

PUBLIC SUMMARY DOCUMENT

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

Sponsor: Roche Products Pty Ltd.

Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission sought PBS listing for the combination treatment of metastatic colorectal cancer (mCRC) with capecitabine and oxaliplatin (XELOX regimen). This required a change to the PBS listing for oxaliplatin to include the treatment in combination with capecitabine.

2. Background

Capecitabine was first listed on the PBS on 1 November 1999, for the treatment of advanced metastatic breast cancer after failure of standard therapy which includes a taxane and an anthracycline, or where those agents are clinically inappropriate.

At its December 2000 meeting, the PBAC recommended the additional listing for capecitabine for treatment of advanced or metastatic colorectal cancer. At its November 2005 meeting, the PBAC recommended further extending the listing for capecitabine to include the adjuvant treatment of patients with Dukes C colon cancer.

Oxaliplatin was recommended by the PBAC at its June 2001 meeting for use as second-line therapy in metastatic colorectal cancer. At its meeting in December 2003, the PBAC recommended extending the listing of oxaliplatin to include first-line treatment of metastatic colorectal cancer in patients with a WHO performance status of 2 or less, to be used in combination with 5-fluorouracil and folinic acid.

3. Registration Status

Capecitabine was first registered by the TGA on 4 September 2000. It is indicated for:

- adjuvant treatment of patients with Dukes' stage C and high-risk stage B colon cancer;
- 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.

4. Listing Requested and PBAC's View

The sponsor proposed that the current PBS restriction for capecitabine in the treatment of advanced or metastatic CRC remain unchanged as this is consistent with the wording of the TGA-approved indication:

Authority Required

Advanced breast cancer after failure of prior therapy which includes a taxane and an anthracycline;

Advanced breast cancer where therapy with a taxane and/or an anthracycline is contraindicated;

Advanced breast cancer in combination with docetaxel after failure of prior anthracycline-containing chemotherapy;

Treatment of advanced or metastatic colorectal cancer;

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.

The sponsor requested a change to the PBS listing of oxaliplatin to allow combination use with capecitabine, as follows:

Authority Required

Metastatic colorectal cancer in combination with capecitabine

OR

Metastatic colorectal cancer in patients with a WHO performance status of 2 or less, to be used in combination with capecitabine or 5-fluorouracil and folinic acid.

5. Clinical Place for the Proposed Therapy

Colorectal cancer is the second most commonly diagnosed cancer in Australia and is a significant cause of morbidity and mortality. The aim of treatment in patients with advanced disease is to improve both the duration and quality of the patient's remaining life.

Capecitabine in combination with oxaliplatin will provide an alternative for first- and second-line treatment of patients with metastatic colorectal cancer.

6. Comparator

The submission nominated 5-fluorouracil (5-FU) with or without leucovorin in combination with oxaliplatin as the comparator. The PBAC considered that 5-FU in combination with oxaliplatin in the regimen modified FOLFOX6 was the appropriate comparator as this is the therapy most likely to be replaced in clinical practice.

7. Clinical Trials

The submission presented five randomised trials comparing combination capecitabine plus oxaliplatin chemotherapeutic regimens with 5-fluorouracil plus oxaliplatin regimens for first-line treatment in patients with metastatic colorectal cancer (mCRC), and one randomised trial comparing combination capecitabine plus oxaliplatin chemotherapeutic regimens with 5-fluorouracil plus oxaliplatin regimens for second-line treatment in patients with metastatic colorectal cancer. Details of the studies published at the time of submission are presented in the table below.

Trials and associated reports presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|-----------------------------------|-----------------------------------|----------------------|
| Direct randomised trial(s) | | |

