

**7.2 AXITINIB,
tablets, 1 mg & 5 mg;
Inlyta[®]; Pfizer Australia Pty Ltd.**

1 Purpose of Application

1.1 The major re-submission sought an Authority Required listing for treatment of second-line treatment of stage IV clear cell variant renal cell carcinoma (RCC).

2 Requested listing

2.1 The Secretariat's suggested wording for the restriction for initial and continuing treatment is presented below as the re-submission's presented restriction was in the incorrect format.

Name, Restriction, Manner of administration and form	Max Qty (Units)	No. of Rpts	Proprietary Name and Manufacturer	
AXITINIB				
axitinib 1 mg tablet, 28	56	2	Inlyta	Pfizer
axitinib 5 mg tablet, 28	56	2	Inlyta	Pfizer

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	---
Severity:	Stage IV
Condition:	clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

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Clinical criteria:	<p>Patient must have progressive disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) following first-line treatment with a tyrosine kinase inhibitor,</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>Patient must not have developed progressive disease following second-line everolimus treatment [<i>insert into everolimus' listing if axitinib is recommended for listing; replace 'everolimus' with 'axitinib'</i>]</p>
Prescriber Instruction	Patients who have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised treatment with this drug.
Prescriber Instruction	Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment.
Administrative Advice	<p><u>Note</u> Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.</p> <p><u>Note</u> No increase in the maximum number of repeats may be authorised.</p> <p><u>Note</u> Special Pricing Arrangements apply</p>

Name, Restriction, Manner of administration and form	Max Qty (Units)	No. of Rpts	Proprietary Name and Manufacturer	
AXITINIB				
axitinib 1 mg tablet, 28	56	5	Inlyta	Pfizer
axitinib 5 mg tablet, 28	56	5	Inlyta	Pfizer

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	---

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Severity:	Stage IV
Condition:	clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuing treatment beyond 3 months
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously been issued with an authority prescription for this drug for this condition,</p> <p>AND</p> <p>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST),</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
Prescriber Instruction	Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment.
Administrative Advice	<p><u>Note</u> Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.</p> <p><u>Note</u> No increase in the maximum number of repeats may be authorised.</p> <p><u>Note</u> Special Pricing Arrangements apply.</p>

- 2.2 The ESC noted that the PCSR (p.1) agreed with the proposal to list both the 1 mg and 5 mg strengths for initial treatment, and all other Secretariat suggested changes.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 Axitinib was TGA registered on 19 July 2012 for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

- 3.2 This was the second consideration by the PBAC.
- 3.3 In November 2013, 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 best supportive care (BSC).
- 3.4 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. There were substantial differences in the two studies used in the indirect comparison 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 overall survival (OS).
- 3.5 Since 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.

4 Clinical place for the proposed therapy

- 4.1 The re-submission proposed axitinib to be used as second-line treatment of Stage IV clear cell renal cell carcinoma (mRCC) as an alternative to everolimus. Since the previous submission, everolimus had been approved by the PBAC for the second-line treatment of Stage IV clear cell RCC.

5 Comparator

- 5.1 The re-submission nominated everolimus as the main comparator. This was considered appropriate. This was a different comparator from the previous submission (best supportive care) but was reasonable since everolimus for second-line treatment of RCC had since been listed on the PBS.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (6) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with axitinib including a clinical need for having alternative second line drug made available for the treatment of RCC.
- 6.3 Kidney Health Australia commented on the increasing incidence of renal carcinoma

in Australia and the comparative lack of PBS-subsidised treatment options compared to other cancers. Kidney Health Australia noted that available treatments in Australia lag behind other national and multinational treatment guidelines in terms of the number of lines of treatment available to patients and prescribers beyond disease progression. Kidney Health Australia further commented that it was of the view that a tyrosine kinase inhibitor (TKI) followed by another TKI and then a mammalian target of rapamycin (mTOR) therapy for progressive disease would provide better outcomes than a sequence of TKI followed by an mTOR therapy followed by another TKI.

Clinical trials

- 6.4 The re-submission was based on one trial (AXIS) comparing axitinib to sorafenib (n=723) and one trial (RECORD-1) comparing everolimus to placebo (n=416). These trials were presented in the previous submission.
- 6.5 An indirect comparison using either sorafenib or BSC as a common reference was not conducted as there were no data available. The re-submission provided a side-by-side comparison and used Simulated Treatment Comparison (STC) and Matching-Adjusted Indirect Comparison (MAIC) methods to compare axitinib with everolimus in terms of the primary outcome of progression-free survival (PFS) and the secondary outcome of overall survival (OS).
- 6.6 Details of the trials presented in the re-submission are provided in the table below. Additional publications for both trials were identified in the updated literature search.

