All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Paclitaxel albumin (Abraxane®)

Abraxis BioScience Limited

Advice No: 0410 - April 2010

Recommendation of AWMSG

Paclitaxel albumin (Abraxane®) monotherapy is recommended as an option for use within NHS Wales for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for who standard, anthracycline containing therapy is not indicated.

AWMSG is of the opinion that paclitaxel albumin (Abraxane®) is not suitable for shared care within NHS Wales.

Clinicians should follow the National Institute for Health and Clinical Excellence (NICE) Guidelines CG81 in the consideration of treatment options for metastatic breast cancer.

The Summary of Product Characteristics specifically states that this drug should be used as monotherapy.

In order to limit potential errors, paclitaxel albumin (Abraxane®) should be prescribed by brand as Abraxane®.

This report should be cited as:

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CI	Confidence interval
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European Public Assessment Report
HER2	Human epidermal growth factor receptor 2
HR-QoL	Health Related quality of life
HR	Hazard Ratio
ICER	Incremental cost effectiveness ratio
invORR	Investigators assessment of Overall Response Rate
ITT	Intention-to-treat
IV	Intravenous
MBC	Metastatic breast cancer
mITT	Modified intention-to-treat
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMB	Net monetary benefit
NMG	New Medicines Group
NNH	Number needed to harm
OS	Overall survival
ORR	Overall Response Rate
PFS	Progression-free survival
PP	Per-protocol
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RECIST	Response Evaluation Criteria in Solid Tumor
recTLRR	Reconciled target lesion response rate
RR	Relative Risk
Sb-paclitaxel	Solvent-based paclitaxel
SPC	Summary of Product Characteristics
TTP	Time to progression
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 28th April 2010

The recommendation of AWMSG is:

Paclitaxel albumin (Abraxane®) monotherapy is recommended as an option for use within NHS Wales for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for who standard, anthracycline containing therapy is not indicated.

AWMSG is of the opinion that paclitaxel albumin (Abraxane®) is not suitable for shared care within NHS Wales.

Clinicians should follow the National Institute for Health and Clinical Excellence (NICE) Guidelines CG81 in the consideration of treatment options for metastatic breast cancer.

The Summary of Product Characteristics specifically states that this drug should be used as monotherapy.

In order to limit potential errors, paclitaxel albumin (Abraxane®) should be prescribed by brand as Abraxane®

2.0 PRODUCT DETAILS

2.1 Licensed indication

Paclitaxel albumin (Abraxane®) monotherapy is indicated for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated[1].

2.2 Dosing

The recommended dose is 260 mg/m^2 administered intravenously (IV) over 30 minutes every three weeks. Paclitaxel albumin should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents[1].

Patients who experience severe neutropenia (neutrophil count < 0.50 x 10^9/l for a week or longer) or severe sensory neuropathy during therapy should have the dose reduced to 220mg/m^2 for subsequent courses. Treatment should be withheld and additional dose reductions made following recovery where there is recurrence of severe neutropenia or severe sensory neuropathy. Further information on dose adjustment and potential drug interactions can be found in the Summary of Product Characteristics (SPC)[1].

2.3 Market authorisation date

11th January 2008[2]

2.4 UK Launch date

11th December 2008[2]

3.0 DECISION CONTEXT

3.1 Background

Breast cancer is the most common form of cancer affecting women in England and Wales with about 40,500 new cases diagnosed and 10,900 deaths recorded in England and Wales each year[3]. Of these new cases a small proportion are diagnosed in the advanced stages, when the tumour has spread significantly within the breast or to other organs of the body. In addition, a significant number of women will go on to develop either a local recurrence or metastases despite previous treatment[3]. Metastatic breast cancer (MBC) remains an incurable disease with a median survival of about two years; treatment is therefore essentially palliative[4]. Treatment for MBC can be categorised into endocrine, chemotherapy and biological therapy[4]. Tamoxifen and aromatase inhibitors are the most widely used endocrine therapy for patients with non-aggressive, hormone sensitive tumours[4,5]. In patients with hormone-insensitive or aggressive tumours, chemotherapy is the usual initial treatment using anthracycline-containing regimens such as doxorubicin or epirubicin combined with cyclophosphamide[3,5,6]. With the growing use of anthracycline-containing therapy as adjuvant therapy, the taxanes (paclitaxel and docetaxel) have become more established as the standard of care in patients with anthracycline-resistant MBC[3,4,7,8]. Biological therapy with trastuzumab is also licensed as a monotherapy for MBC in patients with tumours that over-express human epidermal growth factor receptor 2 (HER2) who have received at least two chemotherapy regimens including, where appropriate, an anthracycline and a taxane[5].

Paclitaxel albumin (Abraxane®) is an albumin bound nanoparticle formulation of paclitaxel[1] which is solvent-free; intended to allow safe infusion of higher doses of paclitaxel, eliminating solvent-related toxicity associated with solvent-based paclitaxel (sb-paclitaxel) and docetaxel[9]. This submission proposes that paclitaxel albumin monotherapy should be considered as an option for the treatment of MBC in patients who have failed first-line treatment for metastatic disease and who would otherwise be considered for sb-paclitaxel or docetaxel[9].

3.2 Comparators

- Sb-paclitaxel
- Docetaxel

Expert opinion identified docetaxel as the most commonly used taxane in Wales for treating MBC patients after failure of first-line therapy[9].

3.3 Guidance and related advice

- The National Institute for Health and Clinical Excellence (NICE) recommend that for patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered using single agent docetaxel (HER2-ve) or trastuzumab (HER2+ve) followed by either single agent vinorelbine or capecitabine for further lines of therapy[3].
- The National Comprehensive Cancer Network current clinical practice guidelines for breast cancer includes albumin-bound paclitaxel, sb-paclitaxel and docetaxel, as the preferred single agent taxanes for recurrent or metastatic breast cancer[6].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Primary clinical evidence in the company submission relates to secondary analyses of a randomised, open-label, phase III trial (Study CA012; n=268). Limited data was also provided in support from a smaller phase II trial (CA201; n=125). The relevant subgroup analyses compared paclitaxel albumin to sb-paclitaxel in patients with MBC in those who had previously failed first-line treatment for MBC. A higher tumour response rate was observed in comparison to sb-paclitaxel. In addition, secondary endpoints from Study CA012, such as time to progression (TTP), progression free survival (PFS) and overall survival (OS), were prolonged in the relevant cohort of patients (i.e. those receiving second or further-line therapy). The safety profile was similar between the two treatments except for a higher incidence of sensory neuropathy associated with paclitaxel albumin. No direct comparative studies between paclitaxel albumin and docetaxel have been identified.

4.2 Review of the evidence on cost-effectiveness

The company submission describes a cost utility analysis of paclitaxel albumin compared against sb-paclitaxel, based on efficacy data derived from a sub-population of the phase III trial CA012 meeting the licensed indication. A further cost utility analysis of paclitaxel albumin compared against docetaxel is described, using indirect comparisons of efficacy and safety data.

