

**7.20 VISMODEGIB
Capsule, 150 mg,
ERIVEDGE[®],
Roche Products Pty Ltd.**

1 Purpose of Application

- 1.1 The minor resubmission requested a change to the basis on which the PBAC recommended a General Schedule, Authority Required listing for vismodegib for the treatment of adult patients with metastatic or locally advanced basal cell carcinoma (BCC) where surgery and radiotherapy are not appropriate.
- 1.2 The resubmission requested a change to the model inputs on which the PBAC based its previous recommendation at the March 2016 meeting.

2 Requested listing

- 2.1 The resubmission did not request any changes to the wording of the listing as described in the March 2016 PBAC Public Summary Document (PSD).

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
VISMODEGIB 150 MG CAPSULE, 28	1	2	\$ [REDACTED] (published) \$ [REDACTED] (effective)	ERIVEDGE Roche Products Pty Limited
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			
Severity:	Metastatic or locally advanced			
Condition:	Basal cell carcinoma			
PBS Indication:	Metastatic or locally advanced basal cell carcinoma			
Treatment phase:	Initial			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
Clinical criteria:	Patient must have basal cell carcinoma (BCC) inappropriate for surgery and curative radiotherapy			

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Prescriber Instructions	<p>Authority applications for initial treatment must include: A completed authority prescription form Histological confirmation of BCC A report from a surgically qualified clinician and radiation oncologist demonstrating inappropriateness for surgery and curative radiotherapy A signed patient acknowledgement</p> <p>Inappropriate for surgery is defined as: Curative resection is unlikely, such as where BCC has recurred in the same location after two or more surgical procedures; and/or Anticipated substantial morbidity and/or deformity from surgery or requiring complicated reconstructive surgery (e.g. removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation or free tissue transfer); and/or Medical contraindication to surgery</p> <p>Inappropriate for curative radiotherapy is defined as: Hypersensitivity to radiation due to genetic syndrome such as Gorlin Syndrome; and/or Limitations due to location of tumour; and/or Limitations due to cumulative prior radiotherapy dose; and/or Progressive disease despite prior irradiation of locally advanced BCC</p>
Administrative Advice	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> <p>Special Pricing Arrangements apply.</p>

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
Severity:	Metastatic or locally advanced
Condition:	Basal cell carcinoma
PBS Indication:	Metastatic or locally advanced basal cell carcinoma
Treatment phase:	Continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input 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 AND Patient must not have progressive disease AND The patient must remain inappropriate for surgery and radiotherapy</p>
Prescriber Instructions	<p>Authority applications for continuing treatment must include: A completed authority prescription form Histological confirmation of BCC A report from a surgically qualified clinician and radiation oncologist demonstrating continued inappropriateness for surgery and curative radiotherapy A statement form from the prescribing doctor that the disease has not progressed</p> <p>Inappropriate for surgery is defined as: Curative resection is unlikely, such as where BCC has recurred in the same location after two or more surgical procedures; and/or Anticipated substantial morbidity and/or deformity from surgery or requiring complicated reconstructive surgery (e.g. removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation or free tissue transfer); and/or Medical contraindication to surgery</p> <p>Inappropriate for curative radiotherapy is defined as: Hypersensitivity to radiation due to genetic syndrome such as Gorlin Syndrome; and/or Limitations due to location of tumour; and/or Limitations due to cumulative prior radiotherapy dose; and/or Progressive disease despite prior irradiation of locally advanced BCC</p>
Administrative Advice	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> <p>Special Pricing Arrangements apply</p>

3 Background

- 3.1 Vismodegib was TGA registered on 9 May 2013 for the treatment of adult patients with metastatic or locally advanced BCC where surgery and/or radiotherapy are not appropriate.
- 3.2 Vismodegib was recommended at the March 2016 PBAC meeting for the treatment of metastatic or locally advanced BCC. However, the PBAC considered that the ICER presented in the submission was optimistic due to the efficacy inputs selected,

the lack of costs associated with adverse events (AEs) and the use of 100% offset of disfigurement from treatment (Paragraph 7.7). As such, the PBAC outlined a number of parameters on which the recommendation was based.