Trials (and associated reports) presented in the submission

Trial	Description	Reports
Axitinib		
Trial A4061032 (AXIS)	Randomised, open-label trial comparing axitinib to sorafenib in patients with clear cell mRCC following failure of one prior systemic first-line therapy	Final Supplemental Clinical Study Report: Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer: Axis Trial. 1 November 2011.
		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. <i>The Lancet Oncology</i> , 2013; 14:552-562.
		Rini B. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. <i>Lancet</i> . 2011; 378 (9807): 1931-1939.
		Cella D. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. <i>British Journal of Cancer</i> , 2013; 108(8): 1571-1578.
		Escudier B et al. Safety and efficacy of second-line axitinib versus sorafenib in metastatic renal cell carcinoma by duration of prior therapy: Subanalyses from a phase III trial. <i>European Journal of Cancer</i> , 2013; 49(Suppl.2): Abs2795.
		Escudier B. Axitinib versus sorafenib in advanced renal cell carcinoma: subanalyses by prior therapy from a randomised phase III trial. <i>British Journal of Cancer</i> , 2014; 1-8 doi:10.1038/bjc.2014.244.
Trial A4061051	Randomised, open-label trial comparing axitinib to sorafenib in Asian	Clinical study report for previously treated Asian patients on Protocol A4061051: AG-013736 (axitinib) for the treatment of metastatic renal cell cancer. 26 September 2012.

	patients with clear cell mRCC following failure of one prior systemic first-line therapy	
Everolimus		
RECORD-1	Randomised, double-blind trial of everolimus versus placebo in patients with clear cell mRCC who had progressed on or within 6 months of stopping treatment with sunitinib or sorafenib, or both.	<p>Motzer R. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. <i>Lancet</i>. 2008; 372: 449-456.</p> <p>Motzer R. Phase III trial of everolimus for metastatic renal cell carcinoma. Final results and analysis of prognostic factors. <i>Cancer</i>. 2010; 116: 4256-4265.</p> <p>Bracarda S. Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis. <i>British Journal of Cancer</i>. 2012; 106: 1475-1480.</p> <p>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. <i>European J of Cancer</i>. 2012; 48: 333-339.</p> <p>Korhonen P: Correcting overall survival for the impact of crossover via a Rank-Preserving Structural Failure Time (RPSFT) model in the RECORD-1 trial of everolimus in metastatic renal-cell carcinoma. <i>J of Biopharmaceutical Statistics</i>. 2012; 22(6): 1258-1271.</p>
		<p>DiLorenzo G. An adjusted indirect comparison of everolimus and sorafenib therapy in sunitinib-refractory metastatic renal cell carcinoma patients using repeated matched samples. <i>Expert Opin. Pharmacother</i>. 2011; 12 (10): 1491-1497.</p> <p>Proskorovsky I. Axitinib and everolimus in the treatment of sunitinib-refractory patients with metastatic renal cell carcinoma (mRCC): Results of a simulated treatment comparison (STC) analysis. Presented at ESMO 2012 Congress; 28 September – 2 October 2012; Vienna, Austria. Abstract 2780.</p> <p>Beaumont J. Patient-reported outcomes in a phase III study of everolimus versus placebo in patients with metastatic carcinoma of the kidney that has progressed on vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. <i>The Oncologist</i>. 2011; 16: 632-640.</p>
		<p>Porta C. Efficacy and safety of everolimus in elderly patients with metastatic renal cell carcinoma: an exploratory analysis of the outcomes of elderly patients in the RECORD-1 trial. <i>European Urology</i>. 2012; 61: 826-833.</p> <p>Tsakamoto T. Phase III trial of everolimus in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from RECORD-1. <i>Japanese Journal of Clinical Oncology</i>. 2011; 41 (1): 17-24.</p> <p>White D. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. <i>American Journal of Respiratory and Critical Care Medicine</i>. 2010; 182(3): 396-403.</p>

Source: Tables B.2-3; B.2-4, pp.B-4-B-6 of the re-submission

6.7 The key features of the pivotal randomised trials are summarised in the table below.

Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Axitinib vs. sorafenib					
AXIS	723	R, OL	Low ^a	Failed one prior systemic 1 st	PFS, OS

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
		Up to 37 months		line therapy	
Everolimus vs placebo					
RECORD-1	416	R, DB Up to ~22 months	Low ^b	Progressed on or within 6 months of stopping treatment with sunitinib and/or sorafenib.	PFS, OS

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised
Source: compiled during the evaluation

^a Patients and investigators were unblinded to treatment assignment, thus there is a risk that there may be systematic bias in performance due to the knowledge of treatment assignment. Patients in AXIS could continue to subsequent therapies upon disease progression, with those randomised to axitinib able to receive subsequent sorafenib, but not vice versa. The results of OS may be confounded.

