

## **PUBLIC SUMMARY DOCUMENT**

**Product:** CETUXIMAB, solution for IV infusion, 100 mg in 50 mL, Erbitux<sup>®</sup>

**Sponsor:** Alphapharm Pty Limited

**Date of PBAC Consideration:** November 2005

### **1. Purpose of Application**

This submission sought a Section 85 Authority required listing on the PBS (and inclusion in the Chemotherapy Pharmaceutical Access Program (CPAP)) for the treatment of metastatic colorectal cancer (MCRC) where the current standard chemotherapeutic options have failed.

### **2. Background**

The PBAC at its March 2005 meeting rejected an authority required application to list cetuximab for treatment for epidermal growth factor receptor (EGFR) expressing metastatic colorectal cancer in patients who have failed irinotecan based therapies, and either failed or are unsuitable for oxaliplatin based therapies, to be used in combination with irinotecan.

The submission was rejected because of uncertain extent of clinical benefit and uncertain, but unacceptable, cost-effectiveness.

### **3. Registration Status**

Cetuximab is registered by the TGA for the treatment of patients with metastatic colorectal cancer that has been demonstrated to be epidermal growth factor receptor (EGFR) positive and whose disease has progressed or is refractory to irinotecan based therapy. Cetuximab can be used at the doses recommended either in combination with irinotecan or as a single agent.

### **4. Listing Requested and PBAC's View**

#### Authority Required

Initial PBS-subsidised treatment, in combination with irinotecan, of metastatic colorectal cancer in patients with a WHO performance status of 2 or less, who have received and failed 5 fluorouracil or capecitabine, received and failed an irinotecan-based therapy, and received and failed or are considered unsuitable for, an oxaliplatin-based therapy.

The sponsor proposed that treatment failure be defined as:

- Progression of disease during, or within 3 months of discontinuing treatment so that rechallenge with the last used treatment option is inappropriate. Progression may be judged by radiological or clinical criteria.
  - Radiological criteria:
    - o Progressive disease – at least 20% increase in the sum of the longest diameter of measurable lesions.
  - Clinical definition: at least two of the following:
    - o Increase in size of palpable metastatic lesion.
    - o Clinically significant deterioration of liver function tests.
    - o Significant weight loss (greater than 10% over assessment period).
    - o Increase in carcinoembryonic antigen (CEA) levels.
    - o Increased analgesic usage.
- Intolerance to therapy
  - Irinotecan: discontinuation due to severe allergic reaction or delayed recovery from toxicity preventing retreatment such as life threatening mucositis, diarrhoea, where rechallenge is inappropriate.

- Oxaliplatin: discontinuation due to severe allergic reaction, persistent severe neurotoxicity, delayed recovery from toxicity preventing retreatment or evidence of respiratory toxicity, where rechallenge is inappropriate.
- A WHO performance status of greater than 2.

The sponsor proposed that unsuitability for an oxaliplatin based regime be defined as:

- Known hypersensitivity to oxaliplatin or other platinum compounds
- Myelosuppression (neutrophils  $<1.0 \times 10^9/L$  or platelets  $<50 \times 10^9/L$ )
- Pre-existing renal impairment (GFR  $<30\text{mL}/\text{min}$ )
- Grade 2 or greater (CTC convention) neurosensory neuropathy.

#### Authority Required

Continuing PBS-subsidised treatment, in combination with irinotecan, of metastatic colorectal cancer in patients with a WHO performance status of 2 or less, where:

- (1) the patient has been previously been issued with an authority prescription for cetuximab; and
- (2) a response to treatment has been observed.

The sponsor proposed that response be defined as:

Based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria:

- disappearance of all measurable lesions; or
- a decrease by 30% or more in the sum of the longest diameter of all measurable lesions taking as reference the baseline sum of longest diameter.

A measurable lesion is a lesion that could be measured accurately in at least 1 dimension (longest diameter recorded) as  $\geq 20\text{mm}$ .