| | | |
|-----------------|--|---|
| NO 16966 | Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. | Cassidy <i>et al. Journal of Clinical Oncology</i> 2008; 26: 2006-2012. |
| NO 16967 | Phase III trial of capecitabine + oxaliplatin (XELOX) vs 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX4) as 2 nd -line treatment for patients with metastatic colorectal cancer (MCRC). | Rothenberg <i>et al. Journal of Clinical Oncology</i> 2007; 25, No 18S: 4031 (abstract). |
| Diaz-Rubio 2007 | Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: Final report of the Spanish Cooperative Group for the treatment of digestive tumors trial. | Diaz-Rubio <i>et al. 2007. Journal of Clinical Oncology</i> 2007; 25 (27): 4224-4230. |
| Ducreux 2007 | Efficacy and safety findings from a randomised phase III study of capecitabine (X) and oxaliplatin (O) (XELOX) vs. infusional 5-FU/LV + O (FOLFOX-6) for metastatic colorectal cancer (MCRC). | Ducreux <i>et al. 2007. Journal of Clinical Oncology</i> 2007; ASCO Annual Meeting Proceedings Part I 25: 18s (suppl): Abstract 4029. |
| Hochster 2006 | Safety and efficacy of bevacizumab (Bev) when added to oxaliplatin/fluoropyrimidine (O/F) regimens as first line treatment for metastatic colorectal cancer (mCRC): TREE-1 and 2 studies. | Hochster <i>et al. 2006. Journal of Clinical Oncology</i> 2006; 23:249s (suppl): Abstract 3515. |
| Porschen 2007 | Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: A final report of the AIO colorectal study group. | Porschen <i>et al. 2007. Journal of Clinical Oncology</i> 2007; 25 (27): 4217-4223. |

Abbreviations 5-FU = 5-fluorouracil; LV=leucovorin=folinic acid; AIO = Arbeitsgemeinschaft Internistische Onkologie; CPT-11 = irinotecan; FOLFOX = 5-FU+LV+oxaliplatin; mCRC = MCRC = metastatic colorectal cancer; O/F = oxaliplatin/fluoropyrimidine

8. Results of Trials

First-line therapy of mCRC

The results of progression free survival (PFS) across the direct randomised trials in the first-line treatment of metastatic CRC are presented in the table below.

| Trial ID | Population for analysis | XELOX median PFS mths (days) | FOLFOX median PFS mths (days) | Hazard Ratio various CIs | Non-inferiority criteria |
|---|-----------------------------|------------------------------|-------------------------------|--|---------------------------------------|
| NO16966 Investigator assessment | EPP | 7.2 (220) | 7.9 (241) | 1.06 (0.92,1.22) | Upper limit of 97.5% CI <1.23 |
| | ITT | 7.3 (222) | 8.0 (245) | 1.05 (0.92,1.20) | |
| | PPP | 7.6 (232) | 8.5 (260) | 1.09 (0.94,1.26) | |
| Diaz-Rubio Investigator assessment | PPP | 8.9 | 9.5 | 95% CI 1.18 (0.9,1.5) ^a | Hazard ratio < 1.27 |
| Ducreux Investigator assessment | ITT | 8.8 | 9.3 | 90% CI 1.00 (0.82, 1.22) | Not tested for non-inferiority |
| Hochster ^{bc} Investigator assessment | As treated participants | 5.9 | 8.7 | NR | Not designed as non-inferiority trial |
| Porschen Investigator assessment | Analysed patient population | 7.1 | 8.0 | 95% CI 1.17 (0.96,1.43) | Hazard ratio <1.29 |
| Pooled result^c | | | | 1.09 (0.99,1.19) | Upper limit of 95% CI <1.23 |
| Chi-square for heterogeneity: $P=0.67$ I^2 statistic with 95% uncertainty interval =0% | | | | | |

^a p=0.153.

^b PFS censored for second-line treatment.

^c Hochster (2006) not included in meta-analysis of results.

CI=confidence interval; EPP=eligible patient population; ITT=intent-to-treat (population); NR=not reported; PPP=per protocol population.

Second-line therapy of mCRC

The results of efficacy outcomes for the direct randomised trial of second-line treatment of metastatic CRC are presented in the table below.

| Trial ID 16967 | Population for analysis | XELOX | FOLFOX | Hazard Ratio | Non-inferiority Criteria |
|--|-------------------------|-------|--------|------------------|--------------------------|
| Progression free survival – investigator assessment | | | | | |
| Median duration, mths | PPP | 5.1 | 5.5 | 1.04 (0.87,1.24) | UL, 95% CI <1.30 |
| | ITT | 4.7 | 4.8 | 0.97 (0.83,1.14) | |
| | | | | | |
| | | | | | |
| Overall survival | | | | | |
| Median duration, mths | PPP | 12.9 | 13.2 | 1.05 (0.88,1.27) | Not tested |
| | ITT | 11.9 | 12.5 | 1.02 (0.86,1.21) | |
| | | | | | |