^b As patients (>80%) in the BSC arm of the trial were permitted to cross over to everolimus post disease progression, OS is likely to be significantly biased.

Comparative effectiveness

6.8 The results of PFS outcomes between the trials and results of the STC and MAIC comparisons of axitinib versus everolimus are shown below.

Summary of progression-free survival (PFS) results from the included trials and results of the STC and MAIC comparisons

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)	Prior sunitinib-treated subgroup	Axitinib (N=194)	Sorafenib (N=195)		
	Progression or death due to any cause n (%)	117 (60.3)	120 (61.5)	-0.01(-0.1,0.1)	0.98 (0.84, 1.15)
	Objective progression	109 (93.2)	114 (95.0)	-0.02(-0.1,0.1)	0.96(0.81, 1.14)
	Death without progression	8 (6.8)	6 (5.0)	0.01 (-0.03, 0.05)	1.34 (0.5, 3.8)
	Median progression-free survival (mth)	4.8	3.4	1.4	HR: 0.741 (0.573-0.958) p=0.0107
Trial A4061051 ^A	Prior sunitinib-containing regimen subgroup	Axitinib (N=67)	Sorafenib (N=34)		
	Progression or death due to any cause n(%)	45 (67.2)	26 (76.5)	-0.1(-0.3, 0.09)	0.9 (0.7, 1.13)
	Objective progression	43 (95.6)	25 (96.2)	-0.1(-0.3, 0.09)	0.9 (0.7, 1.14)
	Death without progression	2 (4.4)	1 (3.8)	0.004(-0.1, 0.1)	1.0 (0.1, 10.8)
	Median progression-free survival (mth)	4.7	2.8	1.9	HR=0.629 (0.377,1.048) P=0.0412
Trial of everolimus					
RECORD-1	Subgroup receiving sunitinib as their only previous anti-neoplastic (1st line) therapy	Everolimus (N=43)	BSC (N=13)	2.8	HR=0.22 (0.09, 0.55) p<0.001
	Median PFS (mth)	4.6	1.8		
	Subgroup receiving sunitinib as only previous VEGRr-TKI	Everolimus (N=124)	BSC (N=60)	2.1	HR=0.34 (0.23, 0.51) p<0.001
	Median PFS (mth)	3.9	1.8		
	ITT population	Everolimus (N=277)	BSC (N=139)	3	HR=0.33 (0.25-0.43) p<0.001
	Median PFS (mth)	4.9	1.9		
Indirect estimates of effect					
Naïve side by side comparison					Axitinib 4.8 months
					Everolimus 4.6 months
STC analysis: everolimus versus axitinib: AXIS and RECORD-1 (subgroup receiving					-0.35 (-0.6119; -0.0889)

sunitinib as their only previous anti-neoplastic 1 st line therapy)	(TR=0.70) (axitinib 5.1, everolimus 3.6 months)
MAIC analysis: everolimus versus axitinib: AXIS and RECORD-1 (subgroup receiving sunitinib as their only previous anti-neoplastic 1st line therapy)	-0.38 (-0.66; -0.11) (TR=0.68) (axitinib 5.7, everolimus 3.9 months)

Note: Shaded cells indicate these result that are used in the indirect comparisons. Italics indicate RD/RR that were estimated during the evaluations using RevMan5, bold typography indicate results significant at the 5% level

Abbreviations: mth=months; NR = not reported; PFS = progression-free survival; STC = Simulated Treatment Comparison; MAIC = Matching-Adjusted Indirect Comparison.

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

Source: Table B.6-1, pB-60 of the re-submission.

6.9 The results of OS outcomes between the trials and results of the STC and MAIC of indirect comparisons of axitinib versus everolimus are shown below.