*See Recommendations and Reasons for the PBAC's view of the proposed restriction.*

### **5. Clinical Place for the Proposed Therapy**

Cetuximab would provide a treatment option for patients who have failed the current standard chemotherapeutic treatments.

### **6. Comparator**

The submission nominated “usual care” consisting of best supportive care (BSC) and the chemotherapy agents currently used third line, capecitabine, 5-FU (+ mitomycin C) and raltitrexed as the comparator. The PBAC considered the choice of comparator appropriate.

### **7. Clinical Trials**

The submission presented the following studies that were also included in the previous submission:

- Study 007 BOND – “key” cetuximab study
- Rosati 2003 – “key” comparator (raltitrexed) study

In addition, in this submission, the Medicare Australia claims database was used to estimate survival for the comparator group.

New data presented in this submission included:

- Rao et al 2004 – “key” comparator (BSC) study
- Lim et al 2005 – “key” comparator (capecitabine) study
- 4 “supportive” comparator studies: Rothenberg (5-FU), Tsavaris (raltitrexed), Hoff (capecitabine), and Lee (capecitabine).

| <b>Trial/First author</b> | <b>Protocol/Publication title</b>   | <b>Publication citation</b>                                |
|---------------------------|---|--|
| Cunningham D              | Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.  | NEJM 2004;351: 337-345                                     |
| Rosati G                  | Raltitrexed and mitomycin-C as third-line chemotherapy for colorectal cancer after combination regimens including 5-fluorouracil, irinotecan and oxaliplatin: a phase II study. | Anticancer Research 2003; 23: 2981-2985.                   |
| Rao S                     | Phase III double-blind placebo-controlled study of farnesyl transferase inhibitor R115777 in patients with refractory advanced colorectal cancer.                               | Journal of Clinical Oncology 2004; 22(19):3950-3957.       |
| Lim DH                    | Mitomycin-C and capecitabine as third-line chemotherapy in patients with advanced colorectal cancer: a phase II study.  | Cancer Chemother Pharmacol 2005; 56:10-14.                 |
| Rothenberg ML             | Superiority of oxaliplatin and fluorouracil-leucovorin: interim results of a phase III trial.   | Journal of Clinical Oncology 2003; 21(11):2059-2069.       |
| Tsavaris N                | Raltitrexed (Tomudex) administration in patients with relapsed metastatic colorectal cancer after weekly irinotecan/5-Fluorouracil/Leucovorin chemotherapy.                     | BMC Cancer 2002; 2:5,                                      |
| Hoff PM                   | Phase II study of capecitabine in patients with fluorouracil-resistant colorectal carcinoma.  | Journal of Clinical Oncology 2004; 22: 2078-2083.          |
| Lee JJ                    | Single agent capecitabine in patients with metastatic colorectal cancer refractory to 5-Fluorouracil/Leucovorin Chemotherapy.   | Japanese Journal of Clinical Oncology 2004; 34(7):400-404. |

## 8. Results of Trials

The key results are summarised in the tables below.

### Efficacy results for BSC and studies of third-line therapies

| <b>Outcome</b>                                   | <b>Rao BSC (n=133)</b> | <b>Rosati raltitrexed third-line (n=21)</b> | <b>Lim capecitabine third-line (n=21)</b> | <b>Study 007 cetuximab + irinotecan (n=218)</b> |
|--|------------------------|---|---|---|
| Overall response: CR+PR (95% CI) <sup>A</sup>    | 0%                     | 0%  | 4.8% (0%, 14%)                            | 23% (18%, 29%)                                  |
| Time to progression in months<br>Median (95% CI) | 2.7<br>(2.6, 2.7)      | 2.3<br>(1.65, 2.95)                         | 2.6<br>(2.5, 2.7)                         | 4.1<br>(2.8, 4.3)                               |

<sup>A</sup> Calculated assuming binomial distribution with lower limit set to 0 if <0.

