

7.19 REGORAFENIB

Tablet 40 mg (as monohydrate), Stivarga[®], Bayer Australia Ltd.

1 Purpose of Application

- 1.1 The minor submission requested an Authority Required (STREAMLINED) listing for regorafenib for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have progressed on first line treatment with a tyrosine kinase inhibitor (TKI). Major submissions for regorafenib were considered at the March 2018 and November 2018 PBAC meetings.

2 Requested listing

- 2.1 The submission requested the following new listing .
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

| Name, Restriction, Manner of administration and form | Max. Qty (packs) | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|------------------|-------------|---|-----------------------------------|
| REGORAFENIB Tablet, 40 mg, 28 | 3 | 2 | \$ [REDACTED] (published) \$ [REDACTED] (effective) | Stivarga Bayer |

| | |
|------------------------------------|---|
| 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 |
| PBS Indication: | For the treatment of patients with hepatocellular carcinoma (HCC) who have progressed on sorafenib treatment <i>Advanced Barcelona Clinic Liver Cancer Stage B or C Hepatocellular carcinoma</i> |
| Treatment phase: | Initial |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | <i>The treatment must be the sole PBS-subsidised therapy for this condition.</i> <i>AND</i> The patient must have a WHO performance status of 1 or less <i>AND</i> Patient must have Child Pugh class A <i>AND</i> Patient must have received prior treatment with sorafenib for a minimum of 20 days at a minimum dose of 400 mg QD <i>Patient must have previously received treatment with a tyrosine kinase inhibitor (TKI) for this condition.</i> <i>AND</i> Patient must have progressed on sorafenib treatment. |

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| | |
|-------------------------------|--|
| Administrative Advice: | <i>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</i> |
|-------------------------------|--|

| Name, Restriction, Manner of administration and form | Max. Qty (packs) | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|---|---------------------|----------------|---|-----------------------------------|
| REGORAFENIB Tablet, 40 mg, 28 | 3 | 2 | \$ [REDACTED] (published) \$ [REDACTED] (effective) | Stivarga Bayer |

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| 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 |
| PBS Indication: | For the treatment of patients with hepatocellular carcinoma (HCC) who have progressed on sorafenib treatment Advanced Barcelona Clinic Liver Cancer Stage B or C Hepatocellular carcinoma |
| Treatment phase: | Continuing |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | The treatment must be the sole PBS-subsidised therapy for this condition. AND The patient must have previously been treated regorafenib with PBS-subsidised treatment with this drug for this condition AND The patient must only be treated until disease progression Patient must not have developed disease progression while being treated with this drug for this condition |
| Administrative Advice: | <i>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</i> |

- 2.3 The requested maximum quantity of 3 packs (total of 84 units) with 2 repeats is sufficient for 12 weeks of treatment at the maximum daily dose of 160 mg. Administrative notes specifying no increase in the maximum quantity and number of repeats have been added.
- 2.4 The sponsor noted that the clinical criteria proposed were intended to reflect the patient population included in the RESORCE trial protocol. Specifically, patients who tolerated sorafenib treatment and progressed on sorafenib treatment. At its November 2018 meeting, the PBAC recommended the listing of lenvatinib as a first line treatment for HCC. At that time, the PBAC also noted that the proposed listing for regorafenib would not allow patients treated with lenvatinib to access second line regorafenib, and that this may create an incentive for patients to preferentially be treated with sorafenib in the first line setting. The PBAC considered that it was not clinically appropriate for the availability of regorafenib as a second line treatment to impact on the choice of the first line treatment (Regorafenib PSD, November 2018, paragraph 7.3).

- 2.5 The minor resubmission noted that the sponsor remained of the view that the sequence of sorafenib followed by regorafenib offers the most robust, cost-effective and evidence-based option for patients with advanced HCC. However, the sponsor also advised that it would be willing to revise and accept the PBAC requested restriction and make regorafenib available for second line treatment for HCC after any TKI therapy. The minor resubmission indicated that the proposed revised restriction for regorafenib was aligned with the PBAC comments in the ratified minutes, to allow use following treatment with a TKI; however, the clinical criteria provided in Table 2 of the resubmission did not reflect this. The secretariat-amended wording above reflects the approach suggested by the PBAC at its November 2018 meeting. The PBAC considered that third line use of regorafenib would not be appropriate and therefore the restriction should specify that patients who have been treated with cabozantinib or another second-line TKI are not eligible for treatment with regorafenib.
- 2.6 Patients in the RESORCE trial were required to have progressed on sorafenib, after a minimum of 20 days at a minimum dose of 400 mg. As such, patients in the trial were likely to be healthier, fitter and more tolerant to TKI therapy than the general second line HCC population.
- 2.7 The initial restriction for regorafenib allows patients to be treated with regorafenib if they have an ECOG performance status of 0 or 1, based on the pivotal trial, whereas the listing for sorafenib allows treatment of patients with a WHO performance status of 2 or less.

