PUBLIC SUMMARY DOCUMENT

Product: Cetuximab, solution for IV infusion, 100mg in 50mL, Erbitux®

Sponsor: Alphapharm Pty Limited

Date of PBAC Consideration: March 2007

1. Purpose of Application

To seek an Authority required listing for the treatment, in combination with radiotherapy, of patients with locally advanced squamous cell cancer of the larynx, oropharynx or hypopharynx in whom the use of cisplatin is either contraindicated or cannot be tolerated.

2. Background

This is the first submission considered by the PBAC for cetuximab for the treatment of squamous cell carcinoma of the head and neck. Previous applications have sought the listing of cetuximab for the treatment of metastatic colorectal cancer.

3. Registration Status

Erbitux is registered:

- 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.
- in combination with radiation therapy is indicated for the treatment of patients with locally advanced squamous cell cancer of the head and neck.

4. Listing Requested and PBAC's View

Authority required
Treatment in combination with radiotherapy, of patients with UICC Stage III, IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx in whom the use of cisplatin is either contraindicated or cannot be tolerated.

Please see the Recommendation and Reasons for the PBAC view

5. Clinical Place for the Proposed Therapy

Cetuximab will provide a treatment option for patients with locally advanced squamous cell cancer of the larynx, oropharynx or hypopharynx in whom use of cisplatin is either contraindicated or cannot be tolerated.

6. Comparator

The submission nominated placebo, as an add-on to radiotherapy alone, as the comparator. The PBAC considered the comparator appropriate.

7. Clinical Trials

An open label head-to-head randomised comparative trial (Bonner Study) comparing cetuximab and radiotherapy with radiotherapy alone was presented. The study's planned follow-up was 5 years. The submission reported the results based on median duration of follow-up of 45.7 months for the radiotherapy alone group, and 45 months for the combined radiotherapy plus cetuximab group.

The trial forming the basis of the submission is detailed below.

Trial	Publication citation
Bonner study	Bonner JH, PM, Giralt J, Azarnia N, Shin D, Cohen R, Jones C, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. The New England Journal of Medicine 2006;354(6):567-578

8. Results of Trials

The results of the key trial are summarised in the tables below.

Results of the comparative randomised trial- loco-regional control (primary outcome)

	Cetuximab + radiotherapy n = 211	**Radiotherapy alone** n = 213
Median duration LRC months (95% CI)	24.4 (15.7 to 45.1)	14.9 (11.8 to 19.9)
Hazard Ratio (95% CI)	0.68 (0.52 to 0.89) p = 0.005	
Patients with LRC % (95% CI)		
One year	63.2 (56.5 to 69.8)	55.3 (48.5 to 62.2)
Two year	50.3 (43.4 to 57.3)	40.7 (33.8 to 47.5)

There was a statistically significant difference in loco-regional control favouring cetuximab in the Bonner trial's primary analysis.

Results of the comparative randomised trial- overall survival (secondary outcome)

	Cetuximab +Radiotherapy n = 211	**Radiotherapy alone** n = 213
Median survival months (95% CI)	49.0 (32.8 to 62.6*)	29.3 (20.6 to 42.8)
Hazard Ratio (95% CI)	0.74 (0.56 to 0.97) p = 0.032	
Patients alive % (95% CI)		
One year	77.6 (72.0 to 83.3)	73.8 (67.9 to 79.8)
Two year	62.2 (55.6 to 68.7)	55.2 (48.4 to 62.0)
Three year	56.1 (49.3 to 62.8)	45.0 (38.2 to 51.9)

- median survival had not been reached at the time of the assessment. Months shown are those for duration of follow-up for the relevant groups.

The PBAC noted that there was a large difference between the population enrolled in the Bonner study and the Australian patients who might receive cetuximab, with the trial having a higher proportion of patients with oropharyngeal disease than is observed in Australia, as patients with oropharyngeal disease are generally considered to respond better to treatment than those with disease of the larynx or hypopharynx. The Committee however agreed with the sponsor that there is currently no evidence to suggest that this difference would result in a

significant difference in effectiveness for cetuximab if listed on the PBS as requested compared to that observed in the Bonner study. The impact of tumour location on the effectiveness of cetuximab in the Bonner study was subject to a predefined subgroup analysis and the confidence intervals of the hazard ratios for these subgroups overlapped for both the primary (locoregional control) and the secondary (survival, progression free survival) outcomes.