### Cetuximab + irinotecan and “usual care” mean survival (months)

|                                  | <b>Cetuximab + irinotecan</b> | <b>“Usual care”</b>                |  |
|----------------------------------|-------------------------------|------------------------------------|--|
| Data source                      | Study 007                     | Medicare Australia claims database | Patient cohort not enrolled in Study 007 |
| Mean survival in months (95% CI) | 11.01 (10.0, 12.0)            | 7.5 (6.6, 8.4)                     | Range: 5.5-7.0                           |

Mean survival was higher in the cetuximab plus irinotecan group in the 007 BOND study (approximately 11 months) than estimated for usual care from the Medicare Australia data

base (approximately 7.5 months).

In a *post hoc* estimation of expected survival of cetuximab + irinotecan patients treated according to the proposed treatment algorithm, total life expectancy in Study 007 (with imputations for censored data) was 11.01 months and in a further analysis was 10.40 months.

No new toxicity data on cetuximab were presented in this submission. The toxicity data from the previous submission are reproduced below.

#### Overview of AE frequencies in Study 007

| AE category                           | Part 1                        |                 | Parts 1 and 2                 |                 |
|---------------------------------------|-------------------------------|-----------------|-------------------------------|-----------------|
|                                       | Cetuximab + irinotecan, N=212 | Cetuximab N=115 | Cetuximab + irinotecan, N=212 | Cetuximab N=115 |
|                                       | %                             | %               | %                             | %               |
| Any AE                                | 100.0                         | 100.0           | 100.0                         | 100.0           |
| Related AE                            | 100.0                         | 98.3            | 100.0                         | 99.1            |
| Any serious AE                        | 34.4                          | 26.1            | 42.5                          | 45.2            |
| Related serious AE                    | 19.3                          | 11.3            | 20.3                          | 15.7            |
| Grade 3 or 4 AE                       | 65.1                          | 43.5            | 70.8                          | 57.4            |
| Related Grade 3 or 4 AE               | 53.3                          | 25.2            | 54.7                          | 30.4            |
| AE leading to withdrawal <sup>A</sup> | 17.9                          | 13.0            | 22.6                          | 21.7            |

<sup>A</sup> of cetuximab or irinotecan; AE = adverse event

However, the re-submission presented new toxicity data on the comparator studies. The toxicities associated with third-line chemotherapy treatments in the Rosati and Lim studies were generally mild-to-moderate and manageable. No toxic deaths occurred in either study. The table below compares the grade 3 or 4 adverse event results of cetuximab plus irinotecan with the results from the “key” comparator studies, which suggests that cetuximab + irinotecan has more toxicity (65.1%) than raltitrexed (18.9%) or capecitabine (33.4%).

#### Comparison of toxicities

| Study  | Chemotherapies             | % of patients with grade 3 or 4 adverse events |
|--------|----------------------------|--|
| 007    | cetuximab + irinotecan     | 65.1   |
| Rosati | raltitrexed + mitomycin C  | 18.9   |
| Lim    | capecitabine + mitomycin C | 33.4   |

*For PBAC’s view of these results, see Recommendation and Reasons.*

### 9. Clinical Claim

The re-submission described cetuximab plus irinotecan as having significant advantages in effectiveness over “usual care” and having similar or less toxicity and that this therapy had advantages over the individual components of BSC (i.e. no chemotherapy), capecitabine, raltitrexed and 5-FU.

*See Recommendations and Reasons for the PBAC’s view.*

### 10. Economic Analysis

The submission presented an updated modelled economic evaluation to that presented in the previous submission. The updates included new costs, cost-offsets and utility values and account of the revised continuation criteria.

Depending on the estimate of survival for the “usual care” comparator, the base case modelled incremental cost/extra life-year gained gave a lower estimate in the range \$45,000- \$75,000 and an upper estimate in the range \$75,000 - \$105,000. The base case modelled incremental cost/extra quality adjusted life year (QALY) gained was estimated in the submission to fall in the range \$75,000-\$105,000. However, it fell in the range \$105,000 - \$200,000 using the utility values relied upon by the PBAC in the previous submission.

*For PBAC’s view of the economic analysis, see Recommendation and Reasons.*

## **11. Estimated PBS Usage and Financial Implications**

The submission estimated that the likely number of patients/year would be <10,000 in Year 5.