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

3 Background

- 3.1 Regorafenib was TGA approved for HCC on 21 December 2017. The TGA indication is "treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib".
- 3.2 The first major submission for regorafenib in HCC was considered at the March 2018 PBAC meeting. The PBAC did not recommend regorafenib for patients with unresectable HCC based on a high and uncertain incremental cost-effectiveness ratio (ICER). The PBAC also considered that the toxicity associated with regorafenib was substantial, with a modest overall improvement in survival (Regorafenib PSD March 2018, paragraph 7.1). The PBAC advised that a future major submission should include a lower price, giving an ICER <\$40,000 per quality-adjusted life year (QALY) gained to reflect the substantial toxicity, with changes to the economic model as specified by the PBAC (Regorafenib PSD March 2018, paragraph 7.12).
- 3.3 A major resubmission was considered at the November 2018 PBAC meeting. Regorafenib was not recommended for listing on the basis that it provided a modest survival benefit in some patients, however, treatment was also associated with substantial toxicity. The PBAC considered that at the proposed price, the ICER for regorafenib remained unacceptably high. At this time the PBAC considered that, given

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the economic analysis presented in the resubmission had addressed the majority of the PBAC’s concerns, the cost-effectiveness of regorafenib would be acceptable with a reduction in price that resulted in a cost per QALY of below \$40,000. The PBAC considered that a resubmission addressing price only could be submitted as a minor submission (Regorafenib PSB November 2018, paragraph 7.11).

3.4 A summary of the previous submissions and current submission is provided in Table 1.

Table 1: Summary of the previous submissions and current resubmission

| | March 2018 submission | November 2018 resubmission | Current resubmission |
|---------------------------|--|---|--|
| Patient population | Patients with unresectable hepatocellular carcinoma (HCC) who progressed following treatment with sorafenib | Unchanged from March 2018 | Patients with unresectable hepatocellular carcinoma (HCC) who progressed following treatment with a TKI |
| Requested PBS listing | <p><u>Initiation:</u></p> <p>The patient must have a WHO PS of 1 or less AND</p> <p>Patient must have Child Pugh class A AND</p> <p>Patient must have received prior treatment with sorafenib for a minimum of 20 days at a minimum dose of 400 mg QD AND</p> <p>Patient must have progressed on sorafenib treatment</p> <p><u>Continuation:</u></p> <p>The patient must have previously been treated with PBS-subsided regorafenib AND</p> <p>The patient must not have progressive disease</p> | <p><u>Initiation:</u></p> <p>Unchanged from March 2018</p> <p><u>Continuation:</u></p> <p>The patient must have previously been treated with PBS-subsided regorafenib AND</p> <p>The patient must only be treated until disease progression OR until no further clinical benefit is observed.</p> <p>Clinical benefit defined as:</p> <ul style="list-style-type: none"> - the absence of deterioration of ECOG status (e.g. ECOG should not deteriorate from baseline status: 0 to 2 or higher, from 1 to 3 or higher) - and/or absence of deterioration of liver function (jaundice, uncontrolled ascites, encephalopathy). | Proposed criteria were unchanged from the March 2018 submission, however the sponsor noted willingness to accept the PBAC requested restriction to allow regorafenib for 2 nd line treatment after any TKI therapy. |
| Requested effective DPMQs | • \$ [REDACTED] | • \$ [REDACTED] | • \$ [REDACTED] (unchanged from November 2018) |
| Comparator | Best supportive care | Unchanged from March 2018 | Unchanged from March 2018. Cabozantinib is also being considered for HCC at the July 2019 PBAC meeting and could be considered a near market comparator. This was not addressed in the minor resubmission. |
| Clinical evidence | RESORCE trial Data-cut: 29 February 2016 33 months follow-up | RESORCE trial Data-cut: 23 January 2017 46 months follow-up | Unchanged from November 2018 |