UL = upper limit; CI=confidence interval; ITT=intent-to-treat population; PPP=per protocol population;

The PBAC accepted the non-inferiority claim for the second-line therapy based on clinical trial study NO16967 (CI < 1.30), as the preset non-inferiority criteria were met. However, the PBAC considered that the claim of non-inferiority in the first-line setting is uncertain because all the point estimates of the hazard ratio for progression free survival (PFS) suggest XELOX might be inferior to FOLFOX. For the key randomised clinical trial for first-line treatment of metastatic colorectal cancer (study NO 16966), the point estimate for the blinded Independent Review Committee (IRC) assessment of PFS for the per protocol population (PPP) did not meet the non-inferiority criterion, suggesting a statistically significant inferiority of XELOX in comparison with FOLFOX. However, the PBAC noted that the unblinded investigator's assessment of PFS demonstrated non-inferiority but this was determined in the eligible patient population (EPP) and based on a subjective measure and an inappropriate population set.

The PBAC took into account the sponsor's pre-Sub-Committee and pre-PBAC responses concerning non-inferiority and accepted the non-inferiority of XELOX in both the first and second-line settings.

For PBAC's comments on these results, see Recommendation and Reasons.

The safety data for capecitabine/oxaliplatin regimens and 5-FU/oxaliplatin regimens were comparable in terms of the incidence of adverse events, serious adverse events, discontinuations due to adverse events and treatment related deaths. There were no important differences in the safety data for capecitabine/oxaliplatin regimens compared with 5-FU/oxaliplatin regimens other than the known differences between the safety profiles of capecitabine and 5-FU monotherapy. The haematological toxicity observed with 5-FU/oxaliplatin was less pronounced with capecitabine/oxaliplatin, while the incidence of gastrointestinal disorders, diarrhoea and palmar-plantar erythrodysesthesia was greater.

9. Clinical Claim

The submission described the combination of capecitabine with oxaliplatin as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over bolus and/or infusional 5-FU plus folinic acid combined with oxaliplatin in both first-line and second-line treatment of metastatic CRC.

The interpretation of the clinical evidence in non-inferiority trials is highly dependent on the non-inferiority margin that is applied. The PBAC noted the non-inferiority margins specified for the randomised trials and the meta-analyses seemed unreasonably large and were not based on the minimal clinically important differences for these outcomes.

10. Economic Analysis

The submission presented cost minimisation analyses for the first- and second-line settings. In the first-line setting, the equi-effective doses were estimated as capecitabine 2,000mg twice daily for two weeks over 7.47 cycles of therapy, as part of the XELOX combination chemotherapy regimen, and 5-fluorouracil to a total of 2,800 mg/m² (bolus plus infusion) plus folinic acid 50mg, each cycle, over 9.09 cycles of therapy, as part of the modified FOLFOX-6 combination chemotherapy regimen. In the second-line setting, the per-cycle equi-effective doses are the same as in the first-line, but the number of cycles of therapy given for equi-effect are considered to be: 5.1 cycles of XELOX and 7.5 for the modified

FOLFOX-6 regimen. In addition, the dose of oxaliplatin given per cycle is different in each regimen.

The results of the cost-minimisation analysis, with revisions made during the evaluation, showed a higher incremental cost for XELOX compared to modified FOLFOX6.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year using capecitabine to be less than 10,000 in Year 1. The overall net cost to the PBS was estimated to be less than \$10 million in Year 1.

12. Recommendation and Reasons

The PBAC recommended a change to the listing for oxaliplatin to allow use with capecitabine in advanced or metastatic colorectal cancer on a cost-minimisation basis compared with the modified FOLFOX6 regimen, noting that based on the proposed drug prices the cost of treatment with XELOX was higher than with modified FOLFOX6 in the first- and second line settings and that the cost of the drugs in the XELOX regimen will need to be reduced to eliminate this differential.

The PBAC noted that the submission requested a change to the wording of the oxaliplatin listing and not the capecitabine listing, to allow the use of oxaliplatin with capecitabine. However, the TGA approved product information for oxaliplatin does not currently allow use in combination with capecitabine, although an application seeking approval of this change is currently under evaluation, and the change will not be made unless and until it is approved. The PBAC also noted that one of the five manufacturers of oxaliplatin had acknowledged and given approval for this submission.