“The PBAC considered that the most plausible estimates for the economic model included a disfigurement rate associated with vismodegib of 20%, a vismodegib response rate of 50%, and a surgical response rate of 90.7%. At least a ■% reduction in drug price would be required to achieve an incremental cost-effectiveness ratio (ICER) between \$45,000 - \$75,000 per disfigurement-free responder using the average treatment duration of ■ weeks, as proposed in the episode of care (EOC) cap” (Paragraph 6.28), and the “recommendation to list is based on a corresponding reduction in price together with acceptance of a Risk Sharing Arrangement” (Paragraph 7.10).

The PBAC also recommended a total financial cap, beyond which ■% of expenditure above the cap would be rebated to the Government, rather than an EOC cap, as proposed by the sponsor (Paragraph 7.11).

- 3.3 Additionally the PBAC did not accept that vismodegib was superior in safety to best supportive care due to the high frequency of AEs and the potentially teratogenic and mutagenic nature of vismodegib (Paragraph 7.6).
- 3.4 The minor resubmission requested PBAC revise its advice in relation to the following aspects of its March 2016 recommendation: the disfigurement rate associated with vismodegib; the response rate associated with vismodegib; the price required to achieve an ICER between \$45,000 - \$75,000 per disfigurement-free responder; and the subsidisation caps. The submission did not address the safety profile of vismodegib in comparison with best supportive care, or include costs of AEs (except pneumonia as per the original submission) in the economic analysis.
- 3.5 The differences between the previous submission and the resubmission are outlined in Table 1.

Table 1: Summary of the previous submission and current resubmission

	Vismodegib March 2016	Current resubmission
Requested PBS listing	Section 85, restricted benefit listing for the treatment of adults with metastatic or locally advanced BCC where surgery and radiation are not appropriate. PBAC Comment: wording of restriction was sufficient to limit access to the target population (para 7.4)	No change
Requested price	Ex-manufacturer price: \$ ■. DPMQ: \$ ■. (No published versus effective price was proposed) PBAC Comment: The PBAC considered that a price reduction of at least ■% was required to achieve a high but acceptable ICER per disfigurement-free responder (para 7.10).	An additional ■% rebate was proposed. Effective ex-manufacturer price after ■% rebate: \$ ■. Effective DPMQ after ■% rebate: \$ ■. The price reduction offered is less than ■%.
Main comparator	Main comparator: Best supportive care or surgery Accepted by PBAC (para 7.5)	No change

