

7.12 SORAFENIB

**Tablet; 200 mg;
Nexavar[®]; Bayer Australia Ltd.**

1 Purpose of Application

- 1.1 The minor resubmission sought to extend the current Authority Required listing to include the treatment of stage IV clear cell variant renal cell carcinoma (advanced RCC) in patients who have failed first line treatment.

2 Background

- 2.1 Sorafenib was TGA registered for the treatment of patients with advanced renal cell carcinoma on 27 September 2006.
- 2.2 This was the fifth submission to the PBAC for listing in advanced RCC.
- 2.3 Two submissions for sorafenib as first-line treatment for advanced RCC were rejected at the November 2006 and March 2008 meetings on the basis of high and uncertain cost-effectiveness ratios.
- 2.4 In November 2012, a major submission to list sorafenib as second-line was rejected on the basis that superior clinical effectiveness over best supportive care for the proposed PBS population had not been demonstrated.
- 2.5 In November 2013, the PBAC rejected a major resubmission to list sorafenib on the PBS for the second line treatment of stage IV renal cell carcinoma on the basis of inadequate evidence of proven superior efficacy over BSC. The PBAC considered the critical issue in the submission was the indirect comparison. The PBAC considered that the indirect comparison was not a valid basis for assessment of comparative effectiveness given the differences between the trial and the absence of any evidence in the re-submission to support the claims that the common references (temsirolimus and everolimus) have equivalent safety and efficacy, and that everolimus is superior to BSC.

3 Requested Listing

- 3.1 The following new indication was sought in addition to the existing listing for advanced Barcelona Clinic Liver cancer stage C hepatocellular carcinoma:

Public Summary Document – November 2014 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SORAFENIB sorafenib 200 mg tablet, 60	<i>Not stated</i>	<i>Not stated</i>	Nexavar	BY

Category / Program	<i>Not stated</i>
Prescriber type:	<i>Not stated</i>
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
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 used as monotherapy for this condition
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 sorafenib.
Prescriber Instruction	Patients who have progressive disease with sorafenib are no longer eligible for PBS-subsidised sorafenib.
Administrative Advice	<u>NOTE:</u> No increase in the maximum quantity or number of units may be authorised.
Administrative Advice	<u>NOTE:</u> No increase in the maximum number of repeats may be authorised.
Administrative Advice	<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.

Administrative Advice	NOTE: Special Pricing Arrangements apply.
------------------------------	---

4 Clinical place for the proposed therapy

- 4.1 Sorafenib is a multi-kinase inhibitor that targets various upstream receptor tyrosine kinases (c-KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR- β) and downstream RAF kinases (serine/threonine kinases) (CRAF, BRAF, V600E BRAF) in both the tumour cell and the tumour.
- 4.2 The minor resubmission proposed sorafenib as a second-line alternative therapy to everolimus for stage IV clear cell renal cell carcinoma. Pazopanib and sunitinib are current PBS-listed first line treatments. Everolimus is currently PBS-listed for the second-line treatment of stage IV clear cell renal cell carcinoma. Axitinib was also under consideration at this same meeting for PBS-listing in the second-line setting.

5 Comparator

- 5.1 The previous major resubmission considered by the PBAC in November 2013 nominated best supportive care which was considered appropriate by the PBAC at that time. The minor resubmission's nominated comparator had changed to everolimus, given the recent PBS-listing of everolimus for advanced RCC in the second-line setting.

6 Consideration of the evidence

Sponsor hearing

- 6.1 As a minor submission, there was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with sorafenib including a clinical need for having alternative second line drug made available for the treatment of RCC.
- 6.3 Kidney Health Australia (through the axitinib agenda item) commented separately 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 No new clinical trials were presented in the minor resubmission.
- 6.5 The evidence base (INTORSECT, RECORD-1 and AXIS) for this minor resubmission remained unchanged from the November 2013 major resubmission.
- 6.6 A concern of the PBAC in November 2013 was that the data from the INTORSECT trial were only provided in the submission in poster presentation form. The PBAC considered that this was inappropriate and did not allow adequate assessment of the trial's quality and validity. It was noted that the INTORSECT trial had since been published in December 2013 in the *Journal of Clinical Oncology* by Hutson et al. This journal article was included in the minor resubmission under 'References'.