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| | March 2018 submission | November 2018 resubmission | Current resubmission |
|---------------------------|---|--|---|
| Key effectiveness data | PFS HR = 0.455 (95% CI: 0.371, 0.558) Median OS gain: 2.8 months (95% CI: 2.8, 3.3) OS HR = 0.627 (95% CI: 0.500, 0.785) | PFS HR = 0.455 (95% CI: 0.372, 0.557) Median OS gain: 2.8 months (95% CI: 2.7, 3.2) OS HR = 0.614 (95% CI: 0.501, 0.753) | Unchanged from November 2018 |
| Clinical claim | Regorafenib was superior to BSC for the treatment of advanced HCC and slightly inferior for safety. ..slightly higher incidence of drug related adverse events which were well tolerated and did not significantly impact patient QoL. | Regorafenib was superior to BSC for the treatment of advanced HCC in terms of efficacy and inferior for safety. ..higher incidence of drug related adverse events which were well tolerated and with no clinically significant impact on QoL. | Unchanged from November 2018 |
| Economic evaluation | <u>Extrapolation</u> : extrapolate regorafenib arm only from 33 months (last observation) <u>Time horizon</u> : 5 years (base case) vs 2.77 years (33 months) in RESORCE trial <u>Utility for PF health state</u> : 0.779 (derived average utility per health state across both treatment groups in RESORCE) <u>Base case ICER</u> : \$75,000-\$105,000/QALY | <u>Extrapolation</u> : applied to both arms from the median point of survival (between cycle 12 and 13 (rego), cycle 9 and 10 (BSC)), not median follow-up, using (no piecewise) Gen. Gamma distribution, informed by all observed survival data (i.e. from day 1). <u>PSCR revised extrapolation</u> : extrapolated both arms from the median point of follow-up. <u>Time horizon</u> : 5 years (base case) vs 3.8 years in RESORCE trial <u>Utility for PF health state</u> : treatment specific utility values from RESORCE as per PBAC request (p 6.43, Mar 18 PSD): 0.776 (Regorafenib) & 0.783 (BSC) <u>Base case ICER</u> : \$45,000-\$75,000 <u>PSCR revised base case ICER</u> : \$45,000-\$75,000 /QALY | Unchanged from the November 2018 submission (based on PSCR) |
| Number of patients | 195 patients in year 1, increasing to 297 in year 6 | 155 patients in year 1, increasing to 236 in year 6 | Unchanged from November 2018 |
| Estimated net cost to PBS | \$less than \$10 million in 2018 (Year 1), increasing to less than \$10 million in 2023 (Year 6). The total financial implications to the PBS over 6 years of \$30-\$60 million. | Less than \$10 million \$2,610,963 in 2019 (Year 1), increasing to less than \$10 million in 2024 (Year 6). The total financial implications to the PBS over 6 years of \$10-\$20 million. | Unchanged from November 2018 |
| Risk sharing arrangement | None proposed | None proposed | None proposed |

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| | March 2018 submission | November 2018 resubmission | Current resubmission |
|---------------|---|--|-----------------------------|
| PBAC decision | Reject. PBAC Comment: (paragraph 7.1) The PBAC did not recommend regorafenib for patients with unresectable hepatocellular carcinoma who progressed following treatment with sorafenib on the basis of a high and uncertain incremental cost-effectiveness ratio. The PBAC considered that the toxicity associated with regorafenib was substantial, with a range of adverse events associated with regorafenib, which may be more frequent and severe in the proposed Australian population compared with the trial population. The PBAC considered that the improvement in overall survival was modest, that this improvement may not be realised in clinical practice, and should be considered in the context of the substantial toxicity associated with regorafenib treatment. | Reject PBAC Comment: (paragraph 7.1) The PBAC did not recommend the listing of regorafenib for the treatment of hepatocellular carcinoma for patients who have progressed on first line treatment with a sorafenib. The PBAC considered that regorafenib provided a modest survival benefit in some patients, however treatment was also associated with substantial toxicity. The PBAC considered that at the proposed price, the incremental cost-effectiveness ratio for regorafenib was unacceptably high. | - |

Abbreviations: BSC = best supportive care, PBS = Pharmaceutical Benefits Scheme, PBAC = Pharmaceutical Benefits Advisory Committee, PF = progression free, PSCR = Pre-Sub-Committee response, ICER = incremental cost effectiveness ratio, QALY = quality adjusted life years, OS = overall survival, PFS = progression free survival, HCC = hepatocellular carcinoma, QoL = quality of life, HR = hazard ratio, TKI = tyrosine kinase inhibitor.

