PUBLIC SUMMARY DOCUMENT

Product: Axitinib, tablet, 1 mg and 5 mg, Inlyta®
Sponsor: Pfizer Australia Pty Ltd.
Date of PBAC Consideration: November 2013

1. Purpose of Application

To request Authority required listing for the treatment of Stage IV clear cell variant renal cell carcinoma (RCC) in a patient who meets certain criteria.

2. Background

Axitinib had not previously been considered by the PBAC.

The PBAC noted that a submission for sorafenib for the treatment of Stage IV (advanced) clear cell renal carcinoma was also on its November 2013 meeting agenda and so considered the two medicines in relation to each other.

3. Registration Status

Axitinib was TGA registered on 26 July 2012 for the treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy.

4. Listing Requested and PBAC's View

Authority required

Initial PBS-subsidised treatment, as monotherapy, of stage IV clear cell variant renal cell carcinoma (RCC) in a patient with a WHO performance status of 2 or less, where disease progression has occurred following treatment with a tyrosine kinase inhibitor.

Continuing PBS-subsidised treatment, as monotherapy, of Stage IV clear cell variant renal cell carcinoma in a patient who has previously been issued with an authority prescription for axitinib and who has stable or responding disease according to Response Evaluation Criteria in Solid Tumours (RECIST).

Listing was requested on the basis of a cost-effectiveness claim compared with best supportive care (BSC). The PBAC considered the proposed restriction's intention to restrict axitinib to second-line treatment to be appropriate, given that sunitinib and pazopanib are listed on the PBS as first-line treatment for renal cell carcinoma.

5. Clinical Place for the Proposed Therapy

Axitinib is a selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor (VEGR) receptors 1, 2 and 3. These receptors are implicated in pathological angiogenesis, tumour growth and metastatic progression of cancer.

The submission proposed axitinib to be used as second-line treatment of Stage IV clear cell RCC after failing treatment with either sunitinib or pazopanib. There are currently no PBS-listed treatment options for the second-line treatment of stage IV clear cell renal cell carcinoma.

6. Comparator

The submission nominated BSC as the comparator. This was accepted as appropriate by the PBAC.

The PBAC considered that sorafenib was also a relevant comparator.

7. Clinical Trials

No head-to-head trials comparing axitinib and BSC were identified in the literature search. The key analysis presented in support of the submission's clinical claim was an indirect comparison of axitinib and placebo, with sorafenib as the common comparator, based on two studies: AXIS and RENCOMP.

The submission also presented a supportive analysis: an indirect comparison conducted using a "simulated treatment comparison" (STC). This analysis was based on data from AXIS and RECORD-1. STC is a relatively new method (main paper published in 2010) developed to estimate comparative effects in the absence of direct comparisons. The STC isolate the results of two arms from different trials and aims to estimate in this case how the prior-sunitinib group from the AXIS trial would have performed if they had been treated with placebo, using data from RECORD-1. This is a different approach to network meta-analysis, a method that attempts to estimate average effects. The PBAC agreed with the Economics Sub-Committee (ESC) and considered that the STC was not sufficiently validated to be able to provide reliable information regarding the relative effect size.

The submission also included five trials as supportive evidence. However, the PBAC considered these trials were not reliable as they were either trials that were not sufficiently powered or non-randomised. Trial A4061051 was a supplementary study to support the registration of axitinib in China and was conducted in a subgroup of Asian patients who had previously received treatment for mRCC (cytokines or sunitinib or both). The trial design was very similar to the AXIS trial however it was not sufficiently powered to detect differences in OS or PFS. Albiges 2011, Lui 2009, Miscoria 2011 and Poffiri 2010 (abstract publications only) were presented to support OS of patients treated with BSC after first line therapy with a TKI (sunitinib or sorafenib). All four studies were non-randomised and retrospective.

Details of the trials and associated reports presented in the submission are presented in the table below.

Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Trial of axitinib for 2nd line treatment of advanced mRCC		
Trial A4061032	Final Supplemental Clinical Study Report: Axitinib (AG-013736) as second line therapy for metastatic renal cell	1 November 2011

Trial	Protocol title/ Publication title	Publication citation
Trial of axitinib for 2nd line treatment of advanced mRCC		
(AXIS)	cancer: Axis Trial	
	Motzer RJ et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial.	The Lancet Oncology, 2013; 14:552-562.
	Rini B. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial.	Lancet. 2011; 378 (9807): 1931-1939
Studies of BSC to facilitate an indirect comparison with axitinib		
RENCOMP	Wahlgren T. Treatment and overall survival in renal cell carcinoma: a Swedish population-based study (2000-2008)	British J of Cancer. 2013. (Advance Online Publication: 26/3/2013)
	Sandstrom P. Overall survival in metastatic renal cell carcinoma: A comparison between sorafenib and best supportive care after first line treatment with sunitinib in Sweden 2000-2009	ESMO, Austria, Sept-Oct, 2012. Poster 848P
RECORD-1	Motzer R. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial	Lancet. 2008; 372: 449-56
	Motzer R. Phase III trial of everolimus for metastatic renal cell carcinoma. Final results and analysis of prognostic factors	Cancer. 2010; 116: 4256-65
	Bracarda S. Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis.	British J of Cancer. 2012; 106: 1475-1480
	Calvo E. Everolimus in metastatic renal cell carcinoma: subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study.	European J of Cancer. 2012; 48: 333-339
	Proskorovsky I. Axitinib (AXI) and Best Supportive Care (BSC) in the treatment of sunitinib-refractory patients with metastatic renal cell carcinoma (mRCC: Results of a Simulated Treatment Comparison (STC) analyses.	ISPOR EU: 29 Oct 2012: Poster 40386
Supporting studies (not used in indirect comparisons)		
Axitinib		
Trial A4061051	Clinical study report for previously treated Asian patients on Protocol A4061051: AG-013736 (axitinib) for the treatment of metastatic renal cell cancer.	26 Sept 2012
Best Supportive Care (BSC)		
Albiges (2011)	Prognosis of patients with metastatic renal cell carcinoma (mRCC) with primary resistance to sunitinib:	European Multidisciplinary

Trial	Protocol title/ Publication title	Publication citation
Trial of axitinib for 2nd line treatment of advanced mRCC		
	Is there any active treatment?	Cancer Congress. 2011; S518: Abstract 7143
Lui (2009)	A retrospective review of treatment discontinuation and survival in patients with advanced renal cell carcinoma treated with sunitinib or sorafenib.	Joint ECCO 15 – 34th ESMO Multidisciplinary Congress Berlin Germany. European J of Cancer. 2009; 7 (2-3): 429. Abstract 7120
Miscoria (2011)	Miscoria M: Analysis of survival after disease progression in patients with renal cell carcinoma (RCC) who failed treatment with sunitinib.	J of Clinical Oncology. 2011 ASCO Annual Meeting Proceedings. 2011; 29 (suppl 1): e15154
Poffiri (2010)	Poffiri E: The outcome of patients who fail sunitinib and do not have access to sunitinib therapy.	Annals of Oncology. 35th ESMO Congress Milan Italy. 2010; 21 (suppl 8): 931P

8. Results of Trials

With regards to comparative effectiveness, the submission reported the results for OS from AXIS and RENCOMP and the indirect comparison. The PBAC agreed that OS was the most relevant outcome for decision making. However, the PBAC agreed with the ESC that the indirect comparison was not informative for decision making purposes given the significant risk of bias in the RENCOMP study. Also there were substantial differences in the studies in terms of their design, the baseline characteristics of patients, the treatments and the methods of analyses. The PBAC agreed with the ESC that the submission did not adequately support the use of progression free survival (PFS) as a surrogate for OS.

Instead, the PBAC considered the following summary of the ITT results from AXIS, RECORD-1 and RENCOMP as presented in the ESC Advice.

