue, peripheral neuropathy, nausea, alopecia, peripheral oedema, diarrhoea, anaemia, neutropenia and pyrexia. Those adverse events more common in the combination arm than the gemcitabine arm included fatigue, alopecia, peripheral neuropathy, peripheral oedema, diarrhoea, neutropenia, pyrexia and decreased appetite.

In the pooled combination group the most frequent reported were neutropenia, fatigue, peripheral neuropathy, thrombocytopenia, anaemia and leukopenia. In the pivotal study the incidence of grade III or higher TEAEs was 89% for the combination group and 75% for the gemcitabine arm. In the pivotal study grade III TEAEs with at least 5% difference between the

combination and gemcitabine arms included neutropenia, fatigue, peripheral neuropathy, thrombocytopenia, leukopenia and diarrhoea.

In relation to treatment related TEAEs in the pooled combination therapy these were in decreasing order of frequency, fatigue, alopecia, nausea, neutropenia, anaemia, diarrhoea, peripheral oedema, thrombocytopenia, vomiting, peripheral neuropathy, pyrexia and decreased appetite. Those with at least a 10% greater incidence for the combination arm compared to the gemcitabine arm included fatigue, alopecia, neutropenia, diarrhoea, peripheral oedema, vomiting, decreased appetite, peripheral neuropathy and rash.

Most, that is 78% of patients in the pooled combination therapy group had at least one grade III or higher treatment related TEAE. The most frequent in at least 10% of patients reported being neutropenia, fatigue, thrombocytopenia, anaemia and leukopenia. In the pivotal study the incidence of grade III or higher treatment related TEAEs was 77% for the combination arm and 50% for the gemcitabine arm, the most frequent of these were on the combination arm compared to gemcitabine alone were neutropenia, fatigue, thrombocytopenia and anaemia.

8.4. Adverse events of special interests

Adverse events of interest in the pooled analysis were those being recognised as associated with Abraxane therapy, namely myelosuppression, peripheral neuropathy, sepsis, pneumonitis, hypersensitivity reactions, cranial nerve palsy and myalgia and arthralgia.

Reviewing the most frequent of these.

8.4.1. Myelosuppression

In the pivotal study grade III/IV neutropenia based on central laboratory values occurred in 38% of patients in the combination arm and 27% in the gemcitabine arm. Grade III/IV anaemia occurred in 13% versus 12% and grade III/IV thrombocytopenia in 13% versus 9%. Febrile neutropenia was reported as a TEAE in 14 or 3% of patients in the combination arm and 6 or 1% of patients in the gemcitabine arm. All of these events were grade III or IV. There were no deaths due to febrile neutropenia. In the combination arm 16% of patients had Abraxane dose delay and 18% of patients had gemcitabine dose delay due to neutropenia. In the gemcitabine arm 11% of patients had dose delay due to neutropenia. Less than 1% of patients in both treatment arms had study drug discontinued due to neutropenia.

8.4.2. Peripheral neuropathy

In the pivotal study peripheral neuropathy was reported for 54% of patients in the combination arm and 13% of patients in the gemcitabine arm. The majority of reports of peripheral neuropathy in both treatment arms were grade II or below and there were few serious adverse effects. The incidence of grade III peripheral neuropathy was 17% in the combination arm and 1% in the gemcitabine arm. There were no reports of grade IV peripheral neuropathy. The incidence of peripheral neuropathy that led to study drug discontinuation was 8% for Abraxane and 4% for gemcitabine in the combination arm with no patient requiring discontinuation in the control arm.

The incidence of grade III peripheral neuropathy increased with cumulative exposure to Abraxane with a 7% incidence up to three cycles of combination therapy whereas for those treated up to six cycles the incidence was 12%. Of those patients who required treatment interruption due to grade III peripheral neuropathy, 44% or 31/70 patients were able to resume Abraxane treatment. The median time to treatment resumption was 23 days.

8.4.3. Pneumonitis

In the two clinical studies pneumonitis was reported for a total of 24 patients including 22 patients in the pivotal study, 17 on the combination arm and five on the control and for two patients in Study CA040. In the pivotal study the frequencies of grade III or higher pneumonitis

and pneumonitis resulting in study drug discontinuation was similar for the two arms being 2% for the combination arm and 1% for the gemcitabine arm. Pneumonitis was reported as a serious adverse event at 3% in the combination and 1% in the gemcitabine arm. Two patients in the combination arm died due to pneumonitis. The median time to the onset to pneumonitis is similar for the two treatment arms at 86 days for combination and 83 days for the gemcitabine arm. The median duration for pneumonitis was longer in the combination arm at 15 days compared to the gemcitabine arm at 10 days.