Source: Compiled during the evaluation. Paragraph references for March 2018 refer to the (regorafenib) public summary document. Paragraph references for November 2018 refer to the (regorafenib) public summary document.

Table 2: Outstanding PBAC matters of concern in previous consideration (November 2018)

| Matters of concern | How the resubmission addresses it |
|--|--|
| In March 2018 the PBAC requested a revised economic analysis with a cost per QALY below \$40,000 to reflect the modest OS benefit and considerable toxicity associated with regorafenib. While the November 2018 resubmission addressed the majority of the PBAC and ESC concerns in the approach to the economic model, the resulting ICER was \$45,000-\$75,000 per QALY. The November 2018 resubmission offered a 24% discount in the DPMQ from the March 2018 submission (\$██████). To achieve an ICER of \$15,000 - \$45,000, a further 42% price reduction would be required (effective DPMQ of \$██████ compared to the proposed \$██████). The sponsor also offered a 10% discount on the price of sorafenib (paragraph 7.8). | Not addressed. The sponsor noted that the DPMQ of \$██████ could not be reduced and considered that the ICER of \$45,000-\$75,000 per QALY was appropriate and cost-effective (p4). |
| The PBAC noted that the financial estimates should be adjusted to exclude use post-progression, consistent with the PBAC's recommendation on the restriction. The PBAC considered that the utilisation estimates presented in the submission and in the pre-PBAC response did not reflect the listing considered appropriate by the PBAC (paragraph 7.10). | Not addressed |

Abbreviations: DPMQ = dispensed price max quantity, PBAC = Pharmaceutical Benefits Advisory Committee, ICER = incremental cost effectiveness ratio, QALY = quality adjusted life years, OS = overall survival, PFS = progression free survival TKI = tyrosine kinase inhibitor.
Source: Compiled during the evaluation. Paragraph references refer to the November 2018 regorafenib minutes.

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

4 Population and disease

- 4.1 First line treatments for advanced HCC include sorafenib and lenvatinib (PBS listed in March 2019). There are currently no PBS listed treatments for patients with HCC after progression on a 1st line treatment. The PBAC noted that transarterial radioembolisation using yttrium-90 (TARE-Y) was recently considered by the Medical Services Advisory Committee (MSAC) for the treatment of unresectable hepatocellular carcinoma. The PBAC noted that there is evidence for a number of other therapies in this setting including cabozantinib, nivolumab, pembrolizumab and ramucirumab and guidelines currently recommend second-line immunotherapy where available. Patients with advanced HCC have a very poor prognosis, with a median survival of less than 8 months (based on the best supportive care (BSC) arm of the RESORCE trial).

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

5 Comparator

- 5.1 The March 2018 and November 2018 submissions nominated BSC as the main comparator. This was unchanged in the minor resubmission. At its July 2019 meeting, the PBAC also considered a major submission for cabozantinib in patients with HCC who had failed treatment with sorafenib or lenvatinib. This could be considered a near market comparator, however, this was not addressed in the minor resubmission.

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 as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.
- 6.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the regorafenib submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the RESORCE trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for regorafenib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)^[1], based on a comparison with placebo.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

Clinical trials

- 6.4 No additional clinical trial data was presented in the minor resubmission.
- 6.5 At its November 2018 meeting, the PBAC considered that the claims of superior comparative effectiveness and inferior comparative safety versus BSC were reasonable.

Economic analysis

- 6.6 The economic model was updated in the Pre-Sub-Committee Response (PSCR) to the November 2018 submission using the median follow-up as the point of extrapolation. This had a small impact on the ICER, increasing it from \$45,000 - \$75,000/QALY. The economic analysis and its inputs were otherwise unchanged from the November 2018 resubmission.

Drug cost/patient/course: \$ [REDACTED].

- 6.7 Based on the estimated treatment exposure (5.41 packs) from the RESORCE trial, the expected cost per patient course was \$ [REDACTED]. This was unchanged from the November 2018 submission.

