PUBLIC SUMMARY DOCUMENT
Product: Capecitabine, tablet, 150 mg and 500 mg, Xeloda®
Sponsor: Roche Products Pty Limited
Date of PBAC Consideration: March 2010

1. Purpose of Application

To provide a revised economic analysis of the administration costs associated with capecitabine treatment compared to 5-fluorouracil (5-FU) when used in combination with cisplatin for the treatment of previously untreated advanced oesophago-gastric cancer following deferral at the July 2009 PBAC meeting.

2. Background

In July 2009, the PBAC deferred a submission to extend capecitabine's Authority required listing to include treatment, in combination with a platinum-based regimen, of a patient with previously untreated advanced oesophago-gastric cancer with a WHO performance status of 2 or less, so that issues regarding the cost of the diagnostic related groups (DRGs) and the magnitude of the cost offsets could be resolved. The main matter of concern to the PBAC was the use of resources to offset the higher drug cost requested for capecitabine. The PBAC considered that the administration costs associated with 5-FU had been overestimated so that the higher cost of capecitabine could be offset.

The PBAC accepted that 5-FU was the appropriate comparator. The PBAC noted that the submission presented one randomised open-label triplet chemotherapy trial (REAL-2) which compared capecitabine plus epirubicin (either with oxaliplatin or cisplatin) with 5-FU plus epirubicin (either with oxaliplatin or cisplatin) in patients with oesophago-gastric cancer (OGC). The PBAC also noted that oxaliplatin was not PBS listed for use in OGC and was much more expensive than cisplatin. Therefore, the PBAC considered that any future restriction proposed by the sponsor should include use of capecitabine with cisplatin only rather than platinum-based therapies. The current submission was in accordance with this advice and requested capecitabine use with a cisplatin-based regimen only.

For further details see the capecitabine Public Summary Document for the July 2009 PBAC meeting at www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-capecitabine-jul09.

3. Registration Status

Capecitabine was registered by the TGA in February 2009 for first line treatment of patients with advanced oesophagogastric cancer in combination with a platinum-based regimen.

4. Listing Requested and PBAC's View

Authority required
Treatment, in combination with a cisplatin-based regimen, of a patient with previously untreated advanced oesophago-gastric cancer with a WHO performance status of 2 or less.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

For patients with locally advanced growth or metastases, the main therapeutic option is chemotherapy. 5-FU has been the backbone of chemotherapy in advanced oesophago-gastric cancer for over forty years and is among the most active single agents against metastatic oesophago-gastric cancer. Combination chemotherapy using two or three-drug combinations has produced higher response rates and longer disease-free survival (DFS) compared with 5-FU alone, with incremental toxicity. Capecitabine would provide an oral alternative to 5-FU in the above treatment algorithms, which the submission claimed may be more convenient for patients and less resource intensive than continuous infusions of 5-FU.

6. Comparator

The submission nominated 5-fluorouracil (5-FU) as the main comparator. This is as previously agreed by the PBAC.

7. Clinical Trials

No changes have been made to the trial data presented in the previous submission: one randomised open-label triplet chemotherapy trial (REAL-2) comparing capecitabine plus epirubicin (either with oxaliplatin or cisplatin) with 5-FU plus epirubicin (either with oxaliplatin or cisplatin) in patients with advanced OGC; and one randomised open-label doublet chemotherapy trial (ML17032) comparing capecitabine plus cisplatin with 5-FU plus cisplatin in patients with advanced gastric cancer. The citations for the REAL-2 and ML17032 trials may be found in the Public Summary Document from the July 2009 PBAC meeting.

8. Results of Trials

No new efficacy data were presented in the re-submission. A summary of the primary efficacy analyses of the REAL-2 and ML17032 trials is presented in the capecitabine Public Summary Document for the July 2009 PBAC meeting.

A summary of the secondary analyses from the REAL-2 trial of overall survival (OS) and progression-free survival (PFS) in the ITT population showed that there was no statistically significant difference in OS between the epirubicin and cisplatin plus capecitabine (ECX) and epirubicin and cisplatin plus 5-FU (ECF) treatment arms [HR = 0.92 (95 % CI: 0.76, 1.11)]. The results were similar for PFS [HR = 0.98 (95 % CI: 0.82, 1.17)].