Comparative effectiveness

- 6.7 The trial results remained unchanged from the previous major resubmission considered in November 2013.
- 6.8 In summary, the minor resubmission stated that if temsirolimus (from INTORSECT) is assumed to have equal efficacy to placebo (from RECORD-1) in a conservative approach to considering sorafenib's efficacy, the gain in overall survival (OS) with sorafenib is 4.4 months. The minor resubmission compared this conservative estimate with that for everolimus, in which it is noted that the PBAC's assessment that the survival gain for everolimus compared to placebo was likely to be between 3 and 4.8 months.
- 6.9 The PBAC noted in November 2013 that the primary outcome of progression free survival (PFS) in the INTORSECT trial was not statistically significant for sorafenib compared to temsirolimus, however the secondary outcome of overall survival (OS) was statistically significant with a p-value of 0.014. There was no explanation provided in the November 2013 re-submission for the finding that OS improved in the sorafenib arm however PFS was unaltered. In these circumstances it is likely that factors other than exposure to the study drugs have influenced the survival outcome. These factors include cancer management delivered following disease progression. In this regard it would be important to present the data on management of all trial patients following disease progression. Setting aside the discussion on OS, the PBAC recalled that oncology submissions have emphasised the patient relevance of changes in PFS and noted that this was quantitatively (albeit not statistically significantly) less in the sorafenib arm (3.91 months) compared with temsirolimus (4.28 months). For all these reasons, PBAC considered the results of this trial were not interpretable in November 2013.
- 6.10 The minor resubmission provided the following 3 potential explanations for the lack of correlation between OS and PFS results:
- Trial design – the first post-randomisation assessment of PFS occurred at a point whereby the median had already been reached;
 - Angiogenic agents are known to have no significant impact on response rate, but rather cause the disease to be controlled (i.e. there is no further growth)

presumably because of the impact of angiogenesis allowing disease destabilisation.

- Tumour control beyond ‘progression’ (defined by RECIST criteria) was possibly better in those treated with sorafenib than temsirolimus. In other words, sorafenib had slower progression (or even stabilisation) beyond the initial 20% increase thereby giving an OS advantage.

Comparative harms

6.11 Everolimus vs. placebo (RECORD-1)

The minor resubmission notes that everolimus has a higher incidence of adverse events than placebo. A summary of adverse events in RECORD-1 occurring in ≥ 10% of patients in either group, irrespective of relation to treatment, is provided below.

Adverse events irrespective of relation to treatment, occurring in ≥10% of patients in the everolimus group

Adverse Events/Abnormalities	Everolimus + BSC, n=274			Placebo + BSC, n=137		
	Overall Incidence	Grade 3	Grade 4	Overall Incidence	Grade 3	Grade 4
Adverse event, %						
Stomatitis	44	4	<1	8	0	0
Infections	37	7	3	18	1	0
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Diarrhoea	30	1	0	7	0	0
Cough	30	<1	0	16	0	0
Rash	29	1	0	7	0	0
Nausea	26	1	0	19	0	0
Anorexia	25	1	0	14	<1	0
Peripheral oedema	25	<1	0	8	<1	0
Dyspnoea	24	6	1	15	3	0
Vomiting	20	2	0	12	0	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	10	0	1	0	0
Headache	19	<1	<1	9	<1	0
Epistaxis	18	0	0	0	0	0
Pruritus	14	<1	0	7	0	0
Pneumonitis	14	4	0	0	0	0
Dry skin	13	<1	0	5	0	0
Dysgeusia	10	0	0	2	0	0
Pain in extremity	10	1	0	7	0	0

Source: Motzer 2010 Table 2 p. 4260 / November 2014 minor resubmission, p.11, Table 4

6.12 Sorafenib vs. temsirolimus (INTORSECT)

Hutson et al (2013) concluded that each drug has a differentiated safety profile, consistent with its class and targeting profile.