Summary of overall survival (OS) results from the included trials and results of the STC and MAIC comparisons

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)	Prior sunitinib-treated subgroup	Axitinib (N=194)	Sorafenib (N=195)		
	Died n (%)	131 (67.5)	131(67.2)	<i>0.00 (-0.09, 0.10)</i>	<i>1.0 (0.9, 1.2)</i>
	Median OS (mth) 95% CI [^]	15.2	16.5	-1.3	0.997(0.782,1.270) p=0.4902
		Axitinib (N=67)	Sorafenib (N=34)		
	Died n (%)	35 (52%)	17(50%)	<i>0.02 (-0.2,0.2)</i>	<i>1.0 (0.7, 1.6)</i>
	Median OS (mth) (95% CI)	14.9 (12.8, 19.8)	14.9 (9.1, NE)	0	0.866 (0.478,1.568) p=0.3163
Trial of everolimus					
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 #	14.8	10	4.8	0.60 (0.22, 1.65) p=NS
	Subgroup receiving sunitinib as only previous VEGRr-TKI (Table 2, Di Lorenzo et al. 2011)	Everolimus (N=127)	BSC (N=60⁻)		
	Median time to death (months)	12.5	NR	NR	NR
Indirect estimates of effect					
Naïve side by side comparison				Axitinib 15.2 months	
				Everolimus 12.5 months	
STC analysis: everolimus versus axitinib: AXIS and RECORD-1 (subgroup receiving sunitinib as their only previous anti-neoplastic 1st line therapy)				-0.368 (-0.69; -0.05) (TR=0.69) (axitinib 15.2, everolimus 10.6 months)	
MAIC analysis: everolimus versus axitinib: AXIS and RECORD-1 (subgroup receiving sunitinib as their only previous anti-neoplastic 1st line therapy)				-0.344 (-0.66; -0.02) (TR=0.71) (axitinib 17.7, everolimus 12.5 months)	

Note: shaded cells indicate results that are used in the indirect comparisons, Italics indicates RD/RR that were estimated during the evaluation using RevMan 5, bold typography indicate results significant at the 5% level

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

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This is a post hoc analysis to adjusted 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.

- Derived from Motzer (2010). The number of BSC patients in the subgroup receiving sunitinib as only previous VEGFR-TKI was not reported in Di Lorenzo (2011).

Source: Table B.6-6, pB-75 of the re-submission.

- 6.10 The reported OS for patients treated with axitinib was 15.2 months compared with 12.5 months for everolimus, however, the results are potentially confounded by the greater use of further systemic therapies following progression on axitinib (60%) compared with everolimus (22.8%).
- 6.11 The evaluation questioned whether the re-submission had provided sufficient evidence to justify a claim of non-inferiority for axitinib versus everolimus, noting the absence of a standard indirect comparison. The methods used instead were the comparison of single arms of the trials and Simulated Treatment Comparison (STC) and Matching-Adjusted Indirect Comparison (MAIC) techniques. The evaluation further noted that the adjustment for the confounding effect of the patient characteristics do not remove the concerns surrounding comparison of two differing populations via two separate trials.
- 6.12 The Pre-Sub-Committee Response (PSCR, p.1) acknowledged the limitations in the comparability of the available clinical evidence but maintained that the STC and MAIC techniques are the most appropriate methodologies to provide an adjusted comparison. The PSCR (p.2) stated that the results suggest that axitinib has improved efficacy over everolimus but that the more conservative therapeutic conclusion of non-inferiority has been made.
- 6.13 The ESC agreed with the evaluation's observations regarding the difficulties with assessing comparative efficacy in the absence of direct evidence and indirect comparative evidence (with a common comparator). The ESC also agreed that the STC and MAIC techniques do not remove the concerns about comparison of two differing populations via two separate trials. Whilst the MAIC uses propensity methods to re-weight the sunitinib-failed axitinib patients to return a matched sample with greater balance with regards to those patient characteristics common to both AXIS and RECORD-1, it does so at the expense of those axitinib patients most different from the RECORD-1 everolimus sample. In particular the MAIC down-weights females, patients with high MSKCC risk score and patients with a longer duration of prior sunitinib treatment – a potentially important treatment sub-group. Furthermore the MAIC, like the STC, does not explicitly adjust for differences in patient characteristics that were either not observed or not common to both trials.
- 6.14 The ESC noted that the adjusted results using two different statistical techniques (tSTC and MAIC) were suggestive of a beneficial treatment effect of axitinib compared to everolimus. On balance, the ESC considered that axitinib might have equivalent efficacy to everolimus but cautioned that this view was formed on a lack of any head-to-head randomised controlled trial data comparing axitinib and everolimus and the lack of any trials that would enable a standard indirect comparison of the two treatments.