In the base case analysis, paclitaxel albumin is estimated to have an incremental cost per quality adjusted life year (QALY) gained of £25,209 compared against sb-paclitaxel. However, the base case analysis and all sensitivity analyses presented in the company submission assume no wastage of vial contents. When vial wastage is factored in, the deterministic incremental cost effectiveness ratio (ICER) increases to £29,571 per QALY gained, and the probability of paclitaxel albumin being cost effective at a given willingness to pay per QALY gained threshold decreases.

When compared against docetaxel, the deterministic base case model estimates that paclitaxel albumin is dominant (i.e. paclitaxel albumin is associated with greater QALY gains and lower overall costs). However, this should be interpreted with caution. Although the net monetary benefit (NMB) is positive for paclitaxel albumin compared with docetaxel at a willingness to pay threshold of £30,000 per QALY gained, probabilistic sensitivity analysis (PSA) indicates that paclitaxel albumin is more likely than not to be less expensive and less effective than docetaxel.

4.3 Limitations of the evidence

- There is a lack of robust, direct comparative efficacy and safety data against docetaxel for patients meeting the licensed indication for paclitaxel albumin.

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

5.1 Clinical evidence

The data presented as primary clinical evidence in the company submission relates to a pre-specified secondary analysis of a randomised, multicentre, open-label, phase III trial (Study CA012), which compared paclitaxel albumin to sb-paclitaxel in patients with MBC. The relevant subgroup analysis from this study, which included only those patients from Study CA012 who had previously failed first-line treatment for MBC (59%; n=268[4]), is discussed below. A smaller randomised, non-blinded, phase II trial (Study CA201; n=210, with another subgroup of patients receiving second line treatment (n=85) is included as supportive evidence[9]. In addition, an indirect comparison between paclitaxel albumin and docetaxel presented in the company submission is also highlighted. The company submission also provided data from the global population of the phase III trial as supportive evidence. Results however involved patients irrespective of whether they had previously received first-line chemotherapy for metastatic disease and the global population is therefore not discussed below.

5.1.1 Studies CA012 and CA201[9]

The primary objectives of these studies were to compare the anti-tumour activity of paclitaxel albumin with that of sb-paclitaxel in female patients with metastatic disease and to evaluate the safety/tolerability of paclitaxel albumin to that of sb-paclitaxel. Both studies had similar protocols, but study CA201 was conducted exclusively in Asian patients[4].

Patients were randomised (1:1) to receive either 260mg/m^2 paclitaxel albumin infused IV over 30 minutes or 175mg/m^2 sb-paclitaxel infused over three hours. In study CA012, balance for anthracycline exposure was ensured by within-country stratification into anthracycline-exposed and –naïve strata. Treatment cycles were administered every three weeks. The primary efficacy endpoint in both studies was the percentage of patients who achieved a confirmed complete or partial response according to Response Evaluation Criteria in Solid Tumor (RECIST) guidelines (see Table 1C, Appendix 1). The company have presented results for the secondary analyses based upon the investigator's assessments of target and non-target lesions for all cycles of therapy referred to here as the overall response rate (investigators assessment of overall response rate [invORR]). Further information regarding the response assessment methodology can be found in Appendix 1. In addition, see section 6.0.

From the subgroup analysis of Study CA012, the results for the intention-to treat (ITT) population showed that significantly more patients treated with paclitaxel albumin had an overall response compared to patients treated with sb-paclitaxel (relative risk [RR] 2.0; 95% Confidence Interval [CI] 1.20 to 3.36, p=0.006). A superior response rate was supported by the limited results of the CA201 study for the per-protocol (PP) population, although not statistically significant (n=85; p=0.181). Further detail of the results can be found in Table 1A, Appendix 1.

Other efficacy measures as assessed by the investigator in Study CA012 included: median TTP; median PFS and patient OS. TTP and PFS outcomes for those patients receiving paclitaxel albumin as at least a second line treatment were found to be statistically significantly superior to sb-paclitaxel, and there was a prolongation of survival demonstrated in favour of paclitaxel albumin (9.7 weeks; p=0.024). Quality of life assessments included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ]-C30. No statistically significant differences between the treatment groups were identified, other than 'pain symptom' at baseline for those patients with confirmed target lesion response (p=0.004)[4]. The results for these secondary endpoints can be found in Table 1A, Appendix 1.

5.1.2 Indirect comparison

An indirect comparison between paclitaxel albumin 260mg/m^2 every three weeks and docetaxel 100mg/m^2 was undertaken by the company[9]. Only one study was identified with data that were well matched to the pivotal trial (study CA012). This study investigated the role of docetaxel monotherapy and included the same comparator to that of study CA012 (sb-paclitaxel 175mg/m^2 three-weekly)[10]. The relevant exclusion and inclusion criteria are compared in Table 1B, Appendix 1.

The results reported no significant difference in efficacy between paclitaxel albumin and docetaxel. There were trends to suggest that paclitaxel albumin treated patients were more likely to achieve a response, however there were trends to suggest longer TTP with docetaxel. PFS for docetaxel was not reported.

5.2 Safety

The most common adverse events related to global population of patients receiving paclitaxel albumin in the pivotal phase III trial were considered qualitatively not to be different from the known adverse events related to currently registered paclitaxel formulations (i.e. those solvent based)[4]. Nevertheless the company report patients treated with sb-paclitaxel (in ≥2nd line MBC) were 1.63 times more likely to experience a serious adverse event than patients treated with paclitaxel albumin (35% versus 21%; p=0.02[9]). In general, neutropenia was the most notable important haematological toxicity (reported in 79% of patients), and was rapidly reversible and dose dependent; leukopenia was reported in 71% of patients. Despite the higher dose of paclitaxel delivered, less Grade 4 neutropenia (< 0.5 x 10^9/l) occurred in patients treated with paclitaxel albumin (9%) than those treated with sb-paclitaxel (22%)[4]. The frequency and severity of neurotoxicity was dose-dependent. In the Phase III study CA012 a higher cumulative paclitaxel exposure was demonstrated with paclitaxel albumin. Peripheral neuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68% of patients on paclitaxel albumin, with 10% being Grade 3, with no cases of Grade 4[4]. Furthermore, sensory neuropathy was the most commonly reported adverse event leading to discontinuation. The frequency of treatment related discontinuation in Study CA201 was comparable at 5% and 3% for paclitaxel albumin and sb-paclitaxel, respectively[9].

