PUBLIC SUMMARY DOCUMENT
Product: TOPOTECAN, capsules, 0.25 mg and 1 mg (as hydrochloride), Hycamtin®
Sponsor: GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought an Authority Required (STREAMLINED) listing for treatment of relapsed or refractory small cell lung cancer (SCLC) where intravenous (IV) therapy is inappropriate.

2. Background

Topotecan hydrochloride capsules had not previously been considered by the PBAC.

3. Registration Status

Topotecan hydrochloride capsules 0.25 mg and 1 mg were TGA registered on 26 August 2009 for treatment of patients with relapsed small cell lung cancer for whom re-treatment with the first-line regimen is not considered appropriate.

4. Listing Requested and PBAC's View

The sponsor proposed a revised listing in the Pre-PBAC response as follows:

Authority Required
Relapsed small cell lung cancer in a patient with ECOG performance status of 0, 1 or 2, where:

- Re-treatment with the first-line regimen is not considered appropriate, and;
- The combination of cyclophosphamide, doxorubicin and vincristine (CAV) is contraindicated.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Small cell lung cancer accounts for approximately 15% of all lung cancers, and is the most aggressive type of lung cancer, with a median survival in untreated patients of 2-4 months. Despite the efficacy of first-line chemotherapy and radiotherapy, most patients will eventually experience disease recurrence or progression, with response to second-line therapy remaining consistently poor. For many patients, second-line IV chemotherapy is not given due to treatment refractory disease, co-existing morbidities, persistent toxicities arising from first-line treatment, or patient preference not to undergo further treatment. For these patients, the only currently available option is best supportive care (BSC).

Oral topotecan is proposed as a treatment option for patients with relapsed SCLC for whom second-line intravenous chemotherapy is inappropriate.

6. Comparator

The submission nominated best supportive care for patients with relapsed small cell lung cancer where IV treatment is considered inappropriate as the comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented one randomised open-label trial (Study 478) comparing oral topotecan (2.3 mg/m^2/day for 5 days in a 21-day cycle) plus BSC with BSC alone in patients with relapsed SCLC for whom chemotherapy is considered inappropriate.

The submission also presented an indirect comparison of three randomised trials comparing oral topotecan with CAV using IV topotecan as common reference. The submission did not include this indirect comparison in the economic model.

Details of the trials published at the time of submission are presented in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct comparison		
Study 478		
O'Brien M, et al	Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer.	Journal of Clinical Oncology 2006; 24: 5441-7
Chen L, et al	Symptom assessment in relapsed SCLC: Cross-validation of the patient symptom assessment in lung cancer instrument.	Journal of Thoracic Oncology 2008; 3: 1137-45
Indirect comparison		
Oral topotecan		
Study 065		
von Pawel J, et al	Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer.	Journal of Clinical Oncology 2001; 19(6): 1746-1749
Study 396		
Eckardt JR, et al	Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer.	Journal of Clinical Oncology 2007; 25(15): 2086-92
CAV		
Study 090		
von Pawel J, et al	Topotecan versus cyclophosphamide, doxorubicin and vincristine for the treatment of recurrent small-cell lung cancer.	Journal of Clinical Oncology 1999; 17(2): 658-667

8. Results of Trials

Oral topotecan + BSC versus BSC alone

The primary outcome of Study 478 was overall survival. The main secondary outcomes were response rate (topotecan plus BSC arm only) and quality of life, assessed using the EQ-5D.

The PBAC noted that treatment with topotecan + BSC resulted in an additional 12 weeks median survival (25.9 weeks; 95%CI: 18.3, 31.6) when compared to BSC treatment (13.9 weeks; 95%CI: 11.1, 18.6). The six months survival rate was also higher in the topotecan + BSC group compared to the BSC group, however statistical significance was not tested for this outcome.

For EQ-5D symptom scores from Study 478, the PBAC noted the mean rate of change (decrease in quality of life score) from baseline per three month interval was significantly

greater for BSC compared to topotecan + BSC treatment. The open-label nature of the trial may have compromised these results.

Grade 3/4 haematological adverse events and diarrhoea occurred significantly more often in patients treated with topotecan + BSC compared with BSC alone. No other significant differences in Grade 3/4 adverse events were observed. In the topotecan + BSC group three patients died due to haematological toxicity, while none of the patients in the BSC group died due to this cause.

Indirect comparison oral topotecan vs. CAV

The submission stated that the meta-analysis of oral topotecan versus CAV, using IV topotecan as a common reference, indicated there was no statistically significant difference in tumour response between oral and IV topotecan. The meta-analysis of Study 065 and Study 396 indicated there is heterogeneity for the primary outcome. Due to different response rates and likely differences in the patient populations in the trials, an additional indirect comparison was performed during the evaluation, excluding Study 065 from the analysis. This analysis also found there to be no statistically significant difference in tumour response between oral topotecan and IV CAV using IV topotecan as common reference.

The submission stated that while an indirect comparison was not performed for overall survival, the point estimates from Study 065, Study 396 and Study 090 suggest that there is unlikely to be a difference between oral topotecan and CAV in terms of overall survival.