The Committee considered that the appropriate comparator in this submission was fluorouracil in combination with oxaliplatin in the regimen FOLFOX6, as this was the therapy most likely to be replaced in clinical practice. The Committee noted that much of the clinical evidence came from trials using the FOLFOX4 rather than FOLFOX6 regimens, but that the two regimens could be considered non-inferior in clinical terms. However, the PBAC noted that the cost-offsets of FOLFOX4 are higher than for FOLFOX6, and considered that the submission's inclusion of these higher offsets was not reasonable.

The PBAC noted that capecitabine in combination with oxaliplatin (XELOX or CAPOX) was intended to be a first- or second-line treatment option for metastatic colorectal cancer, and hence the submission presented five randomised trials comparing combination capecitabine plus oxaliplatin chemotherapeutic regimens with 5-fluorouracil plus oxaliplatin regimens for first-line treatment in patients with metastatic colorectal cancer (mCRC), and one randomised trial comparing combination capecitabine plus oxaliplatin chemotherapeutic regimens with 5-fluorouracil plus oxaliplatin regimens for second-line treatment in patients with metastatic colorectal cancer.

The PBAC accepted the non-inferiority claim for the second-line therapy based on clinical trial study NO16967 (CI <1.30), as the preset non-inferiority criteria were met. However, the PBAC considered that the claim of non-inferiority in the first-line setting is uncertain because all the point estimates of the hazard ratio for progression free survival (PFS) suggest XELOX might be inferior to FOLFOX. For the key randomised clinical trial for first-line treatment of

metastatic colorectal cancer (study NO16966), the point estimate for the blinded Independent Review Committee (IRC) assessment of PFS for the per protocol population (PPP) did not meet the non-inferiority criterion, suggesting a statistically significant inferiority of XELOX in comparison with FOLFOX. However, the PBAC noted that the unblinded investigator's assessment of PFS demonstrated non-inferiority but this was determined in the eligible patient population (EPP) and based on a subjective measure and an inappropriate population set.

The PBAC considered that even if it is accepted that XELOX is statistically inferior to FOLFOX4 it can be argued that the difference between the regimens is not clinically relevant and in current clinical practice capecitabine is accepted as interchangeable with 5-fluorouracil. The PBAC took into account the sponsor's pre-Sub-Committee and pre-PBAC responses concerning non-inferiority and accepted the non-inferiority of XELOX in both the first and second-line therapy.

The PBAC noted that based on drug cost alone, the XELOX based regimen is more expensive than the FOLFOX regimen but that the higher costs for XELOX are subsequently offset by the higher preparation, administration and other non-drug costs associated with the FOLFOX regimen. However, the PBAC considered that it was still likely that XELOX is more expensive than the FOLFOX regimens, even FOLFOX6 regimens which are associated with a decreased cost because of less dose splitting (i.e. one 46 hour infusion versus two 22 hour infusions of fluorouracil and also less bolus regimens).

Recommendation

CAPECITABINE, tablet, 150 mg and 500 mg

Restriction:

Authority Required

Advanced breast cancer after failure of prior therapy which includes a taxane and an anthracycline;

Advanced breast cancer where therapy with a taxane and/or an anthracycline is contraindicated;

Advanced breast cancer in combination with docetaxel after failure of prior anthracycline-containing chemotherapy;

Treatment of advanced or metastatic colorectal cancer;

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)
Number of repeats: 2 (both strengths)

OXALIPLATIN, solution concentrate for I.V. infusion, 50 mg in 10 mL, 100 mg in 20 mL and 200 mg in 40 mL, powder for I.V. infusion, 50 mg and 100 mg.

Restriction:

Authority Required

Metastatic colorectal cancer in a patient with a WHO performance status of 2 or less, to be used in combination with:

- (a) capecitabine; or
- (b) 5-fluorouracil and folinic acid;

Adjuvant treatment of stage III (Dukes C) colon cancer, in combination with 5-fluorouracil and folinic acid, following complete resection of the primary tumour.

NOTE:

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

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

NOTE:

The solution concentrate for I.V. infusion 50 mg and powder for I.V. infusion 50 mg (after reconstitution) are bioequivalent.

NOTE:

The solution concentrate for I.V. infusion 100 mg and powder for I.V. infusion 100 mg (after reconstitution) are bioequivalent.

Maximum quantity: 1

Number of 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.