The submission estimated that the financial cost/year to the PBS would be <\$10 million in Year 5.

## **12. Recommendation and Reasons**

The PBAC considered that the proposed continuation rule would not be enforceable given that there is some doubt as to whether stable disease (SD) would be adhered to as a criterion for ceasing treatment, noting (a) the preferred approach by the expert panel is to continue treatment if SD is observed at 6 weeks, and (b) the TGA recommends that cetuximab treatment be continued until progression of the underlying disease. The PBAC agreed that an element of clinical judgement is required (even with baseline and 6-week radiological assessment) when distinguishing between partial response and stable disease in patients with metastatic colorectal cancer. This suggests the likelihood of misclassifications when assessing the patient’s eligibility under this continuation rule. Further, the under-powered post hoc sub-group analyses represented a weak evidentiary basis to differentiate between “response” and “failure” (especially between partial response and stable disease) in terms of their prognostic value for quantifying differences in subsequent patient-relevant outcomes. This was an issue that affected the continuation rule for imatinib mesylate for patients with gastrointestinal stomal tumours resulting in the July 2004 PBAC meeting recommending its removal.

The PBAC noted that when cetuximab is added to irinotecan, there is a resultant improvement in response rates, disease control and median time to progression. The sponsor noted that a number of patients in Study 007 crossed over from the cetuximab monotherapy arm to the combination arm and thus a statistically significant overall survival gain could not be demonstrated. However, in the absence of a head-to-head randomised trial comparing the cetuximab and irinotecan combination to any of the current alternatives, the PBAC considered that considerable uncertainty remains as to the extent of incremental survival gain that can be attributed to cetuximab plus irinotecan. As previously, the PBAC considered the claimed incremental survival gain over these comparators based essentially on a comparison across single-arm studies applied in the model to be uncertain.

The PBAC also noted that the submission claimed that cetuximab plus irinotecan is of similar or less toxicity than “usual care”. However, a comparison across the single-arm studies provided shows that the proportion of patients with grades 3 and 4 adverse events of cetuximab plus irinotecan is greater than those of the components of “usual care”. The sponsor maintains that the incidence of grade 3 and 4 adverse events per patient derived from

the cetuximab approved Product Information (PI) is similar to those derived from the PI for capecitabine and to those derived from other studies of raltitrexed and best supportive care. Further, the sponsor claimed that the toxicity is mainly due to the irinotecan component of the combination. Although the economic model is claimed to adopt an approach that does not favour cetuximab by assuming the cost of treating adverse effects of “usual care” is \$0, the PBAC considered that uncertainty remains over the comparative toxicity of cetuximab plus irinotecan and “usual care”.

The PBAC noted that Study 007 reports that the mean duration of cetuximab + irinotecan therapy was 18.52 weeks (median duration of 18 weeks). This corresponds to 4.3 months, which is similar to the median time to progression (4.1 months). The PBAC thus agreed that therapy with cetuximab is not expected to be associated with any “Time Without Symptoms (of disease) or Toxicity” (TWiST). Further, the submission’s assumed utility prior to progression is biased in favour of cetuximab for this stage of metastatic colorectal cancer and for the potential impact of disutility associated with the toxicity of cetuximab + irinotecan therapy.

The PBAC concluded that the incremental cost per extra QALY gained is thus biased in favour of cetuximab and, as previously, the submitted base-case range of modelled incremental cost per extra QALY gained was unacceptably high. The PBAC therefore rejected the submission because of uncertain clinical benefit and of unacceptable and uncertain cost-effectiveness.

### **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**

Additional comments on the expected tolerability of cetuximab + irinotecan compared to usual care in routine practice were submitted by the sponsor in pre-committee consultation responses. A summary of our comments is included on the sponsor's website at [www.alphapharm.com.au](http://www.alphapharm.com.au)

The sponsor objects to the use of the word "biased" in Section 12. A summary of our rationale is included on the sponsor's website at [www.alphapharm.com.au](http://www.alphapharm.com.au)