Scottish Medicines Consortium

Re-Submission

gemcitabine 200mg and 1g powder for solution for infusion (Gemzar®) (No. 154/05)

Eli Lilly and Company Ltd

10 November 2006

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 resubmission

gemcitabine (Gemzar®), in combination with paclitaxel, is accepted for restricted use within NHS Scotland for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

Gemcitabine in combination with paclitaxel modestly improves outcomes, compared to paclitaxel monotherapy, in those previously treated with an anthracycline.

For this indication gemcitabine is restricted to use by oncologists specialising in the treatment of breast cancer.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

In combination with paclitaxel, for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

Dosing information

Gemcitabine 1250mg/m^2 as a 30-60 minute intravenous infusion on days 1 and 8 of each 21-day cycle. This is recommended in combination with paclitaxel 175mg/m^2 which should be given first on day 1 as a 3 hour intravenous infusion.

Product availability date

November 2004

Summary of evidence on comparative efficacy

The evidence to support this licence extension comes from the results of one open-label phase III study which has not yet been published in full. The results given here are from abstract reports and presentations of an interim analysis and data on file.

The study enrolled females aged at least 18 years with unresectable, locally recurrent or metastatic breast cancer who had received adjuvant anthracycline-containing chemotherapy. Patients were also required to have adequate organ function and bone marrow reserve and a Karnofsky Performance Status score $\geq$ 70 (measured on a scale of 0 to 100 with 70 equating to being at least able to self-care, but unable to work or carry out other normal activities).

Five hundred and twenty-nine patients were randomised to receive gemcitabine (1250mg/m^2) on days 1 and 8 plus paclitaxel (175mg/m^2) on day 1 (n=267) or paclitaxel (175mg/m^2) alone on day 1 (n=262) of each 21-day cycle. Treatment was to continue until disease progression or development of unacceptable toxicity. The primary endpoint of the study was initially planned to be progression-free survival but the Food and Drug Administration requested that this was changed to overall survival, and that a planned interim analysis be added, using time to documented progression of disease (TtDPD) as the primary endpoint.

The median number of cycles given was 6 and 5 for the combination and paclitaxel monotherapy arms. The results of this planned interim analysis found that the TtDPD was 5.4 (95% confidence interval [CI]: 4.6, 6.1) months in the combination arm and 3.5 (95% CI: 2.9, 4.0) months in the paclitaxel monotherapy arm (p=0.0013) equating to a hazard ratio of 0.73 (95% CI: 0.61, 0.89), p=0.0015. The overall response rates, as assessed by the investigator, were 39% and 26%, respectively (p=0.0007). Overall survival has been reported after a median follow-up of 16 months when approximately 75% of the deaths needed for the final survival report had occurred. At this interim point, the overall survival was 18.5 (95% CI: 16.5, 21.2) months in the paclitaxel/gemcitabine arm and 15.8 (95% CI: 14.4, 17.4) months in the paclitaxel arm (p=0.018) equating to a hazard ratio of 0.78. One-year survival in the combination arm was 71% compared to 61% in the monotherapy arm (p=0.019).

Whilst patients receiving gemcitabine plus paclitaxel reported significant improvements in quality of life compared to paclitaxel monotherapy from baseline towards the end of treatment (by cycles 5 and 6), there were no statistically significant improvements in global quality of life, pain relief or analgesia level between the two treatment groups when averaged over time.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The main dose-limiting toxicity associated with gemcitabine is suppression of the bone marrow. During the key study described above, the incidence of haematological adverse events was higher in the gemcitabine/paclitaxel arm than in the paclitaxel arm. The following were reported at grade 3 and 4 levels of severity: neutropenia 48% versus 11%, leukopenia 11% versus 1.5%, anaemia 6.8% versus 2.3% and thrombocytopenia 5.7% versus 0%. Febrile neutropenia was reported in 5.0% of combination and 1.2% of monotherapy treated patients. The only non-haematological adverse event to occur significantly more often in the gemcitabine/paclitaxel arm was fatigue (6.5% versus 1.6%).

Summary of clinical effectiveness issues

The likely clinical effectiveness of the gemcitabine/paclitaxel combination is difficult to predict. Available data suggest that the combination does offer modest advantages over paclitaxel alone in terms of time to progression, response rates and survival. However publication of final results is awaited.

Guidance from the Scottish Intercollegiate Guidelines Network (SIGN) recommends that anthracyclines should be prescribed in preference to non-anthracycline regimens in the adjuvant setting. Taxanes are therefore more likely to be considered earlier in practice for patients with advanced disease. However, it is unclear how this proposed combination compares in terms of survival and toxicity to docetaxel monotherapy and to the licensed combination of docetaxel and capecitabine. Available data from indirect comparisons, one comparative study and a Cochrane systematic review suggest that docetaxel may be more effective than paclitaxel.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing gemcitabine plus paclitaxel with 4 other taxane-based treatments; gemcitabine plus docetaxel, docetaxel monotherapy, paclitaxel monotherapy, and docetaxel plus capecitabine. Gemcitabine plus paclitaxel is licensed for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy, where prior therapy should have included an anthracycline unless clinically contraindicated. A Markov model with a 3-year time horizon was used and the main data source was a pooled analysis of a number of studies involving the relevant treatments. The manufacturer estimated a cost/QALY of £17,168 compared to treatment with docetaxel monotherapy. The cost/QALY when anthracycline-naïve patients were excluded was estimated at £16,534. An analysis was also provided using the reduced cost of paclitaxel post-patent expiration, which reduced the cost/QALY estimate.