Summary of overall survival (OS) results from the included trials/studies

Trial/Study	Population/ Outcome	Number of events n(%)		Mean Diff (95%CI)	HR or RR (95% CI) p-value
Trials of axitinib					
Trial A4061032 (AXIS)	**ITT**	**Axitinib (N=359)**	**Sorafenib (N=355)**		
	Died n (%)	211(59.6%)	214(60.3%)	-0.01 (-0.09, 0.06)	0.997 (0.9, 1.1)
	Median OS (mth) 95%CI	20.1 (16.7-23.4)	19.2 (17.5-22.3)	0.9	0.969(0.80-1.174) P=0.3744
	Prior sunitinib-treated subgroup	**Axitinib (N=194)**	**Sorafenib (N=195)**		
	Died n (%)	131 (67.5)	131(67.2)	<0.01(-0.9,0.1)	1.0 (0.9, 1.2)
	Median OS (mth) 95%CI^	15.2	16.5	-1.3	0.997(0.782,1.270) p=0.4902
Studies /Trials of BSC					
RENCOMP Sandstrom et al (2012)	**Prior 1st line sunitinib**	**Sorafenib (N=59)**	**BSC (N=76)**		
	Median OS (mth) unadjusted*	9.2 (5.2, 13.2)	5.8 (3.9-7.7)	3.4	**0.640(0.426, 0.961) P=0.031**
	Median OS (mth) Adjusted Model 1[a]	9.6	6.6	3	0.652(0.412, 1.030) P=0.067
	Median OS (mth) Adjusted Model 2[b]	9.9	6.6	3.3	**0.621(0.412, 0.936) P=0.023**
RECORD-1	**ITT**	**Everolimus (N=277)**	**BSC (N=139)**		
	Median OS (mth) unadjusted	14.78	14.39	0.39	0.87 (0.65, 1.17) P=0.162
	Median OS (mth) post hoc RPSFT[c]	14.8	10*	4.8	0.60 (0.22, 1.65) p=NS
		16.8	8.3	8.2	

Abbreviations: BSC=basic supportive care, OS=overall survival, NA=not applicable, NR=not reported, Mean Diff=mean absolute difference

^ Not powered to detect difference in overall survival or progression free survival

**Simulated Treatment Comparison (STC) analysis – no CI reported

[a] covariates in multivariate cox model also include: age at start of 2nd line treatment (age 65+ vs age<65), gender, whether nephrectomy was performed or not, lead time between RCC and mRCC (1yr+ vs <1yr), days since mRCC diagnosis and start of systemic therapy with sunitinib (<1yr vs 1 yr+), days if sunitinib treatment (90days+ vs <90days), treating institution size (large vs small) and region of Sweden.

[b] covariates in multivariate cox model also include: age 2nd line treatment started (age 65+vs age<65), lead time between RCC and mRCC (1yr+ vs <1yr), gender, nephrectomy (yes vs no).

[c] this is a post hoc analysis to adjust for crossover using the rank-preserving structural failure time analysis (RPSFT) – Source: Motzer (2010), page 4261. The unadjusted OS for BSC was 14.4 months.

* prior sunitinib treated patients

+ prior sunitinib and/or sorafenib treated patients

The PBAC noted that no significant differences in median OS between axitinib and sorafenib treated patients were observed for either the ITT or the prior sunitinib treated subgroup in the AXIS trial. Analysis of the RENCOMP study estimated a statistically significant unadjusted hazard ratio (HR), which was used in the indirect comparison. However, when a multivariate Cox proportional model was used incorporating all factors that were considered a priori to influence survival, the difference was no longer statistically significant.

The PBAC considered that the results of the AXIS trial support a conclusion of non-inferiority of axitinib to sorafenib, but the indirect comparison of axitinib versus BSC via AXIS and RENCOMP does not support the conclusion of superior OS for axitinib over BSC.

The PBAC considered that insufficient data were presented to inform a judgement about the size of effect of axitinib over BSC. The sub-group analysis (prior-sunitinib treated patients) that was used to estimate the effect size of axitinib versus BSC in the target population for PBS listing is not valid, as it is also based on the same flawed comparison as the observational data set.

The PBAC also considered that the STC analysis was not reliable and that the results were not helpful for decision making given that the analysis involved a comparison of two single treatment arms rather than a comparison of randomised treatment allocation. The PBAC acknowledged that the STC approach attempts to correct for baseline imbalances between the two trials.