Estimated PBS usage & financial implications

- 6.8 Based on financial estimates from the November 2018 submission, at year 6 (2024), the estimated number of patients was 236 and the net cost to the PBS/RPBS would be less than \$10 million. The total estimated financial implications to the PBS/RPBS over 6 years of subsidising regorafenib were \$10- \$20 million. The PBS listing of lenvatinib in first line HCC may decrease the potential patient utilisation of regorafenib, based on the TGA indication for regorafenib that specifies use following sorafenib, however, the impact is likely to be minimal if the PBS listing for regorafenib does not exclude use after first line lenvatinib. The financial estimates have not been updated to reflect the listing considered appropriate by the PBAC (Regorafenib PSD November 2018, paragraph 7.10). The financial estimates were based on the following assumptions:
- that patients would be treated beyond progression (as in the RESORCE trial);
 - that eligible patients must have been able to tolerate sorafenib; and
 - that eligible patients were BCLC-C only.
- 6.9 The PBAC noted that the estimated number of patients treated with first line sorafenib in the submission was higher than would be expected based on the DUSC estimates of sorafenib use from 2015 and 2016. However, the submission estimated only a small proportion of patients treated with first-line sorafenib would receive second-line treatment with regorafenib, in part due to the exclusion of BCLC-B patients and patients who were unable to tolerate sorafenib.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of regorafenib (Stivarga[®]), for the treatment of patients with unresectable HCC who have progressed on first line treatment with a tyrosine kinase inhibitor. In November 2018, the PBAC considered that regorafenib provided a minor added survival benefit in some patients which was balanced against substantial additional toxicity and that, at the proposed price, the ICER for regorafenib was unacceptably high. The PBAC noted that the current submission included no substantive changes to that proposed in November 2018, specifically noting no change in the proposed price and hence ICER. The PBAC reiterated its November 2018 advice that at the proposed price the ICER for regorafenib remained unacceptably high.
- 7.2 The PBAC noted that there are currently no PBS listed treatments for unresectable HCC after patients progress on first-line sorafenib or lenvatinib. The PBAC noted that that there is evidence for a number of other therapies in this setting including cabozantinib, nivolumab, pembrolizumab and ramucirumab and guidelines currently recommend second-line immunotherapy where available. In addition, the PBAC noted the MSAC's recent consideration of transarterial radioembolisation with yttrium-90 as an alternative treatment in patients with unresectable HCC.
- 7.3 The PBAC noted that the minor submission did not propose any changes to the restriction proposed in the November 2018 submission, but that the sponsor advised it would be willing to accept the PBAC requested restriction to make regorafenib available for second line treatment for HCC after any TKI therapy. The PBAC reiterated its November 2018 advice that it was not clinically appropriate for the availability of regorafenib as a second line treatment to impact on the choice of the first line treatment for HCC and that the restriction for regorafenib should be revised to allow use following treatment with a TKI. The PBAC considered that the restriction should also specify that patients who have been treated with cabozantinib or another second-line TKI are not eligible for treatment with regorafenib as no evidence was presented for sequential use of these treatments.
- 7.4 The PBAC considered that the comparator of BSC, as previously accepted, remained appropriate for the minor resubmission. The PBAC noted that cabozantinib was also considered at this meeting for the same indication and should be considered a near market comparator.
- 7.5 No additional clinical trial data was presented in the minor resubmission. The PBAC maintained that the claim of superior comparative effectiveness and inferior comparative safety compared with BSC was reasonable.
- 7.6 The PBAC noted that the economic analysis and its inputs were unchanged from those presented in the PSCR to the November 2018 resubmission. The PBAC considered that, at \$45,000 - \$75,000/QALY, the ICER remained high given the substantial toxicity and minor added benefit of regorafenib. The PBAC recalled its concern that the benefits observed in the RESORCE trial may be smaller in the PBS population due to

their poorer prognosis and the reduced tolerability of regorafenib (Regorafenib PSD, March 2018, paragraph 7.7). As such, the true ICER would likely be higher than \$45,000 - \$75,000/QALY gained. The PBAC reiterated its advice from both previous submissions that the cost-effectiveness of regorafenib would be acceptable with a reduction in price that resulted in an ICER of \$15,000 - \$45,000/QALY or less, in order to satisfy the PBAC that its cost-effectiveness is acceptable.

7.7 The PBAC noted that there was some uncertainty in the estimated number of patients treated with sorafenib and the number likely to be eligible for treatment with regorafenib.

7.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Bayer is disappointed to receive a negative recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC) for the reimbursement of Stivarga® (regorafenib) in the treatment of hepatocellular carcinoma (HCC). Bayer maintains that the proposal was at a level of cost-effectiveness which was indicative of the current unmet need and low number of patients. Bayer will not be re-submitting for this indication in the future.