The manufacturer has used a number of possible comparators in the analysis. This is not inappropriate as there does not appear to be single comparator for this particular patient population as treatment often depends on what prior therapy patients receive in the adjuvant setting. In general, it appears that costs and resource use data have been handled appropriately and the appropriate sources were used. It appears from the analysis that the results produced are generally robust to changes in the model parameters. The sensitivity

analysis did not include varying the transition probabilities used in the model, which may have impacted on the results.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In 2001, National Institute for Health and Clinical Excellence (NICE) guidance recommended taxanes (docetaxel and paclitaxel) as an option for the treatment of advanced breast cancer where initial cytotoxic chemotherapy (including an anthracycline) has failed or is inappropriate. In 2003, capecitabine in combination with docetaxel was recommended in preference to docetaxel monotherapy in patients in whom anthracycline-containing regimens are unsuitable or have failed. In addition, capecitabine monotherapy was recommended as an option for patients with locally advanced or metastatic breast cancer who have not previously received capecitabine in combination therapy. In 2002, vinorelbine monotherapy was recommended as one option for second-line or later therapy for advanced breast cancer when anthracycline-based regimens have failed or are unsuitable.

SIGN guidance on the management of breast cancer in women (No. 84) was updated in January 2006. This recommends that

- anthracyclines be used in preference to non-anthracyclines in the adjuvant setting.
- taxanes should be considered in patients with advanced disesase.
- either capecitabine or vinorelbine be considered for patients with advanced breast cancer.

Additional information: previous SMC advice

The SMC has issued advice on two chemotherapeutic agents for advanced breast cancer:

In March 2003, capecitabine was recommended for restricted use in NHS Scotland by oncologists with appropriate expertise in treating locally advanced/metastatic breast cancer. It is an orally active treatment which has improved outcomes both as monotherapy in those previously treated with an anthracycline and a taxane and in combination with docetaxel in those previously treated with an anthracycline.

In January 2004, pegylated liposomal doxorubicin (Caelyx®) was not recommended for use within NHS Scotland. This pegylated liposomal formulation of doxorubicin hydrochloride is now licensed as monotherapy for the treatment of metastatic breast cancer where there is an increased cardiac risk. An inconclusive study has suggested that it was not inferior to conventional doxorubicin in terms of progression-free survival.

It was less cardiotoxic than conventional doxorubicin, but was associated with other troublesome adverse events, particularly palmar-plantar erythrodysesthesia. The product is significantly more expensive than the standard preparation and its cost-effectiveness in managing metastatic breast cancer has not been addressed by the company in their submission.

In February 2005, the SMC considered a full submission for gemcitabine and issued the following guidance, Gemcitabine (Gemzar®) in combination with paclitaxel for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant

chemotherapy is not recommended for use within NHS Scotland. Gemcitabine in combination with paclitaxel has improved outcomes, compared to paclitaxel monotherapy, in those previously treated with an anthracycline. However the economic case has not been demonstrated.

Additional information: comparators

Other taxane based regimens of which docetaxel plus capecitabine is preferred according to NICE; other taxane options include docetaxel or paclitaxel monotherapy. Capecitabine and vinorelbine are also licensed for advanced breast cancer but are more likely to be used after taxane therapy has failed.

Additional information: costs

Drug	**Dose** (assuming body surface area 1.6m^2)	**Cost per cycle / 21 days**
Combination regimens		
Gemcitabine	**1250mg/m^2 (2g) IV on days 1 and 8**	**£651**
Paclitaxel	**175mg/m^2 (280mg) IV on day 1**	**£1010 Total: £1661**
Docetaxel	75mg/m^2 (120mg) IV on day 1	£860
Capecitabine	1250mg/m^2 (2g) orally twice daily on days 1 -14	£275 Total: £1135
Single agents		
Docetaxel	100mg/m^2 (160mg) IV on day 1	£1070
Paclitaxel	175mg/m^2 (280mg) IV on day 1	£1010
Capecitabine	1250mg/m^2 (2g) orally twice daily on days 1-14	£275
Vinorelbine	25-30mg/m^2 (40-48mg) IV weekly	£357-£420 / 21 days

Doses are shown for general comparison and do <u>not</u> imply therapeutic equivalence.

Additional information: budget impact

The manufacturer estimated net budget impact of £147K in year 1, rising to £797K in year 5. The net budget impact with reduced price paclitaxel for years 1 and 5 is £58K and £314K respectively. This is based on 36 patients in year 1 and 194 patients in year 5.

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 02 November 2006.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

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.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Jones SE, Erban J, Overmoyer B et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. Journal of Clinical Oncology 2005; 23: 5542-51.

Ghersi D, Wilcken N, Simes J et al. Taxane-containing regimens for metastatic breast cancer. The Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD 003366. DOI: 10.1002/14651858.CD003366.pub2