For more detail on PBAC's view, see section 7 'PBAC outcome'

Comparative harms

- 6.15 Axitinib and everolimus have different safety profiles. The safety results could not be compared through a formal indirect comparison due to heterogeneity between the AXIS and RECORD-1 trials. In the RECORD-1 trial, everolimus patients experienced more haematological adverse events (AEs) (anaemia, lymphopenia), than those treated with axitinib in the AXIS trial. Other AEs experienced more frequently with everolimus included non-infectious pneumonitis and infections. Conversely, patients treated with everolimus did not report Grade 3 fatigue or diarrhoea as frequently as those treated with axitinib. Discontinuations due to adverse events were:
- All-causality adverse events: axitinib 9%; everolimus 13%
 - Treatment-related adverse events: axitinib 4%; everolimus 10%.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Benefits/harms

- 6.16 Given the lack of any head-to-head randomised controlled trials comparing axitinib and everolimus and the lack of any trials that would enable an indirect comparison of the two treatments, the comparative benefits/harms of axitinib and everolimus could not be quantified.

Clinical claim

- 6.17 The re-submission described axitinib as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over everolimus. The ESC considered that the evidence presented in the re-submission was insufficient to support the claim.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

- 6.18 A cost-minimisation analysis of axitinib versus everolimus was presented.
- 6.19 The re-submission's proposed equi-effective doses were axitinib 5 mg twice daily and everolimus 10 mg once daily.
- 6.20 As everolimus was recommended for PBS listing in RCC on a cost-effectiveness basis against best-supportive care, there are no prior PBAC determined dose-relativities for everolimus to other drugs in RCC that may assist in an assessment of the claimed equi-effective doses between axitinib and everolimus.
- 6.21 The evaluation noted that the claimed equi-effective doses may not accurately represent the axitinib doses used in the trials as a much larger proportion of axitinib patients in the AXIS trial had dosing interruptions compared to everolimus patients in the RECORD-1 study, and, a fairly large proportion (20%) of axitinib patients were on a total daily dose of 20 mg.
- 6.22 The re-submission and PSCR (p.2) justified the proposed equi-effective doses by noting that the dosing trends over multiple treatment cycles indicate that 5 mg twice daily is the most common dose used and that this is supported by real-world

dosing data from US pharmacies (Chen et al., 2013) which demonstrated that the most commonly dispensed dose of axitinib was 5 mg twice daily, and 16% and 19% of prescriptions were dispensed at a level above or below 5 mg twice daily, respectively. The PSCR (p.2) further noted that patients escalated to a daily axitinib dose of 20 mg did not necessarily remain at this dose but could be reduced back down.

- 6.23 The ESC noted that the TGA recommended dosing for axitinib is a starting dose of 5 mg twice daily. The dosing recommended in the everolimus Product Information for the treatment of advanced renal cell carcinoma is 10 mg once daily. The median daily total dose of axitinib in the AXIS trial was 9.9 mg per day and the mean daily dose of axitinib 10.6 mg per day. The RECORD-1 study protocol specified a once daily oral dose of everolimus 10 mg. Therefore, the ESC considered that there was a reasonable basis for the proposed equi-effective doses
- 6.24 The evaluation questioned whether an inclusion of the costs associated with the management of serious adverse events (SAEs) is required in any cost-minimisation analyses of axitinib to everolimus as it appeared that 12.3% of axitinib patients with treatment-related SAEs may be more appropriately compared to 9.3% of everolimus patients. The PSCR (p.3) maintained that the re-submission's estimate of the rate of SAEs in the everolimus study was conservative because various other adverse events could have been counted for the everolimus patients but were not. The ESC considered that since the safety results could not be compared through a formal indirect comparison for reasons of heterogeneity between the AXIS and RECORD-1 trials, including costs associated with the management of SAEs in any cost-minimisation analyses should only occur when more conclusive data indicates so.

Drug cost/patient/course



- 6.25 It was assumed that all patients receive treatment until disease progression, which is consistent with the requested restriction and estimated to be an average of 141 days of treatment, based on the AXIS trial. On average, each patient is estimated to take $141 / 28 = 5.04$, rounded to 5, scripts of axitinib.

