paclitaxel albumin powder for suspension for infusion (contains 100mg paclitaxel as paclitaxel albumin) (Abraxane®) No. (556/09) Abraxis BioScience Limited

05 March 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

paclitaxel albumin (Abraxane®) is accepted for restricted use within NHS Scotland.

Licensed indication under review: 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.

SMC restriction: Use is restricted to patients who would otherwise receive docetaxel or 3-weekly solvent-based paclitaxel as second-line treatment for metastatic breast cancer.

In one study the overall response rate for paclitaxel albumin was significantly superior to solvent-based paclitaxel in a subgroup analysis of patients who had previously received one or more lines of therapy for metastatic disease.

The health economic case was only demonstrated for a subset of the licensed indication which is the basis for the SMC restriction.

Note that paclitaxel albumin may have substantially different pharmacological properties compared to other formulations of paclitaxel and is licensed for use in a 3-weekly dosage schedule.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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.

Dosing information

Paclitaxel 260mg/m^2 (as paclitaxel albumin) administered intravenously over 30 minutes every 3 weeks.

Paclitaxel albumin should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents.

Product availability date

12 January 2009

Summary of evidence on comparative efficacy

Paclitaxel albumin is a solvent free nanoparticle albumin bound paclitaxel powder for suspension for infusion that eliminates solvent related toxicities.

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication namely, the licensed population who, in addition, would otherwise be considered for standard solvent-based (sb) paclitaxel or docetaxel.

One phase III randomised, controlled, multi-centre, open-label, outpatient, non-inferiority study has been conducted to evaluate the safety/tolerability and anti-tumour effect of paclitaxel albumin compared with sb-paclitaxel in women with histologically or cytologically confirmed measurable metastatic breast cancer. Eligible patients were candidates for single-agent paclitaxel therapy who had failed prior adjuvant or metastatic chemotherapy, had not received paclitaxel or docetaxel for treatment of metastatic carcinoma and had an Eastern Cooperative Oncology Group performance status ≤2.

Patients were randomised equally (and stratified according to prior anthracycline use) to paclitaxel albumin 260mg/m^2 intravenously (iv) over 30 minutes without steroid pre-medication and without granulocyte-colony stimulating factor (G-CSF) prophylaxis (unless regimen modification failed to prevent neutropenia) or to sb-paclitaxel 175mg/m^2 iv over 3 hours. Patients treated with sb-paclitaxel received standard pre-medication in line with the manufacturer's guidance from the country in which the study was being conducted. Both regimens were repeated every three weeks for six cycles. Patients without progressive disease (PD) after six cycles could continue their assigned treatment at the investigator's discretion provided the pre-specified withdrawal criteria had not been met.

The primary efficacy endpoint was the proportion of patients who achieved a confirmed complete response (CR) or partial response (PR) according to RECIST guidelines. The primary efficacy analysis included two types of response: target lesion and overall (target and non-target lesions). For the target lesion response rate (recTLRR), the primary analysis used a reconciliation of two datasets (investigators' assessment and assessments by an Independent Radiology Laboratory [IRL]) according to a predefined algorithm.

In addition, the overall response rate obtained from the investigators' assessment (invORR) was analysed and was considered more clinically meaningful than the recTLRR as it included non-target lesions. The primary efficacy analysis consisted of three nested tests which were conducted sequentially, contingent on the prior tests being successful; non-inferiority with all patients stratified by first-line versus >first-line therapy; superiority with all patients stratified by first-line versus >first-line therapy and superiority tested for first-line therapy patients only. Secondary endpoints included time to progression (TTP), overall survival, quality of life and safety.

The intent-to-treat (ITT) population comprised 454 patients and 268 patients (59%) received the study drugs for second-line or later therapy. In the ITT population the invORR was significantly greater for paclitaxel albumin (33% [76/229]) than for sb-paclitaxel (19% [42/225]); Risk Ratio (RR) 1.75; 95% confidence interval (CI) 1.27 to 2.42. In addition, for the subgroup analysis in patients receiving second-line or later therapy (relevant to the indication under review) the invORR was 27% (35/132) versus 13% (18/136); RR 2.00, 95% CI 1.20 to 3.36. The recTLRR in the ITT population was 24% (55/229) versus 11% (25/225) and was significantly superior for the paclitaxel albumin group (RR 2.11; 95% CI 1.38 to 3.24).

The median TTP in the ITT population was significantly longer for paclitaxel albumin (23.0 weeks) than for sb-paclitaxel (16.9 weeks); HR 0.75. In the subgroup analysis of patients receiving second-line or later therapy the median TTP was also superior for the albumin paclitaxel group (20.9 weeks versus 16.1 weeks; HR=0.73, p=0.020). In the ITT population there was a trend for increased median overall survival in the paclitaxel albumin group (65.0 weeks versus 55.7 weeks). However in the subgroup analysis of patients receiving second-line or later therapy the median overall survival was significantly longer for patients treated with paclitaxel albumin (56.4 weeks) than for sb-paclitaxel (46.7 weeks); HR=0.73, p=0.024.