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The company have chosen to present results using the invORR, although the primary efficacy analysis for the pivotal trial (CA012) using the recTLRR originally results in an underestimate of response rates relative to those based on invORR. Reasons given in the company submission as to why the invORR is emphasised more than recTLRR in the report are:
    - because the invORR is more clinically meaningful and is comparable with literature reports of response rates to taxanes
    - the primary efficacy tests of non-inferiority and superiority, which were based on recTLRR, were met and surpassed
    - analyses of invORR and recTLRR yield the same conclusion with regard to the relative efficacy of paclitaxel albumin versus sb-paclitaxel [9]
- OS, although considered a secondary efficacy measure in the submission, is regarded within cancer treatment to be more clinically meaningful than response rate.
- Expert opinion identified docetaxel as the most commonly used taxane in Wales for treating MBC patients after failure with first-line therapy[9]. No studies however have been identified that directly compared paclitaxel albumin with docetaxel.
- Only limited analysis of ≥2nd line treatment patients was available from study CA201; which was conducted exclusively in Asian patients.
- The company considered the differing performance measure indicators (Eastern Cooperative Oncology Group [ECOG]) and Karnofsky scores) used in the indirect comparison to be comparable; also that the impact of the difference in anthracycline inclusion criteria between the two studies was relatively limited.
- The company acknowledged limitations to the studies within their submission e.g. their open-label design, mixed prior treatment history, uncontrolled therapy following trial discontinuation and the fact that they did not examine the role of HER2 status.

- The dose of paclitaxel albumin administered in the pivotal trial (study CA012) was nearly 50% higher than that for sb-paclitaxel, therefore greater efficacy could be expected. Patients in the paclitaxel albumin group received an average paclitaxel dose intensity 49% greater than that received by patients in the sb-paclitaxel group (mean [standard deviation] 85.13[3.118] versus 57.02 [3.008] mg/m^2 per week, respectively.
- Sb-paclitaxel and docetaxel have poor solubility and require a complex solvent system for their commercial formulations; the biological surfactants involved have been associated with toxicities and implicated as contributing to hypersensitivity reactions[7-9]. Paclitaxel albumin is solvent-free[1]; by eliminating solvent-related toxicities it is intended to allow the infusion of significantly higher doses of paclitaxel than those used in solvent-based formulations, with shorter infusion schedules (30 minutes versus three hours) and no premedication[9].
- Paclitaxel albumin is indicated for mono-therapy and should not be used in combination with other anticancer agents[1].

7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

7.1 Context

The company submission[9] describes a cost utility analysis of paclitaxel albumin compared against sb-paclitaxel, based on efficacy data derived from a sub-population of the phase III trial CA012 that had received prior chemotherapy[9]. A further cost utility analysis of paclitaxel albumin compared against docetaxel is described. As direct comparative data are not available for paclitaxel albumin and docetaxel an indirect comparison has been conducted. A structured literature review identified one comparative trial of sb-paclitaxel and docetaxel[10] that met the inclusion criteria for the indirect comparison.

7.2 Methods

Modelling approach: A simple state transition model has been developed to simulate the clinical pathway followed by a hypothetical cohort of patients meeting the licensed indication for paclitaxel albumin[1,9] (see Table 2A, Appendix 2 for details). Patients enter the model in a progression-free state, where they remain until they progress to progressive disease followed by death. The effectiveness of paclitaxel albumin and the comparators is based on OS, PFS and response rates derived from clinical trial data. Specific utility weights are estimated for each health state within the model, incorporating decrements associated with adverse events of treatment. Each cycle of the model is three weeks long, in line with chemotherapy treatment cycles, and a time horizon of five years has been adopted as the company reports that over 99% of the hypothetical cohort reach the absorbing state of death by five years[9].

Inputs: OS and PFS data for the paclitaxel albumin arm of the model are derived from a sub-population of the phase III trial CA012 that had received prior chemotherapy[9]. These survival data have been extrapolated to the five year time frame using Weibull parametric modelling. For the comparator sb-paclitaxel, the hazard ratios (HR) from the Kaplan-Meier curves of PFS and OS obtained in trial CA012 have been used to adjust the paclitaxel albumin PFS and OS curves generated by the Weibull modelling[9].

An indirect comparison of docetaxel and paclitaxel albumin has been conducted using trial CA012 and a phase III trial of docetaxel and sb-paclitaxel[10]. PFS for docetaxel was not reported in this phase III trial[10], therefore, the HR for TTP has been estimated as a proxy for PFS for docetaxel relative to paclitaxel albumin. The company's basis for using TTP HR as a proxy for PFS HR is that in clinical trial CA012 (paclitaxel albumin versus sb-paclitaxel), the HR for PFS and TTP were numerically very similar[9].

The estimated HR for PFS is 0.85 (95% CI 0.61 to 1.19). The HR for OS derived from this indirect comparison is 0.97 (95%CI 0.69 to 1.36). These HRs would mean that PFS and OS are numerically greater with docetaxel than paclitaxel albumin, but are not statistically significantly different. On this basis, the OS and PFS curves for docetaxel are assumed to be the same as for paclitaxel albumin (i.e. HRs of 1.0 assumed for adjusting the Weibull modelled survival curves). The point estimates of the HR are tested in sensitivity analyses in the range +/-30%.

Response rates for patients who are progression free are also derived from study CA012 for paclitaxel albumin and sb-paclitaxel, and from the indirect comparison for docetaxel. A HR of 1.0 has been assumed for docetaxel in the base case analysis on the basis that the point estimate for response derived from this indirect comparison was not statistically significantly different (HR 0.53, 95% CI 0.23 to 1.19).

Adverse events are incorporated from the same sources as the survival and response inputs. However, the rates of adverse events are based on the whole population of trial CA012, rather than the sub-population meeting the licensed indication for paclitaxel albumin[9]. The company indicates that this is a conservative approach as adverse event rates are greater in the whole trial population than in the sub-population meeting the licensed indication. Only grade III or IV adverse events that occurred in 3% of patients or more are included. A range of assumptions are employed, guided by company-sought expert opinion, such as only 10% of cases of neutropenia requiring treatment, and no specific treatment costs beyond routine monitoring costs for pain, neuropathies and skin reactions. The indirect comparison is reported to estimate that rates of febrile neutropenia, infection, and stomatitis are elevated in docetaxel recipients compared with paclitaxel albumin recipients, and these are associated with the greatest adverse event costs based on weighted averages of National Reference Costs[9].

Utility values for weighting life years were obtained from the same source as those used in the 2009 NICE clinical guideline on advanced breast cancer management[3]. This source was a published economic analysis of taxanes in breast cancer, which collated estimates of utilities for health states based on studies in health care professionals[11]. Utility decrements associated with adverse events are incorporated and, with the exception of febrile neutropenia, are response specific[9]. From the company submission it appears that patients who are in progression do not experience a decrement in utility due to adverse events.

In the base case analysis, drug regimens and doses are costed using British National formulary (BNF) list prices[5] on a cost per mg basis, which assumes no vial wastage. A secondary analysis that costs drug regimens on a per vial basis, which accounts for potential drug wastage, is also described. All other sensitivity analyses that have been reported in the company submission have been conducted using the cost per mg approach.