The PBAC previously accepted that capecitabine is non-inferior in terms of comparative effectiveness over 5-FU.

No new toxicity data were presented in the re-submission. A summary of the safety results from the REAL-2 and ML17032 trials is presented in the capecitabine Public Summary Document for the July 2009 PBAC meeting.

For PBAC's view, see Recommendations and Reasons.

9. Clinical Claim

The re-submission described capecitabine as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over 5-FU. This was unchanged from the previous submission and was previously accepted by the PBAC.

For PBAC's view, see Recommendations and Reasons.

10. Economic Analysis

The resubmission presented two cost minimisation analyses: one for triplet therapy based on the REAL-2 study (ECX versus ECF) and one for doublet therapy based on the ML17032 study (CX versus CF). This is appropriately changed from the previous submission which provided a weighted analysis of doublet and triplet therapy. Cost of drug acquisition was calculated using trial-based mean cumulative doses, which is one of three approaches presented in the original submission. This approach is reasonable.

The difference in pharmaceutical acquisition costs between the capecitabine containing arms and the 5-FU containing arms are offset by differences in the cost of preparation and drug administration (includes costs of visits and central venous access devices (CVAD) placements and removals). The analysis excludes the cost of adverse events, which is unchanged from the previous submission and may not be reasonable, and tumour assessment costs, which is changed from the previous submission and is appropriate.

Costs were estimated for five treatment settings compared to two in the previous submission. These were then weighted to arrive at the final estimate of total costs. The weights applied to distribute patients across treatment settings are uncertain and may not be appropriate. The sensitivity analyses presented were limited and did not address many of the previous concerns of the PBAC regarding uncertainty surrounding the costs of chemotherapy administration and CVAD removal. Furthermore, there was no analysis of the impact of variation in the treatment survey responses other than the proportion of patients requiring a CVAD through the worse/best case scenario analysis.

During the evaluation of the Submission, further sensitivity analyses were conducted, including changes to various cost estimates and changed treatment setting weights. When all proposed changes were incorporated, the use of capecitabine in triplet and doublet chemotherapy regimens remained cost-saving, however the cost savings are not to the PBS.

The cost savings that accrue as a result of using the intervention in preference to the comparator are not in terms of PBS items. The savings are derived through the cost of drug administration, which are; MBS item numbers, prostheses costs, and the cost of drug administration in hospitals. Although the intervention is not cost-saving to the PBS, the intervention is cost saving from a government health budget perspective.

For PBAC's view, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients was <10,000 in Year 1 and the financial cost per year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated to be < $10 million in Year 1.

12. Recommendation and Reasons

The PBAC recommended listing of capecitabine for treatment of advanced oesophago-gastric cancer in combination with cisplatin-based regimen on a cost-minimisation basis with 5-fluorouracil. The equi-effective doses are capecitabine 625 mg/m^2 twice daily and 5-fluorouracil 200 mg/m^2 per day (triplet therapy) and capecitabine 1000 mg/m^2 twice

daily for 14 days of each 3 week cycle and 5-fluorouracil 800 mg/m^2 continuous infusion day 1 to 5 of each 3 week cycle (doublet therapy).

The PBAC considered that the stage of the disease should be added to the restriction as this reflects the patient population enrolled in the clinical trials. The PBAC also considered that doublet therapy should be allowed even though it is not as effective as triple therapy but would provide clinicians with an alternative treatment option for patients in whom epirubicin cannot be tolerated or is contraindicated.

No changes had been made to the trial data presented in the previous submission. However, the PBAC noted the updated results of the REAL-2 study with respect to a secondary analysis of the trial data, which was not published at the time of the first submission. The analysis found that there was a significantly higher rate of venous thromboembolic events (TEs) in the ECX arm compared to the ECF arm when CVAD-related thrombosis was excluded (9.1 % vs 4.4 %, p=0.038). However, the PBAC considered that the overall incidence of TEs was more clinically relevant and agreed with the Pre Sub-Committee Response that CVAD-related thrombosis events should not be excluded. When all thromboembolic events were examined, the incidence of thromboembolism for ECX compared with ECF was not significantly different (13.3 % versus 16.9 %, p=0.267).