Estimated PBS usage & financial implications

- 6.26 This re-submission was not considered by DUSC.
- 6.27 The re-submission used a market share approach based on PBS prescription data for patients initiating onto a first-line TKI (sunitinib or pazopanib). The table below summarises the estimated use and financial implications of listing axitinib on the PBS. Shaded cells represent the estimates provided in the re-submission and a comparison with those presented in the November 2013 submission is also provided.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	██████████	██████████	██████████	██████████	██████████
Number treated - Nov 2013	██████████	██████████	██████████	██████████	██████████
Uptake rate ^a	██████████	██████████	██████████	██████████	██████████

	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake rate Nov 2013					
Scripts ^c					
Scripts - Nov 2013 ^d					
Estimated net cost to PBS/MBS					
Net cost to PBS					
Net cost to PBS Nov 2013			0		
Net cost to MBS					
Net cost to MBS Nov 2013					
Estimated total net cost					
Net cost PBS/MBS					
Net cost PBS/MBS Nov 2013					

Source: Compiled during the evaluation

^a [redacted] of first-line patients alive assumed to uptake second-line treatment, axitinib share of second-line market assumed to be up to [redacted]

^b Up to [redacted] of first-line patients who have progressed and are alive are assumed to uptake axitinib.

^c Assumed 5 scripts per patient.

^d Assumed average of [redacted] scripts per patient

The redacted table shows that the number of patients estimated to receive treatment with axitinib is less than 10,000 per year. The estimated net cost to the PBS/MBS is less than \$10 million per year.

- 6.28 The ESC noted that the large differences in the estimated net cost to the PBS between the current re-submission compared to the November 2013 are driven by the fact that the current re-submission's estimates are in the context of a cost-minimisation analysis against everolimus whereas the November 2013 estimates were derived in the context of everolimus (or any other second line RCC treatment) not being PBS listed.
- 6.29 The evaluation questioned whether it was reasonable to assume that the additional annual growth in the second-line market would be 11%. The annual growth in the second-line market of 11% was based on the growth in the first-line market after the listing of pazopanib, which also happens to correspond to the proportion of patients considered to be contraindicated for treatment with everolimus and would only be treated with axitinib. The ESC noted that the re-submission did not conduct sensitivity around the additional growth of the second-line market after the PBS listing axitinib but that in theory, based on the Secretariat's proposed additional clinical criteria of 'Patient must not have developed progressive disease following second-line everolimus treatment' (and vice-versa for everolimus' restriction if axitinib was to be PBS listed), growth in the second-line market would mainly be driven by intolerance and possible switching between second-line therapies and an increase in net costs to the PBS would therefore be small.
- 6.30 The ESC further noted that as the effective price of everolimus in RCC was not known to the sponsor of axitinib, the estimated drug treatment costs were likely to differ to those estimated in the above table. 'Special Pricing Arrangements' apply to the price of everolimus and the same arrangements were sought by the re-submission for axitinib. The acceptability of Special Pricing Arrangements was a matter for Departmental consideration.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Quality Use of Medicines

- 6.31 The re-submission stated that part of the QUM approach for axitinib would involve a patient support program. As in the previous submission, the aim of the program is to improve patient compliance, minimise adverse events and to improve patient outcomes for axitinib.

Financial Management – Risk Sharing Arrangements

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended listing axitinib as an Authority Required benefit for the treatment of Stage IV clear cell variant RCC in a patient with a WHO performance status of 2 or less, after failure of prior PBS-subsidised first-line treatment for this condition, on a cost-minimisation basis with everolimus. The equi-effective doses are axitinib 5 mg twice daily and everolimus 10 mg once daily.
- 7.2 The PBAC recalled that it had previously rejected a submission in November 2013 seeking second-line treatment of Stage IV clear cell RCC on the basis of inadequate data to support the claim of superior clinical effectiveness over best supportive care (BSC). The PBAC noted that since November 2013, everolimus for use in second-line treatment of renal cell carcinoma after first line therapy (pazopanib and sunitinib) had been recommended for listing in March 2014 and that listing had become effective since 1 September 2014. The re-submission's clinical positioning of axitinib as an alternative second-line treatment to everolimus concurred with clinical practice guidelines developed by the European Society for Medical Oncology (ESMO) and presented at the ESMO Congress 2014 by Escudier et al (2014)¹. The PBAC did however note the large number of conflicts of interest declared by several of these authors.
- 7.3 The PBAC acknowledged the clinical need for having an alternative option for second line therapy in the treatment of RCC as conveyed by the ESMO clinical practice guidelines and in the sentiment expressed in the consumer comments. The PBAC noted in particular that various consumer comments appeared to convey an unrealistic expectation that axitinib would offer a curative treatment option and was concerned that this expectation was not in accord with the results of the clinical evidence presented.
- 7.4 The PBAC accepted everolimus as the appropriate comparator for the November 2014 re-submission as this would be the therapy most likely to be replaced by axitinib in clinical practice. The PBAC further noted that sorafenib was under consideration at