6.13 Sorafenib vs. axitinib (AXIS)

In November 2013, the PBAC noted that hand-foot skin syndrome (51% v 27%; RR=1.87; 95% CI: 1.53, 2.27), rash (32% v 13%; RR=2.52; 95% CI: 1.84, 3.44) and alopecia (32% v 4%, RR=8.31; 95% CI: 4.86, 14.18) were reported more frequently with sorafenib; whereas hypertension (29% v 40%; RR=0.72; 95% CI:0.58, 0.88),

nausea (22% v 32%, RR=0.67; 95% CI: 0.52, 0.86), dysphonia (14% v 31%; RR=0.44, 95% CI: 0.32, 0.59) and hypothyroidism (8% v 19%, RR=0.43; 95% CI: 0.28, 0.64) were reported less frequently.

Clinical claim

- 6.14 The minor resubmission claimed non-inferior comparative effectiveness and non-inferior (“similar”) comparative safety for sorafenib compared to everolimus.

Economic analysis

- 6.15 In the previous major submission considered in November 2013, the submission presented a modelled economic evaluation (cost utility analysis, CUA) based on the claim of superior efficacy against best supportive care.
- 6.16 This minor November 2014 resubmission proposed listing sorafenib on a cost-minimisation basis against everolimus.
- 6.17 The minor resubmission proposed that the equi-effective doses are sorafenib 800 mg and everolimus 10 mg.

Estimated PBS usage & financial implications

- 6.18 The minor resubmission did not provide any estimates on the financial implications to the PBS and changes in PBS usage. The minor resubmission’s justification for not providing any further estimates of PBS usage and financial implications was that listing was sought on a cost-minimisation basis and that the effective price of everolimus was not known to the sponsor of sorafenib.

7 PBAC Outcome

- 7.1 The PBAC recommended extending sorafenib’s existing listing to include second-line treatment of stage IV clear cell variant renal cell on a cost-minimisation basis against everolimus. The equi-effective doses are sorafenib 800 mg and everolimus 10 mg.
- 7.2 The PBAC recalled that it had recommended everolimus for use as second-line treatment of RCC after pazopanib and sunitinib in March 2014 and that listing had become effective since 1 September 2014. Consumer comments received for this sorafenib resubmission commented on a lack of second line treatment options in Australia for patients with RCC. The minor resubmission’s proposal of sorafenib as a second-line alternative therapy to everolimus for RCC would therefore meet the perceived treatment gap to some extent. The recent PBS listing of everolimus for second-line treatment of RCC also influenced the choice of comparator for the resubmission.
- 7.3 Previously, best supportive care was nominated as the comparator in the submission last considered by the PBAC in November 2013. Following the March 2014 PBAC recommendation and listing of everolimus for second-line use in RCC, the minor resubmission nominated everolimus as the comparator. The PBAC considered this to

be appropriate. The PBAC also recalled that in November 2013, it had considered that axitinib was also a relevant comparator.

- 7.4 The PBAC noted that no new clinical trials were presented in the minor resubmission to inform an assessment of comparative efficacy and safety for sorafenib compared to everolimus. The evidence base (INTORSECT, RECORD-1 and AXIS trials) for the minor resubmission remained largely unchanged from the November 2013 major resubmission, with the exception being that results from the INTORSECT trial had since been published in December 2013.
- 7.5 In terms of assessing comparative effectiveness, the PBAC recalled its previous concerns that results of the indirect comparison did not provide a reliable basis for estimating the effectiveness of sorafenib. However, the PBAC noted that this was in the context of best supportive care being the comparator and an assessment of the incremental benefit of sorafenib over best supportive care. As everolimus was now accepted as the appropriate comparator, noting that axitinib was also under consideration for the same second-line RCC listing as everolimus and sorafenib at this meeting, the PBAC considered an acceptance that axitinib provides similar health benefits compared to everolimus would provide a sufficient basis to accept that sorafenib would also provide similar health benefits compared to everolimus since the PBAC had previously considered in November 2013 that the available data, including the head-to-head AXIS trial, appeared to demonstrate non-inferior efficacy between sorafenib and axitinib.
- 7.6 As there were no head-to-head randomised controlled trials comparing sorafenib to everolimus or any trials that would enable a reliable indirect comparison of sorafenib to everolimus, the comparative benefits/harms of sorafenib compared to everolimus could not be quantified. However, based on the safety data present in the INTORSECT, RECORD-1 and AXIS trials, the PBAC accepted that sorafenib's comparative safety would be likely to be comparable to everolimus' and axitinib's safety profile in clinical practice.
- 7.7 The PBAC therefore accepted the minor resubmission's clinical claim of non-inferior comparative effectiveness and non-inferior ("similar") comparative safety for sorafenib compared to everolimus.
- 7.8 Given the clinical claim of non-inferiority, the PBAC considered the submission's cost-minimisation approach to the economic analysis to be appropriate. The PBAC noted that the minor resubmission further proposed to list sorafenib at an equivalent cost per patient per course of treatment compared to everolimus. However, the minor resubmission's cost per course of treatment calculations assumed the treatment duration with everolimus is [REDACTED] ([REDACTED]) whilst the treatment duration with sorafenib is [REDACTED] ([REDACTED]), which resulted in different DPMQs (dispensed price for maximum quantities) and sorafenib's price being higher than everolimus' price. The PBAC did not agree with this approach given the lack of a common comparator across the trials and the resulting imprecision in estimates of comparative efficacy. Instead, the PBAC recommended that equi-effective doses between sorafenib and everolimus be determined by the most common doses used in the trials alone which equated to a daily dose of sorafenib 800 mg and everolimus 10 mg.