With regards to comparative harms, the most frequently reported adverse events (AEs) for axitinib (all grades) were diarrhoea (55%), hypertension (40%), fatigue (39%), decreased appetite (34%), nausea (32%), and dysphonia (31%). The most common adverse event or laboratory abnormalities of grade ≥3 or higher for axitinib were hypertension (16%), diarrhoea (11%) and fatigue (11%). In AXIS, 54.6% and 26.5% of patients started or increased their dose of existing hypertension or hypothyroidism medication after starting treatment with axitinib.

Compared to sorafenib, significantly more patients treated with axitinib experienced greater than or equal to grade 3 vomiting and fatigue with axitinib, but fewer rashes, Palmar-Plantar erythro-dysaesthesia, hypophosphatemia and lipase elevations.

The PBAC noted that the submission did not incorporate the costs associated with the management of axitinib related adverse events in the modelled economic evaluation. The PBAC did not consider this omission to be appropriate.

9. Clinical Claim

The submission described axitinib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC based on results reported for OS and PFS derived from the indirect comparison. The PBAC considered this reasonable with respect to safety, but not reasonable with respect to efficacy.

The PBAC considered that the indirect comparison presented in the submission and the simulated treatment comparison did not adequately support the claim of superior effectiveness over BSC.

The PBAC considered that the results of the AXIS trial would support a conclusion of non-inferiority of axitinib to sorafenib. The PBAC noted the sponsor's comments in its pre-PBAC response that the recommended doses in the AXIS trial were 5 mg twice daily for axitinib and 400 mg twice daily for sorafenib.

10. Economic Analysis

The submission presented a stepped modelled economic evaluation (cost utility analysis, CUA) based on the claim of superior efficacy. The submission presented an ICER between $45,000 and $75,000 per quality adjusted life year (QALY) based on the OS outcome from the indirect comparison, applied to a single cohort population similar to patients of AXIS extrapolated to 6 years (from 3 years in the trial) and applying utility weights from the AXIS trial.

The PBAC considered that the clinical data did not support the claim of superior efficacy of axitinib over BSC. Therefore, as the clinical efficacy was not substantiated, the PBAC did not find the economic modelling to be valid or informative.

11. Estimated PBS Usage and Financial Implications

The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of axitinib.

The estimated net cost per year to the Government was between $10 and $30 million in Year 5.

The PBAC agreed with the Drug Utilisation Sub-Committee (DUSC) that the estimates presented in the submission were overestimated, with the main issues relating to the number of patients treated with a tyrosine kinase inhibitor (TKI - sunitinib or pazopanib) first line, the number of patients treated with second line axitinib, the duration of treatment with axitinib and the cost-offsets used.

12. Recommendation and Reasons

The PBAC rejected the submission to list axitinib on the PBS for the second-line treatment of Stage IV clear cell RCC on the basis of inadequate data to support the claim of superior clinical effectiveness over BSC.

The PBAC considered that the indirect comparison presented in the submission was not informative for decision making purposes given the significant risk of bias in the RENCOMP study. Also there were substantial differences in the two studies in terms of their design, the baseline characteristics of patients, the treatments and the methods of analyses. The PBAC agreed with the ESC that the submission did not adequately support the use of progression free survival (PFS) as a surrogate for OS.

Because the claim of clinical efficacy was not substantiated by the data presented, the PBAC did not find the economic modelling to be valid or informative.

The PBAC considered that the results of the AXIS trial would support a conclusion of non-inferiority of axitinib to sorafenib.

The PBAC acknowledged that a clinical need exists for treatment of Stage IV RCC, noting that no second line treatments are currently available on the PBS. The PBAC also acknowledged the views of consumers regarding the unmet clinical need for PBS subsidised

therapies for the second-line treatment of stage IV renal cell carcinoma. However PBAC considered that recommending treatment options on the PBS for renal cell carcinoma in the second line setting would still need to be made on the basis of strong clinical evidence supporting clinical efficacy over BSC.

The PBAC noted that the submission meets the criteria for an Independent Review.

Outcome:
Rejected

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

Provision of overall survival evidence is an ongoing challenge in oncology necessitating alternative approaches to address reimbursement requirements in the context of the data deficiencies from clinical trials involving cancer patients. The Sponsor is considering its options.