The re-submission presented two cost minimisation analyses, one for triplet therapy based on the REAL-2 study (ECX versus ECF) and one for doublet therapy based on the ML17032 study (CX versus CF). The PBAC considered this to be appropriate. Cost of drug acquisition was calculated using trial-based mean cumulative doses.

The PBAC noted that the difference in pharmaceutical acquisition costs between the capecitabine containing arms and the 5-FU containing arms are offset by differences in the cost of preparation and drug administration (includes costs of visits and CVAD placements and removals). Changes in the methodology compared to the previous submission included:

- an increase in the drug preparation fee;
- the use of MBS item costs in the private treatment settings;
- a change in the AR-DRG code used to cost CVAD placements and removals;
- the type of CVAD used, when placed and removed; and
- the introduction of the type and costs for use of infusion devices.

The approach to calculate the cost-offsets was considered appropriate. However, the following uncertainties were identified. Costs were estimated for five treatment settings compared to two in the previous submission. These were weighted to arrive at the final estimate of total costs. The PBAC noted that for triplet therapy, the difference between ECX and ECF total treatment cost per patient across the settings varies from cost savings of $2,874 to $7,821, with a weighted differential cost saving of $5,291. For doublet therapy, the difference between CX and CF total treatment cost per patient across the settings varies from a cost saving of $537 to $3,764, with a weighted differential cost saving of $2,142. The PBAC considered that the weights applied to distribute patients across treatment settings were uncertain and may not be appropriate. However, the PBAC noted that regardless of the weights used, capecitabine remained cost saving.

The PBAC noted that the patterns of drug administration used in the economic evaluation are obtained from a small treatment pattern survey and may not reflect practices across the public and private treatment settings. The distribution of patients across the five treatment settings is also uncertain due to the methodology used which applied multiple sources of information and required mapping of ICD-10 codes to MBS codes.

The PBAC considered that the assumption that a new CADD pump is bought for each of these patients (at a cost of $4950) was not reasonable and overestimated costs, as the pumps may be re-used and are expected to last 2 to 5 years. The Pre-Sub Committee Response agreed that costs were overestimated. However, the PBAC noted that even if the lowest cost estimate of $190 is used as recommended in the Commentary, the intervention remained cost-saving.

The PBAC noted that the cost of outpatient PICC placement when medical intervention is required and PICC removal (when on a different day from chemotherapy) was still based on the NHCDC cost report (non-admitted medical oncology) and thus remained overestimated. The cost from the NHCDC cost report (general surgery) may have been more appropriate.

The PBAC considered that the use of a single AR-DRG code (R63Z) was not appropriate for subsequent chemotherapy administration visits which require a few minutes of nursing time to connect/disconnect an ambulatory 5-FU infusion pump. However, the PBAC noted that the use of alternative costings still result in cost savings.

The PBAC considered it would be more appropriate to charge only one MBS item for subsequent visits and MBS item 13918 for the first day of treatment of each cycle. The Pre-Sub Committee Response noted that if the MBS item 13945 is used to cost the access/flushing of the CVAD, capecitabine treatment remains cost saving.

The PBAC noted that the cost savings are derived through the cost of drug administration, which are MBS item numbers, prostheses costs, and the cost of drug administration in hospitals and that the intervention is not cost-saving to the PBS. However, even in the worst case scenario the treatment costs of capecitabine were still cost saving in both treatment groups.

The PBAC considered that further discussion was needed to determine the true cost of drug administration in the various settings. Further, the price of capecitabine should be reviewed in 12 months time after consideration by the Department of drug administration costs in the various settings.

Recommendation

CAPECITABINE, tablets, 150 mg and 500 mg

Extend the current restriction to include:

Authority required

Advanced (Stage III or IV) oesophago-gastric cancer, previously untreated, in combination with a cisplatin-based regimen, in a patient with a WHO performance status of 2 or less.

Maximum quantity:	60	(150 mg)
	120	(500 mg)
Repeats:	2	

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no further comment.