8.4.4. Sepsis

In the two clinical studies sepsis was reported for a total of 37 patients included 32 patients in the pivotal study, 22 on the combination arm and 10 in the gemcitabine arm. In the pivotal study all grades of sepsis were predominantly gram negative sepsis due to abdominal biliary obstruction for 22 patients in the combination arm and 10 patients in the gemcitabine arm. Sepsis was fatal for five patients in the combination and two patients in the gemcitabine arm. It is noted that sepsis occurred in both neutropenic and non-neutropenic patients and it is noted that at least grade III neutropenia at the time of onset of the sepsis was reported in eight or 32% of 25 episodes in the combination arm. It is also noted that in those who died of sepsis, neutropenia was observed in 3/5 cases in the combination arm and 0/2 cases in the gemcitabine arm. The median time to onset of sepsis was 76 days for the combination arm and 34 days for gemcitabine arm. It is apparent that complications arising from the underlying metastatic pancreatic cancer were a very significant contributing factor including episodes of cholangitis brought on by tumour compression of the common bile duct. This accounts for at least half of the events. Nevertheless the mortality for biliary sepsis was low being only one patient. A further factor noted to be of significance was the presence of biliary stents in patients with cancer at the head of the pancreas.

8.4.5. Deaths

In the pivotal study the incidence of TEAEs with an outcome of death was identical in the two treatment arms being 18 patients, 4% each.

Treatment related fatal serious adverse events were reported by the investigator to have occurred in eight or 2% of the total 465 patients in the pooled combination therapy group. There were two patients with treatment related adverse events with outcome of death among the 402 patients who received gemcitabine alone in the pivotal study.

8.4.6. Serious adverse events

In the pivotal study the overall incidence of SAEs were similar in the two treatment arms being 50% for the combination and 43% for the gemcitabine arm. Pyrexia was the most frequently reported SAE in the combination arm. Serious adverse events reported with at least a 2% difference in the combination arm compared to the gemcitabine arm were pyrexia and febrile neutropenia. It is of interest that serious adverse events of pulmonary embolism were reported a greater than 2% difference in the gemcitabine arm than the combination arm. Otherwise all other serious adverse events were observed in similar percentages in the two treatment arms.

In the pivotal study treatment related SAEs were noted for 29% of patients in the combination arm and 13% in the gemcitabine arm. The most common of these being again pyrexia and febrile neutropenia. All other treatment related SAEs were observed in similar percentages in the two treatment arms.

8.4.7. Adverse events resulting in study discontinuation

In the pivotal study the overall incidence of patients with TEAEs resulted in permanent discontinuation of study drug was 35% for Abraxane and 30% for gemcitabine in the combination arm and 24% in the gemcitabine arm. The most common reported TEAEs resulting in Abraxane discontinuation were peripheral neuropathy in 8%, fatigue in 4% and thrombocytopenia in 2%.

8.4.8. Treatment emergent adverse events resulting in dose reduction

In the pivotal study the overall incidence of TEAEs requiring dose reduction was 38% for Abraxane and 44% for gemcitabine in the combination arm and 31% in the gemcitabine arm. Most common adverse events reported requiring dose reduction were neutropenia in 10% and peripheral neuropathy in 6%.

8.4.9. Treatment emergent adverse events resulting in dose interruption

In the pivotal study the overall incidence of TEAEs resulting in dose interruption was low and similar in the combination arm at 1% for Abraxane and 2% for gemcitabine and to the gemcitabine arm at 2%.

8.4.10. Treatment emergent adverse events resulting in dose delays/dose not given

In the pivotal study the overall incidence of TEAEs resulting in dose delay or dose not given was 63% for Abraxane and 61% for gemcitabine in the combination arm and 48% in the gemcitabine arm. The most common causes being neutropenia, thrombocytopenia, fatigue, peripheral neuropathy, anaemia and diarrhoea. The incidence of neutropenia and thrombocytopenia resulted in a dose delay was generally greater for the combination arm than the gemcitabine arm. This is similar for the incidence of peripheral neuropathy. There was a greater incidence of infections and infestations in the combination arm compared to the gemcitabine arm.