7.3 Results

Base case analyses: In the primary base case analysis (cost per mg approach) the incremental cost per QALY gained for paclitaxel albumin compared against sb-paclitaxel is estimated to be £25,209. This is based on additional costs of around £4,000 (mainly due to drug acquisition costs, but also due to additional adverse event costs) and a gain of 0.1641 QALYs and assumes no drug wastage. When drug wastage is incorporated, this marginally increases total costs for each treatment, which translates into an increase in the incremental cost per QALY gained to £29,571. In both costing approaches, paclitaxel albumin is estimated to be more effective and to be associated with lower total costs compared with docetaxel (including lower drug acquisition costs and lower adverse event costs), i.e. paclitaxel albumin dominates docetaxel (see Table A).

Sensitivity analyses: One way sensitivity analyses explored base case parameter values in the range +/-30% except for where this was implausible/illogical (e.g. body surface area, parameters constrained to the range 0 to 1). PSA were also performed using suitable parameter distributions and 1,000 simulations. All sensitivity analyses presented in the company submission were conducted using the cost per mg approach to costing drugs.

Table A. Base case analyses – Paclitaxel albumin versus sb-paclitaxel and docetaxel[1]

	Paclitaxel albumin	sb-Paclitaxel	Docetaxel
Cost per mg analyses			
Total costs	£19,189	£15,052	£19,885
Total life years	1.4344	1.1710	1.4344
Total QALYs	0.8030	0.6389	0.7993
ICER (£/QALY gained for paclitaxel albumin versus comparator)		**£25,209**	**Paclitaxel albumin dominates**
Cost per vial secondary analyses			
Total costs	£19,917	£15,064	£20,560
Total QALYs	0.8030	0.6389	0.7993
ICER (£/QALY gained for paclitaxel albumin versus comparator)		**£29,571**	**Paclitaxel albumin dominates**

For the comparison of paclitaxel albumin and sb-paclitaxel, the ICERs across the 15 one-way sensitivity analyses that are presented ranged from around £14,000 to around £38,000 per QALY gained. The most influential parameter was the HR for OS, which when explored in the range 0.51 to 0.95 (i.e. within a range that reflects a survival benefit with paclitaxel albumin compared with sb-paclitaxel) produced ICERs in the range £22,000 to £39,000 per QALY gained. The company notes that only five of the 15 one-way sensitivity analyses resulted in an ICER exceeding £30,000 per QALY gained[9]; however, only two of the sensitivity analyses resulted in an ICER lower than £20,000 per QALY gained. PSA indicates that, at a willingness to pay threshold of £20,000 per QALY gained, the probability of paclitaxel albumin being cost effective is around 10%, and at £30,000 per QALY gained is around 60%[9].

Although not presented in the company submission, the model indicates that when the one-way sensitivity analyses are conducted using the cost per vial approach to costing the drugs (i.e. incorporating drug wastage), the ICERs across the 15 sensitivity analyses range from around £17,000 to almost £50,000 per QALY gained, and all 15 exceed £30,000 per QALY gained at the upper limit of the parameter values that are explored. PSA indicates that, at a willingness to pay threshold of £20,000 per QALY gained, the probability of paclitaxel albumin being cost effective is less than 5%, and at £30,000 per QALY gained is around 40%[9]. These analyses have subsequently been confirmed by the company.

For the comparison of paclitaxel albumin and docetaxel, the results of 15 one-way sensitivity analyses are presented using a Net Monetary Benefit (NMB) approach as the base case analyses indicate that paclitaxel albumin dominates docetaxel and there are technical difficulties in presenting ICERs when either the incremental costs or benefits are negative. The company has assumed a willingness to pay of £30,000 per QALY gained for these analyses. The most influential parameters were the cost per cycle of docetaxel and paclitaxel albumin, and the HRs for OS and PFS, which resulted in NMBs in the approximate range -£1,000 to £2,700. A positive NMB indicates paclitaxel albumin is the more cost effective of the two treatments, and a negative NMB indicates docetaxel is the most cost effective, at the £30,000 per QALY threshold. Most NMB estimates were small, indicating that there are only marginal differences between the two treatments as modelled.

Further analysis was conducted using the point estimates of PFS and OS obtained from the indirect comparison, which numerically favoured docetaxel, rather than assuming a HR of 1.0. This produced a NMB of £316, which would suggest that paclitaxel albumin is marginally more cost effective than docetaxel. However, it should be noted that this positive NMB estimate results from lower total costs of treatment with paclitaxel albumin and lower overall effectiveness compared with docetaxel. This is also important to note for the PSA. The company reports that the probability of paclitaxel albumin being cost effective compared with docetaxel at a willingness to pay threshold of £30,000 per QALY gained is around 60%; however, for the majority of the simulations that were run, paclitaxel albumin was associated with lower total costs and also lower effectiveness compared with docetaxel.

Although not presented in the company submission, the model indicates that when the one-way sensitivity analyses are conducted using the cost per vial approach to costing the drugs (i.e. incorporating drug wastage), there is little impact on the NMB estimates compared with using a cost per mg approach.

7.4 WMP critique of the company's economic evidence

- It is not clear that the base case analyses presented in the company submission, based on a cost per mg approach to costing drugs, provide the most plausible point estimates of the cost effectiveness of paclitaxel albumin. The use of a cost per vial approach to drug costing, which takes account of potential drug wastage, results in a higher ICER for the comparison of paclitaxel albumin and sb-paclitaxel. For the comparison of paclitaxel albumin and docetaxel, the base case analyses indicate that paclitaxel albumin is dominant. However, this should be interpreted with caution. Although the NMB is positive for paclitaxel albumin compared with docetaxel at a willingness to pay threshold of £30,000 per QALY gained, the PSA indicates that in the majority of simulations paclitaxel albumin was both less expensive and/or less effective than docetaxel.

Strengths of the economic evidence provided in the company submission include:

- The modelled clinical pathway and comparators appear adequately representative of the decision problem
- In the absence of direct comparative evidence, a structured literature search was conducted to inform the indirect comparison of paclitaxel albumin and docetaxel.
- The approach to modelling survival with paclitaxel albumin treatment beyond the time frame of the clinical trial appears appropriate, and the company reports having back-tested this against available trial data for paclitaxel albumin and the sb-paclitaxel formulation.
- A wide range of one-way and PSA have been conducted to explore the impact of parameter value assumptions. Scenario analyses have also been conducted using an alternative approach to drug costing, which takes account of drug wastage and may be more representative of drug wastage in the clinical setting.

