

PUBLIC SUMMARY DOCUMENT

Product: Capecitabine, tablets, 150 mg and 500 mg, Xeloda®

Sponsor: Roche Products Pty Ltd

Date of PBAC Consideration: November 2005

1. Purpose of Application

The submission sought to extend the current authority required listing for capecitabine to include the adjuvant treatment of patients with Dukes' C colon cancer.

2. Background

At its December 2000 meeting, the PBAC recommended extending the listing (for use in breast cancer) for capecitabine to include "treatment of advanced or metastatic colorectal cancer".

3. Registration Status

Capecitabine is registered by the Therapeutic Goods Administration (TGA) for the following:

- Treatment of patients with advanced or metastatic colorectal cancer;
- Treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen unless therapy with these and other standard agents are clinically contraindicated;
- In combination with docetaxel, for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.
- For the adjuvant treatment of patients with Dukes' C and high-risk stage B colon cancer.

4. Listing Requested and PBAC's View

Authority required

Adjuvant treatment of Dukes' C colon cancer.

The PBAC recommended the addition of notes to the restriction to clarify the extent of PBS subsidy.

5. Clinical Place for the Proposed Therapy

Capecitabine would provide an alternative to 5-fluorouracil (5-FU) and low dose leucovorin as adjuvant chemotherapy for patients with colon cancer who do not receive combination chemotherapy. Capecitabine is a pro-drug of 5-FU.

6. Comparator

The submission nominated Mayo Clinic regimen for 5-FU plus leucovorin as the main comparator. The PBAC considered this appropriate.

7. Clinical Trials

The submission presented a single randomised, open-label, phase III, non-inferiority trial (X-ACT) comparing capecitabine with IV bolus 5-FU in combination with low-dose leucovorin as adjuvant chemotherapy in patients who underwent surgery for Dukes' C colon cancer.

This trial details are as follows:

Trial/First author	Protocol title	Publication citation
Twelves et al.	Capecitabine as Adjuvant Treatment for Stage III Colon Cancer.	N Engl J Med 2005;352:2696-704.

8. Results of Trials

The results of the key trial are summarised in the table below. The PBAC noted that the pre-specified non-inferiority criteria in the primary analysis were met.

Results of the comparative randomised trial (X-ACT)

Primary and secondary outcomes	Capecitabine	5-FU/LV	Hazard ratio (95% CI)	p-value
Disease-free survival				
Patients with event	348/1004 (34.7%)	380/983 (38.7%)	0.87 (0.75, 1.00)	0.0528
Time to event				
- Median	Not reached	5.0 years		0.0526
- 95% CI for median	Not reached	(4.2, not reached)		
Overall survival				
- Patients with event	200/1004 (19.9%)	227/983 (23.1%)	0.84 (0.69, 1.01)	0.0706
Time to event				
- Median	Not reached	Not reached		0.0702
- 95% CI for median	Not reached	Not reached		
Relapse-free survival				
Patients with event	327/1004 (32.6%)	362/983 (36.8%)	0.86 (0.74, 0.99)	0.0407*
Time to event				
- Median	Not reached	5.0 years		0.0405*
- 95% CI for median	Not reached	(5.0, not reached)		

5-FU = 5-fluorouracil, LV = leucovorin, CI = confidence interval

* statistically significant at the 5% significance level

There was a trend (not reaching statistical significance) towards a higher rate of disease-free survival in patients treated with capecitabine compared with 5-FU-leucovorin (5-FU/LV). There was no statistically significant difference in overall survival between treatments. There was a significant difference favouring capecitabine in relapse-free survival between the two treatments.

There was a higher incidence of hand-foot syndrome (a tingling sensation of the palms and feet, progressing to severe pain, tenderness, redness and swelling) with capecitabine and a higher incidence of nausea, vomiting, diarrhoea, stomatitis, alopecia and neutropenia with 5-FU/LV. In the capecitabine arm, 60% developed hand foot syndrome and of these 25% had an event of grade 3 or 4 severity.

9. Clinical Claim

The submission claimed that in terms of effectiveness, capecitabine was no worse than the Mayo Clinic regimen of 5-FU/LV. Overall the PBAC accepted the claim.

See Recommendations and Reasons for PBAC's view.

10. Economic Analysis

A preliminary (trial-based) economic evaluation adopting a cost-minimisation approach was presented. The resources included were drug costs, drug acquisition costs, drug preparation, drug administration costs and visit costs. In addition to being more convenient, the oral formulation generated cost off-sets compared to the costs of infusing the comparator regimen.

The equi-effective doses in the context of cost-minimisation were based on the mean cumulative dose of each drug from the X-ACT Study, which were estimated to be 422 g/patient for capecitabine, 19.5 g/patient for 5-FU and 955.30 mg/patient for leucovorin.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients that would be treated with capecitabine to be < 2,000 in Year 4 of listing.

The net impact of extending the capecitabine listing was estimated to be between \$1 million to \$5 million in Year 4 of listing.

12. Recommendation and Reasons

Listing was recommended on a cost-minimisation basis, concluding that the direct comparison presented in the submission indicated that capecitabine was no worse than the Mayo Clinic regimen of 5-FU plus leucovorin in terms of disease free survival. The toxicity profile of capecitabine was noted to be different from the comparator but was considered to be no worse overall.

The PBAC noted that on drug costs alone, capecitabine was more expensive than the drug costs for the comparator. However the PBAC noted that the economic analysis included the costs of specialist visits for each episode of intravenous administration of 5FU/leucovorin, which it had accepted previously.

Recommendation

Extend listing to include:

CAPECITABINE, tablets, 150 mg and 500 mg

Restriction:

Authority required

Adjuvant treatment of Stage III (Dukes C) colon cancer, following complete resection of the primary tumour.

NOTE

In the adjuvant setting, the recommended treatment duration is 24 weeks.

Capecitabine is not PBS-subsidised for the treatment of patients with Stage II (Dukes B) colon cancer.

Capecitabine is not PBS-subsidised for the adjuvant treatment of patients with rectal cancer.

Maximum quantity 60 (150 mg)/120 (500 mg)

Repeats: 2 (all strengths)

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