Patient health related quality of life was assessed using the European Organisation of Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, version 3, which contains 30 items grouped into scales. Virtually no statistically significant differences between the treatment groups were noted in baseline values and mean change from baseline to each visit for scale scores.

Summary of evidence on comparative safety

In the pivotal study adverse event (AE) related discontinuations, dose reductions and dose delays were infrequent (3 to 7%) with no significant differences between groups despite the average dose intensity in the paclitaxel albumin group being approximately 50% higher than in the sb-paclitaxel group.

For the ITT population the incidences of sensory neuropathy (71% versus 56%), nausea (30% versus 21%), diarrhoea (26% versus 15%) and vomiting (18% versus 10%) were significantly higher in the paclitaxel albumin than the sb-paclitaxel group. Gastrointestinal toxicities were easily managed and were rarely grade 3 or 4. However, neutropenia (34% versus 49%) and flushing (2.6% versus 14%) were significantly more common in patients treated with sb-paclitaxel. Febrile neutropenia was uncommon in both groups and no septic deaths occurred. No severe treatment-related hypersensitivity reactions occurred in patients on paclitaxel albumin despite absence of pre-medication compared with five patients treated with sb-paclitaxel who experienced grade 3 hypersensitivity reactions. However, in post-marketing surveillance rare reports of severe hypersensitivity reactions have been reported.

AE rates in the subgroup of patients receiving second-line or later therapy were similar to the whole population.

There were 14 deaths in patients whilst on study and all were as a result of disease progression. One death (on sb-paclitaxel) was considered by the investigator to be possibly related to treatment but may also have been as a result of sepsis and/or disease progression.

The European Medicines Agency (EMEA) noted that in the pivotal study the most common AEs related to treatment with paclitaxel albumin were qualitatively not different from the known AEs related to currently registered paclitaxel formulations.

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication, namely the licensed population who, in addition, would otherwise be considered for standard sb-paclitaxel or docetaxel.

Results of the pivotal study showed the superiority of paclitaxel albumin over sb-paclitaxel for the primary endpoint of invORR and this was also observed in subgroup analyses of patients receiving second-line or later therapy (relevant to the indication under review). Although the study was not powered for the subgroup analysis, thus limiting meaningful conclusions, the EMEA considered that the risk-benefit balance of paclitaxel albumin 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, was favourable. However a trend toward shorter survival in patients on paclitaxel albumin compared with those on sb-paclitaxel was observed in the sub-group of patients receiving first-line therapy and this group was not included in the licensed indication.

In the pivotal study the percentage of patients treated first-line for metastatic disease was 41% compared with 42%, 13% and 4.4% of patients who were treated as second-line, third-line and fourth-line or greater and this was comparable between treatment groups.

The summary of product characteristics for paclitaxel albumin notes that it is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared with other formulations of paclitaxel. Consequently it is not interchangeable with other paclitaxel formulations or dosage schedules. Moreover the albumin stabiliser avoids the use of castor-oil-based or tween surfactants that necessitate pre-medication to avoid hypersensitivity reactions. This formulation means that there is no requirement for pre-medication prior to paclitaxel albumin administration and it may be infused over 30 minutes compared with three hours and one hour for sb-paclitaxel and docetaxel respectively. This may offer efficiency benefits to patients and health services.

An indirect comparison was included in the company's submission in order to compare paclitaxel albumin with docetaxel. Data from the subgroup of patients receiving second-line or later therapy from the pivotal study presented previously was compared with a study of docetaxel versus sb-paclitaxel. Results of the indirect comparison suggested that there was no significant difference in efficacy between paclitaxel albumin and docetaxel. Significant differences in AE rates that favoured paclitaxel albumin were noted for neutropenia, stomatitis and peripheral oedema. However limitations of the indirect comparison included the open-label design of the studies, use of a subgroup, uncontrolled therapy following study discontinuation and differences in the proportion of patients who had received prior metastatic treatment.

Summary of comparative health economic evidence

The manufacturer proposed a sub-set role, as second- or third-line treatment for metastatic breast cancer where docetaxel or sb-paclitaxel would otherwise have been used. The manufacturer therefore presented two cost utility analyses, against docetaxel and against sb-paclitaxel. Experts indicated that docetaxel was the more relevant comparator. Both analyses took a lifetime perspective and estimated QALYs as well as costs - covering costs of the medicines, administration, management of adverse events and treatment of the disease as it progressed. Resource use and utilities were taken from a recent National Institute for Health and Clinical Excellence (NICE) clinical guideline on managing advanced breast cancer.