Limitations of the economic evidence provided in the company submission include:

- The lack of robust, direct comparative efficacy and safety data for paclitaxel albumin and docetaxel.
- The base case analyses of paclitaxel albumin compared against docetaxel are based on the assumption of equal effectiveness, which marginally favours paclitaxel albumin. The indirect comparison of clinical trial evidence found OS and TTP (used as a proxy for PFS) to be numerically longer with docetaxel.
- TTP may not necessarily be a reliable proxy for PFS.
- The base case analyses and all sensitivity analyses presented in the company submission assume no drug wastage, which results in more favourable ICER and NMB estimates compared with when drug wastage is taken into account.
- The rates of adverse events used in the model are reported to be standardised by only including those occurring in 3% of more of the trial populations, and excluding leucopenia and thrombocytopenia, in order to assist comparison with available docetaxel data. The model uses adverse event rates from the entire CA012 patient population rather than patients who received these agents as second-line therapy or greater, and this is reported to be conservative as rates of the adverse events included in the model were higher in the entire population than in the licensed sub-population. Company-sought expert opinion is reported to have guided assumptions on the approach to adverse event management.
- The headline results from the PSA for the comparison of paclitaxel albumin and docetaxel need to be interpreted with caution due to a majority of simulations resulting in paclitaxel albumin being both less expensive and less effective than docetaxel.

7.5 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have identified two published economic analyses of paclitaxel albumin, which have reached what may be considered as conflicting conclusions[12,13]. The first was conducted for a Canadian health care setting and concluded that the incremental cost per QALY gained over sb-paclitaxel was more favourable for paclitaxel albumin than for docetaxel ($56,800 versus $739,600)[12]. This study was funded by Abraxis Biosciences, the manufacturer of paclitaxel albumin. The second analysis was conducted for the UK health setting[13] and concluded that docetaxel improved QALYs by 0.22 compared with paclitaxel albumin, resulting in an incremental cost per QALY gained for docetaxel versus paclitaxel albumin of £14,694. This study was funded by Sanofi-Aventis, the manufacturer of docetaxel.

There are numerous differences between these published analyses and the company's analyses. Key among these is that both published analyses used efficacy data derived from all patients in the paclitaxel albumin trial, rather than using the sub-population meeting the UK licensed indication as considered in the company submission. Their applicability to the current decision problem is therefore limited.

8.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

8.1 Methods

UK market research data from the IMS Oncology Analyzer® are reported to have been used to estimate the prevalence of metastatic breast cancer and of second- or subsequent-line use of taxane therapy (data not provided)[9]. The prevalence rate of metastatic breast cancer, and of taxane use in the absence of paclitaxel albumin, are assumed to be constant over the five year time horizon and have been applied to Welsh population estimates from Office for National Statistics data[14]. Only patients currently treated with taxane monotherapy were considered eligible for paclitaxel albumin, and based on the company data these patients are currently split as 68% taking docetaxel and 32% taking sb-paclitaxel. The estimates of eligible patient numbers are reported to have been verified by company-sought Welsh expert clinician[9]. Uptake of paclitaxel albumin is stated to be 10% in year 1, rising to 30% in year 5[9]; however, there is a discrepancy between the annual number of patients reported in the submission to be taking each treatment and those reported in the actual model (this has subsequently been resolved). The individual patient cost data for paclitaxel albumin and the comparators sb-paclitaxel and docetaxel (including the drug acquisition costs, administration costs and costs of treating adverse effects, etc.) have been taken from the base case cost-effectiveness model (plus VAT at 17.5%) and multiplied by the eligible patient population estimates.

8.2 Results

The annual budget impact estimates included in the company submission are summarised in Table B. The economic model estimates cost savings with paclitaxel albumin associated with management of adverse effects and administration costs. The net budget impact is driven largely by drug acquisition costs.

Table B. Annual budget impact estimates for each of the next 5 years

	2010	2011	2012	2013	2014
No. of ≥ 2nd-line patients eligible for treatment	92	93	93	94	95
No. treated with sb-paclitaxel	27	26	25	24	23
No. treated with docetaxel	56	54	52	49	47
No. treated with paclitaxel albumin	9	13	17	21	25
Net impact on chemotherapy costs: (ignoring wastage)	£10,179	£14,207	£18,291	£22,431	£26,629
Net impact on chemotherapy costs (including wastage)	£13,058	£18,250	£23,515	£28,852	£34,263
Net impact (inc. admin costs, cost per mg)	£9,033	£12,604	£16,225	£19,896	£23,618
Net impact (inc. admin costs, inc. wastage)	£11,911	£16,647	£21,449	£26,317	£31,252
Net impact (inc. all costs) using a cost per mg approach to drug costs (ignoring wastage)	**£13,332**	**£18,614**	**£23,969**	**£29,399**	**£34,904**
Net impact (inc. all costs) using a cost per vial approach to incorporate potential wastage	**£16,210**	**£22,657**	**£29,193**	**£35,820**	**£42,538**

8.3 WMP Critique

The budget impact estimates are based on the overall cost estimates generated in the economic model. The limitations of the economic model (see section 8.4) therefore feed through to the budget impact analysis. It is not possible to verify the estimates of eligible patient numbers as these are based on market research data that have not been provided. The net budget impact estimates based on a cost per vial approach to drug costs, which incorporates the potential for drug wastage, would seem to be the more plausible of the two analyses.

8.4 Comparative unit costs

Table C provides example costs for paclitaxel albumin and comparator regimens. These are based on BNF list prices[5] and the assumption of patient body surface area 1.75m^2, as employed in the company's economic analysis[9]. Additional pre-medication is not included and vial wastage is assumed.

Table C. Example comparator costs

Regimen	Example doses	Approximate cost per 3-week cycle*[5]
Paclitaxel albumin (Abraxane®)	260mg/m^2 given once every three weeks	£1230
sb-paclitaxel (non-proprietary)	175mg/m^2 given once every three weeks	£668
Docetaxel (Taxotere®)	100mg/m^2 given once every three weeks	£1232
This table does not imply therapeutic equivalence of the regimens and doses *Based on patient body surface area 1.75m^2 and assumes wastage from unused vials		

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

Paclitaxel albumin (Abraxane®) should only be administered under the supervision of a qualified oncologist within a unit specialised in the administration of cytotoxic agents[1] and would not be deemed suitable for shared care.

9.2 Previous NICE advice

NICE Guidance on Advanced Breast cancer: diagnosis and treatment (CG81) February 2009[3]. See section 3.3.

9.3 Ongoing studies

The company submission highlights that no additional evidence is likely to be available within the next 6 to 12 months[9]. However, follow-up of patients in the CA201 trial (which compares efficacy and safety for paclitaxel albumin and sb-paclitaxel in Asian patients) is ongoing. Patient survival data for this study has not yet matured (35% of patients had died at the time of the analysis)[9].

9.4 Patient organisation information

One patient organisation submission was made by Breast care Cancer.

9.5 Medical expert summary

Medical expert views were provided.

.