¹ Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
B. Escudier, T. Eisen, C. Porta, J. J. Patard, V. Khoo, F. Algaba, P. Mulders & V. Kataja, on behalf of the ESMO Guidelines Working Group. *Annals of Oncology* 23 (Supplement 7): vii65–vii71, 2012

this same meeting for the same indication.

- 7.5 The PBAC noted that no new clinical trials were presented and so the supporting evidence base (AXIS and RECORD-1) for the re-submission remained unchanged from November 2013. To address methodological limitations associated with indirect comparisons lacking a common comparator, the resubmission presented a side-by-side comparison and used Simulated Treatment Comparison (STC) and Matching-Adjusted Indirect Comparison (MAIC) methods to compare the AXIS trial (axitinib vs. sorafenib) with the RECORD-1 trial (everolimus vs. placebo) in terms of the primary outcome of progression-free survival (PFS) and the secondary outcome of overall survival (OS). The resubmission also presented trial A4061051 (comparing axitinib to sorafenib) as supportive evidence.
- 7.6 The PBAC observed that the reported PFS for patients treated with axitinib was 4.8 months compared with 4.6 months for everolimus in the naïve side by side comparison. For OS, the reported OS for patients treated with axitinib was 15.2 months compared with 12.5 months for everolimus in the naïve side by side comparison. The PBAC further noted that the effect of the STC and MAIC analyses was to increase the difference in the reported OS between treatments, favouring axitinib.
- 7.7 The PBAC accepted the evaluation's advice that the results were potentially confounded by the greater use of further systemic therapies following progression on axitinib (60%) compared with everolimus (22.8%). The PBAC agreed with ESC advice that the STC and MAIC techniques did not remove the concerns surrounding comparison of two differing populations via two separate trials. In general, the PBAC did not consider the MAIC and STC methods informative for decision-making. However, the acceptability of the presented evidence to inform decision making was balanced against the low likelihood that further clinical trial data would become available in the immediate future and the sense of the limited treatment options available to current sufferers of RCC.
- 7.8 The PBAC observed that the axitinib population in the AXIS trial represented a true second-line population in that all patients received first-line treatment with either sunitinib, bevacizumab, temsirolimus or cytokines. In contrast, the majority of patients in RECORD-1 were 'third-line' patients – 21% had received one prior systemic treatment but 79% had received more than one prior treatment. In RECORD-1, a higher number of prior therapies, was associated with an increased median overall survival (11.6 months for one prior therapy versus 16.6 months for more than 1 prior therapy, $p=0.0152$), suggesting that patients selected for third-line or later therapy may have more indolent disease (Escudier & Gore, 2013). This could represent a bias in favour of everolimus. Therefore, noting the limitations of the comparative evidence and the methodological limitations of the STC MAIC analyses, the PBAC was of the view that the comparative efficacy of axitinib compared to everolimus is likely to be at least equivalent.
- 7.9 The comparative efficacy of different drug class sequencing (i.e. a tyrosine kinase inhibitor (TKI) followed by another TKI versus a TKI followed by a mammalian target of rapamycin (mTOR) inhibitor) was also considered by the PBAC. Upon consideration of the wider literature on this issue, the PBAC considered that overall, the body of evidence suggests that TKI-TKI sequencing and TKI-mTOR sequencing

are equally valid treatment approaches for the management of metastatic RCC.