The clinical evidence for the comparison with docetaxel came from an indirect comparison based on one docetaxel trial and a subgroup reflecting the licensed indication in the pivotal clinical trial of paclitaxel albumin described above. The comparison had limitations because the docetaxel data could not be restricted to patients being treated in second or third-line alone. The manufacturer suggested that there was evidence of equal efficacy. Including the costs of adverse events, which were stated to be lower with paclitaxel albumin, the results indicated that paclitaxel albumin dominated docetaxel, because it was £697 less expensive per patient and yielded 0.0037 more QALYs. While the indirect comparison had limitations, it suggested that paclitaxel albumin is no less effective than docetaxel in terms of overall response and similar in terms of TTP and overall survival, and adverse event rates may be lower.

Clinical evidence for the comparison with sb-paclitaxel came from the subgroup reflecting the licensed indication in the pivotal clinical study, with extrapolation used to extend curves based on data for progression-free survival and overall survival to the patients' expected lifetimes. For paclitaxel albumin compared to sb-paclitaxel, the incremental lifetime cost was £4,137 and the incremental QALYs 0.1641, giving a net cost per QALY gained of £25,209.

Sensitivity analysis suggested that the key factors influencing the ICER were survival estimates, cost per cycle of chemotherapy, utility values and progression rates. Wastage of unused vials (potentially the more likely scenario, given the manufacturer's estimate of patient numbers) reduced the cost-effectiveness of paclitaxel albumin so that it was very close to £30k/QALY. However, the technique used to fit a curve to trial data for extrapolation purposes produced a relatively poor fit and when a better fitting curve was used the cost per QALY for the base-case fell to just over £20,000 per QALY. This suggested that the economic case based upon the 'best fit' survival curve together with vial wastage would still be acceptable.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 84, *Management of Breast Cancer in Women* in 2005. The guideline notes that taxanes, capecitabine or vinorelbine should be considered in patients with advanced disease. However SIGN could not make a firm recommendation of the precise place of capecitabine and vinorelbine in the

treatment of advanced breast cancer due to paucity of randomised trials. A need for an update to this guideline is currently being considered.

NICE published clinical guidance 81, *Advanced breast cancer: diagnosis and treatment* in February 2009 (updating and replacing NICE technology appraisal guidance 62, 54 and 30). The guideline notes that 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 in the following sequence:

- first-line: single-agent docetaxel
- second-line: single-agent vinorelbine or capecitabine
- third-line: single-agent capecitabine or vinorelbine (whichever was not used as 2nd line treatment).

It also notes that gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.

Additional information: comparators

Single agent docetaxel, paclitaxel, capecitabine or vinorelbine and gemcitabine/paclitaxel are used in patients with advanced breast cancer not suitable for treatment with an anthracycline.

Cost of relevant comparators

Drug	Dose regimen	Cost per 3 weeks (£)
Single agents		
paclitaxel albumin	**260mg/m^2 iv on day 1 of a 21 day cycle**	**1,230**
docetaxel*	100mg/m^2 iv on day 1 of a 21 day cycle	1,232
(sb) paclitaxel*	175mg/m^2 iv on day 1 of a 21 day cycle	668
vinorelbine	60mg/m² orally administered once weekly increased to 80mg/m^2 from week 4	726 to 924
vinorelbine	25 to 30 mg/m^2 iv once weekly	417 to 504
capecitabine	1.25g/m^2 orally twice daily on days 1 to 14 of a 21 day cycle	317
Combination therapy		
gemcitabine/ (sb)-paclitaxel	1,250mg/m^2 iv on days 1 and 8 175mg/m^2 iv on day 1	1,444

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 16 December 2009, BNF edition 58 (September 2009) and MIMS (December 2009). iv=intravenous. Costs based on a body surface area of 1.8m^2. * Costs do not include pre-medication regimens.

Additional information: budget impact

Based on an assumption of 160 patients in Scotland and a market share rising from 10% in Year 1 rising to 30% by Year 5, the manufacturer estimated net budget impact for the NHS to be £30k rising to £78k and the net medicines impact to be £32k rising to £83k. However, this assumed that there is a 50% discount at local health board level on sb-paclitaxel.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including ***05 February 2010.***

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

The undernoted reference was supplied with the submission. The reference shaded grey is additional to that supplied with the submission.

Gradishar WJ, Tjulandin S, Davidson N, Shaw H, et al (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol, 23: 7794-7803.

The European Medicines Agency (EMEA) European Public Assessment Report. Paclitaxel albumin (Abraxane®). EMEA/47053/2008 **www.emea.europa.eu**.