REFERENCES

1. Abraxane®. Summary of Product Characteristics. Abraxis BioScience Limited. Aug 2009. Available at: http://www.emc.medicines.org.uk/. Accessed Dec 2009.
2. Abraxis BioScience Limited. Form A: Initial appraisal information. Abraxane®. March 09.
3. National Institute for Clinical Excellence (NICE) Guidance on Advanced Breast cancer: diagnosis and treatment (CG81) February 2009. Available at: http://www.nice.org.uk/nicemedia/pdf/CG81FullGuideline.pdf Accessed Dec 2009.
4. European Medicines Agency. European Public Assessment Report: Abraxane®. Aug 2009. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/abraxane/H-778-en6.pdf Accessed Dec 2009.
5. British Medical Association/Royal Pharmaceutical Society of Great Britain. British National Formulary No. 58. September 2009.
6. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Breast Cancer. Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed December 2009.
7. Taxotere®. Summary of Product Characteristics. Sanofi-aventis. Dec 2008. Available at: http://www.emc.medicines.org.uk/. Accessed Dec 2009.
8. Paclitaxel. Summary of Product Characteristics. Hospira UK Ltd. Jan 2009. Available at: http://www.emc.medicines.org.uk/. Accessed Dec 2009.
9. Abraxis BioScience Limited. Form B: Detailed appraisal information. Abraxane®. Nov 2009.
10. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005; 23: 5542-51.
11. Cooper NJ, Abrams KR, Sutton AJ, et al. A Bayesian approach to Markov modelling in cost-effectiveness analyses: application to taxane use in advanced breast cancer. J R Statist Soc A 2003; 166: 389-405.
12. Dranitsaris G, Cottrell W, Spirovski B, et al. Economic analysis of albumin-bound paclitaxel for the treatment of metastatic breast cancer. J Oncol Pharmacy Prac 2009; 15: 67-78.
13. Benedict A, Cameron DA, Corson H, et al. An economic evaluation of docetaxel and paclitaxel regimens in metastatic breast cancer in the UK. PharmacoEconomics 2009; 27: 847-59.
14. Office for National Statistics. Population estimates for UK, England, Scotland, Wales and Northern Ireland. Available at: http://www.statistics.gov.uk/statbase/Product.asp?vlnk=15106 (accessed 07 December 2009.
15. Therasse P, Arbuck SG, Eisenhauer et al (2000). New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer. National Cancer Institute of the United States. National Cancer Institute of Canada. J Natl Cancer Inst, 92(3): 205-216.

Appendix 1 Additional Clinical Information

Table 1A: Randomised trials directly comparing paclitaxel albumin versus sb-paclitaxel

Ref	Study type	No. patients	Inclusion/ exclusion criteria[9]	Baseline characteristics	Treatment regimens	Outcomes
CA012 [1,4]	Controlled, randomised multicentre, open-label, Phase III, non-inferiority study North America, UK, Russia and Ukraine	Randomised n=460 (ITT: n=454; PP: n=429) ITT (1st line treatment/ > 1st line treatment): Paclitaxel albumin: 97/132 sb-paclitaxel: 89/136	**Inclusion:** • Metastatic breast cancer, candidate for paclitaxel therapy in accordance with standard of care • Female, non-pregnant and not lactating ≥ 18 years • No relapse with breast cancer within one year of completing adjuvant sb-paclitaxel or docetaxel • No other malignancy within the past five years, except nonmelanoma skin cancer • Specified baseline haematology and clinical chemistry levels[9] • Expected survival of 12 ≥ weeks **Exclusion:** • brain metastases • Only evidence of metastasis was lytic or blastic metastases or pleural effusion or ascites. • Clinically serious concurrent illness • ECOG (Zubrod) performance status of > 2 • Unlikely to complete the study (Week 15 visit) • hormonal therapy within two weeks prior to first dose, chemotherapy (except for palliative bisphosphonate therapy for bone pain) within four weeks prior to first dose, investigational drug or immunotherapy within 4 weeks prior to first dose or concurrent radiation therapy (except for palliative radiotherapy for bone pain) • Had received paclitaxel or docetaxel because of metastatic carcinoma. • Pre-existing peripheral neuropathy of NCI CTC Grade ≥ 1	**Based on the global population (n=454):** Age (mean ± SD)[9]: Paclitaxel albumin: 53.1 ± 10.18 sb-paclitaxel: 53.3 ± 10.05 Postmenopausal[9]: Paclitaxel albumin: n=189 (83%) sb-paclitaxel: n=187 (83%) ECOG 1 or 2: 64% Previous anthracycline exposure: Paclitaxel albumin:77% sb-paclitaxel: 78% No prior chemotherapy: 14% Chemotherapy in adjuvant setting only: 40% Chemotherapy in the metastatic setting only: 40% Chemotherapy in both metastatic and adjuvant settings: 19%	Paclitaxel albumin 260 mg/m^2 infused IV over 30 minutes or sb-paclitaxel 175 mg/m^2 infused IV over three hours, administered every three weeks Administration of sb-pacltaxel was supported by prescription of premedication. Treatment duration: six cycles (18 weeks)	**Results for patients receiving >1st line therapy as assessed by the investigator (n=268):** Paclitaxel albumin versus sb-paclitaxel (ITT population) : Overall response rate(%)[1]: 26.5 (95%CI: 18.98 to 34.05;n=132) versus 13.2 (95%CI: 7.54 to 18.93;n=136); RR[9]= 2.003 (95% 1.196 to 3.355); p=0.006[a] Median time to disease progression (weeks)[1†] 20.9 (95% CI:15.7 to 25.9; n=131) versus 16.1 (95% CI: 15.0 to 19.3; n=135); p=0.011[b] Median progression free survival (weeks)[1†] 20.6 (95% CI: 15.6 to 25.9; n=131) versus 16.1 (15.0 to 18.3; n=135); p=0.010[b] ; HR=0.714[4] Survival (weeks)[1†]: 56.4 (95% CI: 45.1 to 76.9, n=131) versus 46.7 (95% CI: 39.0 to 55.3; n=136); p=0.020[b]; HR =0.726[4] EORTC QLQ-C30 questionnaire: Paclitaxel versus sb-paclitaxel (Pain symptom only): 3.8 (1.73) versus 2.7 (0.98); p=0.004