The indirect comparison indicated that, compared with CAV treatment, oral topotecan was associated with significantly less neutropenia and more thrombocytopenia, anaemia and diarrhoea. Using the odds ratio (OR), the result for neutropenia was not statistically significant. Both oral topotecan and CAV treatment were associated with death due to haematological toxicity.

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

9. Clinical Claim

Oral topotecan + BSC versus BSC alone

The submission described topotecan plus BSC as superior in terms of comparative effectiveness and inferior in terms of comparative safety compared with BSC for the treatment of patients with relapsed SCLC where further intravenous chemotherapy is inappropriate.

Indirect comparison oral topotecan vs. CAV

The submission described oral topotecan as non-inferior in terms of comparative effectiveness and having a different safety profile over CAV treatment.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

Oral topotecan + BSC versus BSC alone

A trial-based economic evaluation was presented, based on the direct randomised trial (Study 478).

A stepped analysis was presented in which health outcomes were presented as life years gained and then as quality-adjusted life years (QALY) gained.

The time horizon in the modelled economic evaluation was the maximum duration of follow-up of the individual patients in the trial, which was up to 71 cycles (4.08 years).

The economic evaluation estimated the incremental cost/extra life year gained (discounted) and the incremental cost/extra QALY gained (discounted) to both be in the range of $15,000 and $45,000.

The submission presented sensitivity analyses which considered variations in the base case assumptions used and patient subgroups as defined in Study 478 namely gender, presence of liver metastases, performance status and time to relapse.

For PBAC's view, see Recommendation and Reasons.

Indirect comparison oral topotecan vs. CAV

The submission did not provide a cost-effectiveness analysis comparing oral topotecan with CAV treatment, on the basis that it requested listing for patients for whom IV chemotherapy is considered inappropriate.

During the evaluation an indicative cost-minimisation analysis was performed, including only drug costs and infusion costs. In this analysis the average dose of topotecan per cycle was used for the calculations. The indicative cost-minimisation analysis showed that oral topotecan is more expensive than IV CAV therapy.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost per year to the PBS to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted the revised restrictions proposed in the sponsor's Pre-Sub-Committee Response and the Pre-PBAC response and considered that it would be difficult to define "contraindication to CAV". In addition, it would also be difficult to define "patients for whom IV therapy is inappropriate" as proposed in the original restriction. The PBAC considered that despite the revised restrictions, topotecan was likely to be used in some patients who prefer oral rather than IV treatment and therefore oral etoposide would also be an appropriate comparator. Further, the submission and clinical trial report did not provide a well defined description of the inclusion criterion "patients not considered suitable for further IV chemotherapy" and therefore it could not be ascertained whether the term would include the same patients in the proposed population compared with the clinical trial.

The PBAC considered that the requested restriction did not match the trial population as some patients in the trial received further intravenous chemotherapy. The PBAC considered that by only comparing topotecan with best supportive care and not with other treatments that topotecan was likely to replace, it was difficult to define its place in therapy. The PBAC noted that for most patients (70%) in the clinical trial the time to progression was greater than 60 days and therefore patients may be eligible for treatments such as oral etoposide, repeat first line therapy (cisplatin/carboplatin and etoposide) or CAV. The PBAC also noted that 38% of patients had limited disease which may enable treatment with a tolerable radiation field and therefore topotecan may have been used in this setting as additional "adjuvant therapy" or maintenance therapy.

The PBAC noted that an indirect comparison of topotecan versus CAV was presented but considered that this may not be appropriate due to differences in baseline patient characteristics across the three trials and between each of the treatment arms within the trials. It also appeared that oral topotecan might be associated with more toxicity compared with CAV treatment.

The PBAC agreed that based on supporting data the clinical claim that topotecan plus BSC is superior in terms of comparative effectiveness and inferior in terms of comparative safety compared with BSC for the treatment of patients with relapsed SCLC where further intravenous chemotherapy is inappropriate was reasonable. However, the PBAC again noted that the term "IV appropriate" was not well defined in the clinical trial and could include patients who prefer not to undergo further IV chemotherapy.

The PBAC noted the sponsor's Pre-Sub-Committee Response regarding a decision of cost-effectiveness being made on the basis of the cost per life year gained but considered that in this case it would not reduce the uncertainty associated with the quality of life outcomes. The PBAC preferred quality adjusted life years and this was the preferred basis of all decisions by the PBAC.

The trial-based economic evaluation based on the direct randomised trial (Study 478) estimated the incremental cost effectiveness ratio to be between $15,000 and $45,000 /LYG (discounted) and between $15,000 and $45,000/QALY (discounted). The PBAC noted that the results of the sensitivity analyses indicate that the model is most sensitive to variation in the assumptions used for calculating the utility values and the subgroup analyses assessing the effect of male gender and the presence of liver metastases. There was a difference in ICER between men ($75,000 – $105,000/QALY) and women (less than $15,000/QALY). Given that 73% of the population are males, the PBAC considered that the base case ICER should probably be closer to the male not the female figure.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit and a high and uncertain incremental cost-effectiveness ratio.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

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

GSK is disappointed with the outcome and is considering options to make the product available to patients.