Overall the adverse events associated with radiation therapy appear to be similar in the cetuximab + radiotherapy arm compared to those in the radiotherapy alone arm. The incidence of the acne, rash, headache, fever, pruritus and chills was higher in patients who received cetuximab and radiotherapy compared to those who received radiotherapy alone.

9. Clinical Claim

The submission claimed that cetuximab plus radiotherapy has significant clinical advantages over radiotherapy alone but has more toxicity.

For PBAC's view see Recommendation and Reasons

10. Economic Analysis

A preliminary economic evaluation adopting a cost-effectiveness approach was presented. The resources included the overall comparative costs and outcomes for each alternative.

The trial-based incremental discounted cost/extra life year gained was estimated to be between $45,000 – $75,000 and the trial-based incremental discounted cost/extra year of loco-regional control gained was estimated to be between $15,000- $45,000.

A modelled economic evaluation was presented. The resources included were similar to the preliminary economic evaluation with the only difference being ongoing consultations with an oncologist.

The base case modelled incremental discounted cost/extra life year gained was estimated to be between $15,000- $45,000 as was the base case modelled incremental discounted cost/extra year of loco-regional control gained.

11. Estimated PBS Usage and Financial Implications

The submission estimates that the number of patients treated would be <1,000 and that the estimated gross cost to the PBS would be, < $3 million in Year 4 of listing.

12. Recommendation and Reasons

The PBAC recommended listing for use in Stage III, IVa or IVb squamous cell cancer on the larynx, oropharynx or hypopharynx in combination with radiotherapy, on the basis of acceptable cost-effectiveness against radiotherapy alone, at the price proposed in the submission. The Committee accepted that loco-regional control was a more relevant end-point in head and neck cancers than in other cancers, and considered that the incremental cost of treatment with cetuximab in these patients was acceptable at between $15,000-$45,000 per extra life year gained, even though the survival gains were not quality adjusted.

The PBAC noted that there was a large difference between the population enrolled in the Bonner study and the Australian patients who might receive cetuximab, with the trial having a higher proportion of patients with oropharyngeal disease than is observed in Australia, as patients with oropharyngeal disease are generally considered to respond better to treatment than those with disease of the larynx or hypopharynx. The Committee however agreed with the sponsor that there is currently no evidence to suggest that this difference would result in a significant difference in effectiveness for cetuximab if listed on the PBS as requested compared to that observed in the Bonner study. The impact of tumour location on the effectiveness of cetuximab in the Bonner study was subject to a predefined subgroup analysis and the confidence intervals of the hazard ratios for these subgroups overlapped for both the primary (locoregional control) and the secondary (survival, progression free survival) outcomes.

The Committee agreed with the restriction wording proposed by the Restrictions Working Group with the following amendments: (1) cetuximab should not be subsidised in patients who have completed cisplatin treatment; (2) the contraindications to cisplatin should be those in the TGA approved product information; and (3) lifetime subsidised treatment should be limited to a maximum of 8 supplies per treatment site, on the basis that a normal treatment course requires 8 supplies, but with a proviso that the maximum can be increased to 10 in a patient in whom radiotherapy is suspended. Furthermore, the Committee requested that Medicare Australia formulate questions for prescribers to ensure that cetuximab is used in combination with radiotherapy, ie not as monotherapy or in combination with cisplatin

The PBAC requested the sponsor provide the Committee with updates of the results of clinical trials in this indication, and that usage be monitored by the DUSC for any evidence that cetuximab is being used first line.

The PBAC recommended the 20 day safety net rule should not apply.

Recommendation

CETUXIMAB, solution for IV infusion, 100mg in 50mL

Restriction:	Authority required Initial treatment of stage III, IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx for the week prior to radiotherapy, where cisplatin is contraindicated according to the TGA approved Product Information. Initial treatment of stage III, IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx in combination with radiotherapy, where cisplatin is not tolerated.
Maximum Quantity:	6
Repeats:	nil

NOTE: No applications for repeats will be authorised

Restriction: Authority required

Continuing treatment of stage III, IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx, in combination with radiotherapy, where cisplatin is either contraindicated or not tolerated.

NOTE: A maximum lifetime supply for this indication is limited to a maximum of 8 treatments per site and to 10 treatments per site for patients in whom radiation is suspended

Maximum Quantity: 4
Repeats: 6

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 chose not to make a comment.