8.5. Clinical laboratory evaluations

8.5.1. Haematology values

More patients in the combination arm at 38% than the gemcitabine arm at 27% had a grade III/IV neutropenia while the rates of grade III/IV anaemia and thrombocytopenia were comparable between the two treatment arms. During cycle 1 (8 weeks) and cycle 2 (4 weeks) more patients with at least 5% greater incidence in the combination arm than gemcitabine arm had grade III/IV neutropenia. During cycles 3 through 6 the percentage of patients with grade III/IV neutropenia was similar in the two treatment groups.

8.5.2. Clinical chemistry values

Review of the various clinical chemistry values revealed that overall changes in hepatic and renal function enzyme levels were sporadic and similar for both the combination and gemcitabine arms.

8.5.3. TEAEs by age groups

In the pivotal study there were 175 patients aged at least 65 years in the combination arm and 177 patients in the gemcitabine arm. In general the patterns and distribution of TEAEs were similar for both those patients < 65 years and those greater than 65 years and similar observations were apparent when comparing the combination arm to the gemcitabine arm. In the combination arm patients aged at least 65 years had a greater incidence of diarrhoea at 51% versus 38% and epistaxis at 22% versus 11% than patients who were < 65 years while alopecia was more frequent in patients < 65 years at 56% versus 42%.

The overall incidence of grade III or higher TEAEs was similar for patients < 65 years to those of greater than 65 years for the combination arm being 87% and 90% respectively. Grade III adverse events occurring in the older age group with at least a 5% greater incidence than those < 65 years included fatigue 22% versus 16%, dehydration 12% versus 4%, decreased appetite 10% versus 2% and diarrhoea 9% versus 4%.

The overall incidence of serious adverse events was 59% in patients greater than 65 years of age and 44% in those < 65 years of age in the combination arm. Dehydration was the only SAE reported with a greater than 5% difference in patients who were greater than 65 years being

9% versus 2%. The incidence of TEAEs resulting in death on the combination therapy arm were 6% for patients who were greater than 65 years compared to 3% of those < 65 years.

The overall incidence of grade III or higher TEAEs was similar for patients who < 75 years compared to those greater than 75 years in the combination arm for the pivotal study being 89% versus 90%. Those with a greater than 5% difference in incidence for those patients greater than 75 years were decreased appetite 18% versus 4% and dehydration 18% versus 6%.

The overall incidence of SAEs and TEAEs with an outcome of death were 75% and 13% respectively in patients who were greater than 75 years and 48% and 3% for those were < 75 years of age in the combination arm of the pivotal study. In the combination arm SAEs reported at least a 5% difference in patients who were greater than 75 years of age were dehydration 13% versus 4% and hyponatremia 5% versus zero. There were no notable differences in the incidences of individual TEAEs with the outcome of death. Among the patients who were at least 75 years of age in the combination arm, there were two deaths due to sepsis.

8.6. Post-marketing data

No specific post-marketing data in relation to the Abraxane/gemcitabine combination is available. The post-marketing history of Abraxane alone indicates that it has never been withdrawn or suspended from market due to safety or efficacy issues with approximately 140,000 patients in the USA and 34,000 outside the USA who have been treated with Abraxane principally for metastatic breast cancer. No data is provided in relation to adverse events associated with this population.

> Comment: Safety data provided in this submission clearly indicates that the addition of Abraxane to gemcitabine results in a somewhat greater incidence of adverse effects particularly myelosuppression, peripheral neuropathy, diarrhoea and fatigue, infectious/sepsis and pneumonitis. This is not unexpected as addition of a further agent with these potential toxicities to gemcitabine with its already known spectrum of toxicity might be expected to result in an increased incidence of toxicity associated with the individual agents involved in the combination. Nevertheless there does not appear to be any new toxicities emergent which could not be anticipated from the known adverse effects associated with Abraxane and gemcitabine. In general terms these adverse effects are well known to oncologists, however with appropriate vigilance in monitoring together with early intervention and relevant prophylaxis the adverse event profile for the drug combination should be adequately managed.

9. First round benefit-risk assessment

9.1. 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 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.

9.2. 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.

9.3. 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.

10. 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 for
  - the indication for the first line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas.[1]

11. Clinical questions

No additional clinical questions arise from this reviewer.

[1] This indication was used during the clinical evaluation. Final indications are included in the AusPAR.

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