PUBLIC SUMMARY DOCUMENT
Product: Capecitabine, tablets, 150 mg and 500 mg, Xeloda®
Sponsor: Roche Products Pty Ltd
Date of PBAC Consideration: July 2009

1. Purpose of Application

To request an extension to the Section 85 Authority required listing for capecitabine to include the treatment in combination with a platinum-based regimen of previously untreated advanced oesophago-gastric cancer.

2. Background

Capecitabine had not previously been considered for this indication by the PBAC.

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 platinum-based regimen, of a patient with previously untreated advanced oesophago-gastric cancer with a WHO performance status of 2 or less.

The PBAC considered that any future restriction proposed by the sponsor should include use of capecitabine with cisplatin only rather than platinum-based therapies.

5. Clinical Place for the Proposed Therapy

Capecitabine would provide an oral alternative to 5-fluorouracil (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

5-fluorouracil (5-FU). 5-FU is a pharmacological analogue of capecitabine.

7. Clinical Trials

The submission presented one randomised open-label triplet chemotherapy trial (REAL-2). It compared capecitabine plus epirubicin (either with oxaliplatin or cisplatin) with 5-FU plus epirubicin (either with oxaliplatin or cisplatin) in patients with advanced oesophagogastric cancer (OGC). One randomised open-label doublet chemotherapy trial (ML17032) was also presented which compared capecitabine plus cisplatin with 5-FU plus cisplatin in patients with advanced gastric cancer. The submission also presented a meta-analysis of survival data from the REAL-2 and ML17032 trials.

Details of the trials and associated reports used in the submission are summarised in the following table:

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
REAL-2/ Cunningham D, 2008	Capecitabine and oxaliplatin for advanced oesophagogastric cancer.	The New England Journal of Medicine 2008; 358(1): 36-46.
ML17032/Kang Y, 2006	Randomised phase III trial of capecitabine/cisplatin (XP) vs. continuous infusion of 5 FU/cisplatin (FP) as first line therapy in patients (pts) with advanced gastric cancer (AGC): efficacy and safety results.	Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I, Vol 24, No. 18S (June 20 Supplement) 2006: LBA4018

8. Results of Trials

In the triplet chemotherapy trial (REAL-2), the primary efficacy endpoint was the assessment of overall survival (OS) in the per-protocol (PP) population. The median and one-year survival rates for the pooled capecitabine regimens compared with the 5-FU regimens (both oxaliplatin-based and cisplatin-based therapy) were 10.9 months versus 9.6 months and 44.6 % (95 % CI: 40.1 %, 49.0 %) versus 39.4 % (95 % CI: 35.0 %, 44.0 %), respectively. The unadjusted hazard ratio for death for the non-inferiority comparison of capecitabine versus 5-FU was 0.86 (95 % CI: 0.80, 0.99). The adjusted (for performance status, extent of disease and age) hazard ratio for death in the pooled capecitabine group, as compared with the pooled 5-FU group, was 0.89 (95 % CI: 0.77, 1.02). The REAL-2 study met the pre-specified non-inferiority criteria for overall survival, as the upper limits of the confidence intervals of both the adjusted and non-adjusted hazard ratios were below the pre-specified margin of 1.23.

The secondary analyses from the REAL-2 trial of 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)].

In the doublet chemotherapy trial (ML17032), the primary efficacy endpoint was the assessment of PFS in the PP population. In two-sided tests, non-inferiority was concluded for a non-inferiority margin of 1.40 (p=0.003) and, subsequently, for a non-inferiority margin of 1.25 (p=0.005). The unadjusted hazards ratio, using a two-sided test in terms of PFS in the PP population for capecitabine + cisplatin was found to be non-inferior to that of 5-FU + cisplatin [HR: 0.81 (95 % CI: 0.63, 1.04)] using a non-inferiority margin of 1.25. Results were consistent for the ITT population.

The results from the meta-analyses of survival data from the REAL-2 and ML17032 were consistent with the results from the individual trials.

The key safety issues from the key REAL-2 trial are summarised as follows:

1. The most frequent treatment-related adverse events were anaemia, neutropenia, diarrhoea, stomatitis, nausea/vomiting, lethargy and alopecia. Hand and foot syndrome, lethargy and thrombocytopenia were more frequent (differences were statistically significant) in the capecitabine groups compared to the 5-FU groups. All grades of stomatitis were more frequent (also statistically significant) in the 5-

FU groups compared to the capecitabine groups;
2. There were less chills, infections and thromboembolic events but more peripheral arterial ischemia and abnormal neutrophil/granulocyte values in the ECX treatment arm compared to the ECF treatment arm.

9. Clinical Claim

The submission described capecitabine as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over 5-FU.

For PBAC's views see Recommendation and Reasons

10. Economic Analysis

The submission presented a cost minimisation analysis with the estimates based directly on the mean drug use in the clinical trials.

The key cost differences between treatments were:

1. the cost of administration (either on an inpatient or outpatient basis), and;
2. the drug acquisition cost of capecitabine vs 5-FU.

For PBAC's views see Recommendation and Reasons

11. Estimated PBS Usage and Financial Implications

The likely financial cost per year to the PBS was less than $10 million in Year 1.

12. Recommendation and Reasons

The PBAC accepted that 5-fluorouracil (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 advanced 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.

One randomised open-label doublet chemotherapy trial (ML17032) was also presented which compared capecitabine plus cisplatin with 5-FU plus cisplatin in patients with advanced gastric cancer. However, the PBAC noted that three-drug regimens were now considered standard in the treatment of advanced gastric cancer, and the combination of capecitabine with cisplatin (and capecitabine monotherapy) was rejected for registration by the TGA Delegate on the grounds of inadequate evidence of efficacy, due to the lack of comparative data with a triple-drug regimen.

The PBAC accepted that capecitabine was non-inferior in terms of comparative effectiveness and safety over 5-FU.

The main matter of concern to the PBAC was the use of resources to offset the higher drug cost requested for the capecitabine tablet.

The PBAC deferred this submission so that the issues regarding the cost of the diagnostic related groups (DRGs) and the magnitude of the cost-offsets can be resolved.

Recommendation
Defer.

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.