- 7.9 The PBAC noted the minor resubmission did not provide any estimates on the financial implications to the PBS and changes in PBS usage. To further ensure that the PBS listing of sorafenib for second line treatment in renal cell carcinoma meets the intent of a cost-minimisation recommendation, the PBAC advised that sorafenib should join the risk sharing arrangement currently in place for everolimus in RCC. The PBAC recognised that listing further second-line treatments such as sorafenib 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.
- 7.10 With respect to implementing a PBS restriction for sorafenib, the PBAC recommended that the intent of the PBS restriction applying to everolimus in second-line RCC also apply to sorafenib. 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.
- 7.11 Advice to the Minister under section 101 (3BA) of the National Health Act
The PBAC, under Section 101(3BA) of the *National Health Act* 1953, advised that sorafenib should be treated as interchangeable on an individual patient basis with axitinib. The PBAC further advised that sorafenib should not be treated as interchangeable on an individual patient basis with everolimus.
- 7.12 As sorafenib is not suitable for prescribing by nurse practitioners for its current PBS indication, the PBAC advised that sorafenib would also not be suitable for prescribing by nurse practitioners in RCC.
- 7.13 The PBAC recommended that the Safety Net 20 Day Rule should not apply, consistent with sorafenib's current PBS indication.

Outcome:

Recommended

8 Recommended listing

8.1 Add new indication:

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (Units)	No. of Rpts	Proprietary Name and Manufacturer
SORAFENIB Sorafenib 200 mg tablets, 60	2	120	2	Nexavar BY

Category Program	/	GENERAL – General Schedule (Code GE)
-------------------------	---	--------------------------------------

Public Summary Document – November 2014 PBAC Meeting

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
PBS Indication:	Stage IV clear cell variant renal cell carcinoma
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
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.
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	Patients who have progressive disease with this drug are no longer eligible for PBS-subsidised treatment with this drug.
Administrative Advice	<u>NOTE:</u> No increase in the maximum quantity or number of units may be authorised.
Administrative Advice	<u>NOTE:</u> No increase in the maximum number of repeats may be authorised.
Administrative Advice	<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.
Administrative Advice	<u>NOTE:</u> Special Pricing Arrangements apply.

Public Summary Document – November 2014 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (Units)	No. of Rpts	Proprietary Name and Manufacturer
SORAFENIB Sorafenib 200 mg tablets, 60	2	120	5	Nexavar BY

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
PBS Indication:	Stage IV clear cell variant renal cell carcinoma
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:	Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST), AND The treatment must be the sole PBS-subsidised therapy for this condition.
Prescriber Instruction	Patients who have progressive disease with this drug are no longer eligible for PBS-subsidised treatment with this drug.
Administrative Advice	<u>NOTE:</u> No increase in the maximum quantity or number of units may be authorised.
Administrative Advice	<u>NOTE:</u> No increase in the maximum number of repeats may be authorised.
Administrative Advice	<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.
Administrative Advice	<u>NOTE:</u> Special Pricing Arrangements apply.

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

Bayer has remained fully committed to Nexavar knowing that it has an important place for use as a second line treatment in patients with advanced kidney cancer as well as its current listing in hepatocellular carcinoma (liver cancer).