Table 1A continued

Ref	Study type	No. patients	Inclusion/ exclusion criteria[9]	Baseline characteristics	Treatment regimens	Outcomes
CA201[9]	Controlled, randomised, multicentre, open-label, Phase II study China	Randomised n=212 (ITT: n=210) 1st line treatment: n= 125 Paclitaxel albumin: n=61 Sb-paclitaxel: n=64 ≥ 2nd line treatment patients: n=85 Paclitaxel albumin: n=43 Sb-paclitaxel: n=42	**Inclusion:** • Female, non-pregnant, non-lactating and 18 to 70 years Histologically or cytologically confirmed breast cancer with evidence of reoccurrence or metastasis • No other malignancy, except non-melanoma skin cancer, CIS • ECOG performance status of ≤1 • Tumour(s) that were measurable by CT assessment. • Either had not received chemotherapy previously for metastatic breast cancer or had received chemotherapy for metastatic breast cancer and failed. • Specified baseline haematology and clinical chemistry levels • No symptoms of cardiac insufficiency at Baseline, ECG had no serious abnormality. • Expected survival of > 12 week **Exclusion:** • Clinical evidence of brain metastases. • Serious concurrent illness • In the investigator's opinion, unlikely to be able to complete the study through the follow-up visit • Received treatment with any other cytotoxic chemotherapy agent or investigational drug within 4 wks • Received taxane (paclitaxel or docetaxel) chemotherapy within 12 months as adjuvant therapy • Received a taxane as treatment for metastatic breast cancer • Pre-existing peripheral neuropathy of grade 2, 3, 4 • History of allergy or hypersensitivity to the study drug or any of its excipients (paclitaxel and human albumin) • Received any other cancer chemotherapy, immunotherapy, or radiotherapy within the past 4 weeks	**Based on the global population (n=210):** Age (mean ± SD)[9]: Paclitaxel albumin: 49.7 ± 9.70 sb-paclitaxel: 48.8 ± 9.03 Postmenopausal[9]: Paclitaxel albumin: n=77 (74%) sb-paclitaxel: n=69 (65%) Prior chemotherapy: Paclitaxel albumin: n=83 (80%) sb-paclitaxel: n=94 (89%) Prior adjuvant chemotherapy: Paclitaxel albumin: n=67 (64%) sb-paclitaxel: n=78 (74%) Prior hormone therapy: Paclitaxel albumin: n=43 (41%) sb-paclitaxel: n=52 (49%)	Paclitaxel albumin 260 mg/m^2 infused IV over 30 minutes or sb-paclitaxel 175 mg/m^2 infused IV over three hours, administered every three weeks Administration of sb-paclitaxel was supported by prescription of premedication. Treatment duration: One to six cycles	**Results for patients receiving >1st line therapy as assessed by the investigator:** Paclitaxel albumin versus sb-paclitaxel (n=85) : Overall response rate (n, %)[9]: 22/43, 51% versus 14/42 (33%); p=0.181

ECG = electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ITT=intention-to-treat; IV=intravenously ; NCI=National Cancer Institute; PP =per-protocol; RR=Relative Risk; SD= Standard Deviation; sb- = solvent-based;
[a]= Chi-Squared Test; [b]= Log Rank Test [†]= at cut off date 23 March 2005

Table 1B: Inclusion and exclusion criteria for indirect comparison

Criteria	CA012[9]	Jones et al.[10]
Inclusion	• Female, nonpregnant and not lactating and ≥18 years • Histologically or cytologically confirmed measurable metastatic breast cancer and was a candidate for paclitaxel therapy in accordance with standard of care • If patient had received paclitaxel or docetaxel as adjuvant therapy, she had not relapsed with breast cancer within one year of completing adjuvant paclitaxel or docetaxel. • No other malignancy within the past five years, except nonmelanoma skin cancer, CIN or CIS • Suitable candidate for single-agent paclitaxel treatment • Baseline haematology: ANC ≥ 1.5 x 10^9/L (1500 cells/mm^3), platelets ≥ 100 x 10^9/L (100,000 cells/mm^3) and haemoglobin ≥ 90g/dL • Baseline clinical chemistry levels: AST and ALT ≤ 2.5 x ULN range if no evidence of liver metastases, AST and ALT ≤ 5.0 x ULN and bilirubin ≤ 26 µmol/L (1.5 mg/dL) if evidence of liver metastases, total bilirubin ≤ 26 µmol/L (1.5 mg/dL), creatinine ≤ 177 µmol/L (2.0 mg/dL) and alkaline phosphate ≤ 5 x ULN (unless bone metastasis was present in the absence of liver metastasis). • Expected survival of 12 ≥ weeks	• Women 18 years or older • Adenocarcinoma of the breast and disease progression after one prior chemotherapy regimen for locally advanced or MBC, or with locally advanced or MBC that progressed during or within 12 months of completing an adjuvant or neoadjuvant chemotherapy regimen • Bidimensional, measurable disease; • Prior therapy with an anthracycline was required, unless medically contraindicated. • Baseline haematology: neutrophils ≥ 2,000/µL and platelets ≥ 100,000/µL; • AST and ALT level less than 3x the ULN if the alkaline phosphatase level was less than 5x the ULN, or AST and ALT less than 1.5x the ULN if alkaline phosphatase level was less than 2.5x the ULN; and creatinine ≤2 mg/dL.. a total bilirubin less than the upper limit of normal (ULN); • Karnofsky performance score (KPS) ≥ 60
Exclusion	• Clinical evidence of active brain metastases, including leptomeningeal involvement requiring steroid or radiation therapy. • Only evidence of metastasis was lytic or blastic metastases or pleural effusion or ascites. • Clinically serious concurrent illness. • ECOG (Zubrod) performance status of > 2. • Unlikely in Investigator's opinion to be able to complete the study through the Week 15 visit, • Had received treatment with hormonal therapy within 2 weeks prior to first dose, chemotherapy (except for palliative bisphosphonate therapy for bone pain) within 4 weeks prior to first dose, investigational drug or immunotherapy within 4 weeks prior to first dose or concurrent radiation therapy (except for palliative radiotherapy for bone pain). • Had received paclitaxel or docetaxel because of metastatic carcinoma. • Pre-existing peripheral neuropathy of NCI CTC Grade ≥ 1. • Allergy or hypersensitivity to study drug or any of its excipients. • Considered unsuitable to receive an experimental drug.	• Prior chemotherapy had to be completed at least 3 weeks before random assignment; exceptions were oral cyclophosphamide (two weeks) and nitrosoureas or mitomycin (six weeks). Prior hormonal therapy in the adjuvant and/or metastatic setting was allowed. • Patients with NCI CTC grade 2 or greater peripheral neuropathy or a history of hypersensitivity reaction to products containing polysorbate 80 or polyoxyethylated castor oil (Cremophor EL) were excluded. • Prohibited prior treatments included taxanes, bone marrow transplantation or stem-cell support, recent radiotherapy to bone marrow, surgery within the prior two weeks, and an investigational drug within four weeks of study registration.