- 7.10 The PBAC noted that axitinib and everolimus have different safety profiles and that there were difficulties in conducting a formal indirect comparison for reasons of heterogeneity between the AXIS and RECORD-1 trials. It was noted that axitinib treatment is generally well tolerated with manageable adverse events. Although the evaluation suggested that 12.3% of axitinib patients with treatment-related SAEs would be more appropriately compared to 9.3% of everolimus patients and not 13% as suggested in the resubmission, in terms of comparative efficacy compared to everolimus, the PBAC was of the view that axitinib is unlikely to result in adverse effects that are more costly to manage than would occur with everolimus.
- 7.11 The PBAC therefore accepted the submission's clinical claim that axitinib is non-inferior to everolimus in terms of comparative effectiveness and safety.
- 7.12 Based on the PBAC's acceptance of the submission's clinical claim, the re-submission's approach to the economic analysis consisting of a cost-minimisation analysis of axitinib versus everolimus, was appropriate. The PBAC agreed with the ESC that there was a reasonable basis for the proposed equi-effective doses of axitinib 5 mg twice daily and everolimus 10 mg once daily. Since the safety results could not be compared through a formal indirect comparison, the PBAC further agreed with the ESC that any potential differences in the incidence of SAEs between axitinib and everolimus should only be accounted for in a cost-minimisation analysis if more conclusive safety data is available. The PBAC noted that everolimus is subject to special pricing arrangements and that a price for axitinib that reflects a recommendation to list on a cost-minimisation basis would still need to be accepted by the sponsor of axitinib.
- 7.13 To further ensure that the PBS listing of axitinib for second line treatment in RCC meets the intent of a cost-minimisation recommendation, the PBAC advised that axitinib should join the risk sharing arrangement currently in place for everolimus for this indication. The PBAC recognised that listing further second-line treatments such as axitinib for RCC may potentially result in growth in the use of second-line treatments in a third-line or later treatment setting where cost-effectiveness has not been demonstrated or accepted. To protect the Commonwealth from higher than expected costs resulting from the use of second-line treatments beyond disease progression, the PBAC recommended that any existing caps in the current risk sharing arrangement remain unchanged.
- 7.14 With respect to implementing a PBS restriction for axitinib, the PBAC recommended that the intent of the PBS restriction applying to everolimus in second-line RCC also apply to axitinib. The PBAC did not agree with the Secretariat's suggestion to insert a clinical criterion that explicitly states that the drug is not PBS-subsidised for disease progression following use of another second-line PBS subsidised therapy, as the PBAC was mindful of not unduly influencing clinical treatment guidelines on RCC which tend to evolve over time.
- 7.15 Advice to the Minister under section 101 (3BA) of the *National Health Act*
The PBAC advised, under Section 101(3BA) of the *National Health Act* 1953, that axitinib should be treated as interchangeable with sorafenib in the second-line treatment of RCC on an individual patient basis. The PBAC further advised that

axitinib should not be treated as interchangeable with everolimus on an individual patient basis in the second-line treatment setting of RCC.

7.16 The PBAC advised that axitinib is not suitable for prescribing by nurse practitioners.

7.17 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max Qty (Units)	No. of Rpts	Proprietary Name and Manufacturer	
AXITINIB				
axitinib 1 mg tablet, 28	56	2	Inlyta	Pfizer
axitinib 5 mg tablet, 28	56	2	Inlyta	Pfizer

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	---
Severity:	Stage IV
Condition:	clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have progressive disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) following first-line treatment with a tyrosine kinase inhibitor, AND Patient must have a WHO performance status of 2 or less, AND The treatment must be the sole PBS-subsidised therapy for this condition,

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Prescriber Instruction	<p>Patients who have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised treatment with this drug.</p> <p>Patients who have progressive disease with this drug are no longer eligible for PBS-subsidised treatment with this drug.</p>
Prescriber Instruction	Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment.
Administrative Advice	<p><u>Note</u> Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.</p> <p><u>Note</u> No increase in the maximum number of repeats may be authorised.</p> <p><u>Note</u> Special Pricing Arrangements apply</p>

Name, Restriction, Manner of administration and form	Max Qty (Units)	No. of Rpts	Proprietary Name and Manufacturer	
AXITINIB				
axitinib 1 mg tablet, 28	56	5	Inlyta	Pfizer
axitinib 5 mg tablet, 28	56	5	Inlyta	Pfizer

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	---
Severity:	Stage IV
Condition:	clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuing treatment beyond 3 months
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

Clinical criteria:	<p>Patient must have previously been issued with an authority prescription for this drug for this condition,</p> <p>AND</p> <p>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST),</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
Prescriber Instruction	<p>Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment.</p> <p>Patients who have progressive disease with this drug are no longer eligible for PBS-subsidised treatment with this drug.</p>
Administrative Advice	<p><u>Note</u> Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.</p> <p><u>Note</u> No increase in the maximum number of repeats may be authorised.</p> <p><u>Note</u> Special Pricing Arrangements apply.</p>

9 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.

10 Sponsor's Comment

The Sponsor had no comment.