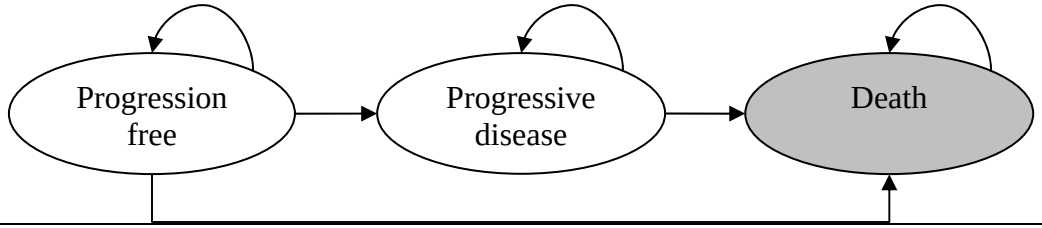
Table 1C: Response Criteria (RECIST guidelines)[15]

EVALUATION OF TARGET LESIONS	
Complete Response (CR):	Disappearance of all known disease and no new sites or disease related symptoms confirmed at least 4 weeks after initial documentation. All sites must be assessed, including non-measurable sites, such as effusions, or markers. Duration of response is ≥ 4 weeks
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameters confirmed at least 4 weeks after initial documentation. PR is also recorded when all measurable disease has completely disappeared, but a non-measurable component (i.e. ascites) is still present but not progressing. Duration of response is ≥ 4 weeks
Stable Disease (SD):	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. Duration of response ≥ 16 weeks since baseline
Progressive Disease (PD):	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started; or the appearance of one or more new lesions; or the unequivocal progression of a non-target lesion.
EVALUATION OF NON-TARGET LESIONS	
Complete Response (CR):	Disappearance of all non-target lesions confirmed at least 4 weeks after initial documentation.
Incomplete Response/Stable Disease (SD):	Persistence of one or more non-target lesions.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Response Assessment Methodology[4]:
Two primary datasets were used: a) the clinical investigators' assessments of response (Investigator Response Assessment Dataset) and b) an independent, blinded assessment of response based on radiological assessments made by a central radiology facility that was not otherwise associated with the study (IRL Response Assessment Dataset). A reconciliation algorithm was established to create a third, derived dataset (the Reconciled Response Assessment Dataset), which conservatively reconciled any differences between the other 2 datasets. The primary analyses of response in the original trials were based upon the target lesion response rate (TLRR) using the Reconciled Response Assessment Dataset; known as recTLRR. The recTLRR includes only target responses confirmed by Cycle 6 and represents a rigorous, conservative, prospective approach to minimise bias.

Appendix 2. Additional Health Economic Model Information

Table 2A. Health economic model detail[9]

Base Case Model		Appropriate?
Comparator(s)	Paclitaxel albumin 260mg/m^2 IV over 30mins, given 3-weekly compared against: i) sb-paclitaxel 175mg/m^2 IV over 3hrs, given 3-weekly; ii) Docetaxel 100mg/m^2 IV over 1hr, given 3-weekly	Yes – as requested by WMP
Population	Simulated cohort of patients meeting licensed indication. Assumed mean age approximately 53yrs (majority post-menopausal). Assumed body surface area 1.75m^2.	Yes – population meets licensed indication
Model type and description	State transition model, with cycle length 3 weeks. Based on progression-free survival and post-progression survival, using data from the direct and indirect comparisons. Once a patient leaves a health state it is not possible to return to that health state. Model summarised as:  	Yes
Perspective	Considers direct medical costs only, from perspective of NHS Wales	Yes
Time Horizon	5-year time horizon, based on modelling of trial data and company-sought expert opinion.	Yes – lifetime horizon of analysis would be appropriate, but the 5-year time horizon is reported to capture >99% of all deaths
Discount rate	3.5% per annum for costs (excluding adverse even costs) and outcomes (rates of 0% and 6% explored in sensitivity analyses)	Yes
Efficacy	Main efficacy outcomes driving the model are progression-free (PFS) and overall survival, derived from a sub-population of the phase III, open-label, non-inferiority trial of paclitaxel albumin versus sb-paclitaxel (CA012). Survival data from the trial for paclitaxel albumin has been extrapolated to the five year time frame using Weibull parametric modelling. For the comparator sb-paclitaxel, the hazard ratio from the Kaplan-Meier curves has been used to adjust the paclitaxel albumin PFS and survival curves generated by the Weibull modelling. For the comparator docetaxel, it is assumed in the base case analysis that paclitaxel albumin and docetaxel are equally efficacious (hazard ratio of 1.0 used) on the basis that an indirect comparison of efficacy data for docetaxel and paclitaxel albumin failed to demonstrate a statistically significant difference between the two agents, based on overall survival and time to progression (TTP). As TTP was numerically very similar to PFS in the trial of paclitaxel albumin and sb-paclitaxel (CA012), it is assumed that the hazard ratio for TTP is an appropriate proxy for the hazard ratio for PFS. The point estimate of the hazard ratio derived from this indirect comparison was 0.97 (95% CI 0.69 to 1.36) for overall survival and 0.85 (95% CI 0.61 to 1.19), which indicate numerically longer PFS and overall survival. The base case hazard ratios have been tested in sensitivity analyses in the range +/-30%.	Yes – the licensed indication is based on the sub-population of trial CA012, and so the use of data from this sub-population would seem appropriate. The Weibull modelling approach to survival for paclitaxel albumin treatment seems appropriate but the assumption of a hazard ratio for TTP, obtained from an indirect comparison of docetaxel and paclitaxel albumin, to model PFS for docetaxel is a limitation. The approach of using a hazard ratio of 1.0 to adjust the Weibull survival curves in the base case docetaxel comparison would favour paclitaxel albumin. The approach of using a hazard ratio of 1.0 for response rates in the base case analysis would favour docetaxel.

	Response rates for patients who are progression free are also derived from study CA012 for paclitaxel albumin and sb-paclitaxel, and from the indirect comparison for docetaxel. A hazard ration of 1.0 has been assumed in the base case analysis on the basis that the the point estimate derived from this indirect comparison was 0.53 (95% CI 0.23 to 1.19).	
Adverse effects	The costs of grade 3 or 4 adverse events that occurred in 3% or more of all patients in trial CA012 (not just the sub-population who meet the licensed indication) or the docetaxel arm using data from the indirect comparison were included in the model. These were reportedly guided by company-sought expert opinion. Utility decrements associated with adverse events are also incorporated.	The use of adverse event rates from the whole population of CA012, rather than for those meeting the licensed indication, is claimed to be conservative, as the rates of adverse events in the whole population is reported to be greater than in the sub-population. Assumptions about costs informed by expert opinion.
Utility values	Based primarily on those used in the NICE clinical guideline, 2009. These were based on elicitation studies using health professionals. A specific utility decrement is assumed for the adverse events of febrile neutropenia, and all other adverse events are assumed to attract a non-specific decrement based on response status.	Yes in the absence of other sources. Values derived from health professionals may deviate from those of patients.
Resource use	Based on assumptions and expert opinion.	Expert opinion may bias resource use estimates, and the submission indicates that there was significant uncertainty in the costs of adverse events, which have been tested in sensitivity analysis.
Costs	Non-drug resource use costed using weighted averages derived from published unit costs. Drug costs based on BNF list prices on a cost per mg basis, with a cost per vial basis (to take account of wastage) used as a secondary analysis.	The sources of cost data are appropriate. Costing drugs on a per mg basis leads to more favourable results that do not take account of potential drug wastage versus the cost per vial approach.
Model Provided?	Yes	Yes
Other considerations	Sensitivity analyses have been conducted only around the analyses in which doses are costed on a per mg basis.	It would have been useful for the company to provide sensitivity analyses around a base case analysis in which drug wastage is accounted for.