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	Vismodegib March 2016	Current resubmission
Clinical evidence	<p>Three non-randomised, open-label, single-arm studies for vismodegib:</p> <ul style="list-style-type: none"> - STEVIE interim update - ERIVANCE (30-month update) - Chang 2014 <p>One retrospective cohort study for surgery:</p> <ul style="list-style-type: none"> - Schwipper (2011) 	<p>Updated data from the ongoing STEVIE study.</p>
Key effectiveness data	<p>Based on a naïve comparison of the objective response rate from the vismodegib STEVIE study with the % of patients with resection within healthy tissue margin from the surgery study and supplementary effectiveness data from two other vismodegib studies.</p> <p><u>Vismodegib objective response rate</u></p> <ul style="list-style-type: none"> - STEVIE Interim analysis (N = 482): 313 (64.9%) - ERIVANCE 30-month update (N = 96): 54 (56.3%) - Chang et al 2015 (N= 95): 38 (40.0%) <p>Only the STEVIE data were used in the economic evaluation (i.e. an objective response rate of 64.9% was used in the economic evaluation).</p> <p><u>Surgery (Schwipper 2011; N = 118)</u></p> <p>Patients with resection within healthy tissue margin: 107 (90.7%). This was provided in the PSCR, and was accepted as the revised base case by the PBAC (para 6.26). The submission had originally used the % of patients considered 'cured' after an average post-operative follow up period of 5-years: 63/118 (53.4%)</p> <p>PBAC Comment: The PBAC considered that the most plausible estimates for the economic model included a vismodegib response rate of 50% and a surgical response rate of 90.7% (para 6.28).</p>	<p>The only new effectiveness data were an updated analysis of the STEVIE study, which provided data from 1,161 patients, versus 482 in the previous submission.</p> <p><u>Vismodegib objective response rate</u> STEVIE Updated analysis (N = 1,161): [REDACTED]</p> <p>The resubmission stated that the vismodegib objective response rate used in the previous submission (64.9%) was confirmed by the updated STEVIE data and thus did not change the response rate to 50% as requested by PBAC.</p> <p><u>Surgery (Schwipper 2011; N = 118)</u></p> <p>Unchanged (per the value presented in the previous PSCR). This was appropriate.</p>
Key safety data	<p><u>Disfigurement and deformity (%):</u> <u>Vismodegib</u></p> <p>Not reported, but 0% disfigurement and deformity was assumed in the economic evaluation</p> <p><u>Surgery (Schwipper 2011; N=118)</u></p> <p>Loss of one or more facial organs: 97 (82.2%)</p> <p>PBAC Comment: The PBAC considered that the most plausible estimates for the economic model included a disfigurement rate associated with vismodegib of 20% (para 6.28). The PBAC did not accept that vismodegib was superior in safety to best supportive care (para 7.6).</p>	<p><u>Disfigurement and deformity (%):</u> <u>Vismodegib</u></p> <p>10% disfigurement and deformity was used in the economic evaluation based on narrative text from two Australian dermatologists who had used vismodegib. Both clinicians stated that in their experience there was no or minimal disfigurement associated with vismodegib. Thus the resubmission stated that they used a conservative estimate of 10%, rather than the 20% requested by the PBAC.</p> <p><u>Surgery (Schwipper 2011; N=118)</u></p> <p>No change</p>
Clinical claim	<p>Equivalent in terms of comparative effectiveness and superior in terms of comparative safety over surgery.</p> <p>PBAC Comment: Vismodegib was not considered equivalent in terms of comparative effectiveness to surgery, as vismodegib was not considered to be curative for BCC (para 7.5).</p>	<p>No claim was made.</p>

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	Vismodegib March 2016	Current resubmission
Economic evaluation - structure	A modelled cost-effectiveness analysis using cost per disfigurement-free responder for the economic evaluation. A four year model was used based on 12.7 month trial data with Kaplan Meier estimates.	The structure of the model was unchanged (inputs were changed, as outlined in Table 5, below).
Economic evaluation - inputs	Refer to Table 5 below	
ICER	Cost per additional disfigurement-free responder versus surgery: <ul style="list-style-type: none"> \$45,000 - \$75,000 with EOC cap. As per the revised base case accepted by the PBAC (per Table 9 and para 6.26 of the March 2016 PBAC PSD). These inputs would have resulted in an ICER of \$105,000 - \$200,000 without the EOC cap.	Cost per additional disfigurement-free responder versus surgery (with █% rebate): <ul style="list-style-type: none"> \$45,000 - \$75,000 with EOC cap; and \$105,000 - \$200,000 without EOC cap.
Number of patients	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 6.	Unchanged.
Estimated cost to PBS	Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total \$20 - \$30 million over the first 5 years of listing (after EOC cap was applied). <u>RSA:</u> The submission proposed an RSA capping the number of PBS-subsidised packs of vismodegib to █ packs per episode of care. The PSCR proposed a subsidisation cap on number of patients with █% of the expenditure above the cap being rebated to Government PBAC Comment: The PBAC recommended a fixed total financial cap of beyond which █% of expenditure above the cap would be rebated to Government (para 7.11).	Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total \$20 - \$30 million over the first 5 years of listing (after EOC cap and █% rebate were applied, no change to patient or script numbers) <u>RSA:</u> The resubmission stated that “Taking into account the EOC cap, patient numbers and █% rebate offered, the effective net cost to PBS (as presented in the resubmission) directly correspond to the updated subsidisation caps with █% rebate for any expenditure above the caps.” Thus the total financial cost presented in the resubmission could be used as a fixed total financial cap. In the pre-PBAC response (p3), the sponsor proposed a fixed total financial cap based on the calculations used in the episode of care cap.
PBAC decision	Recommended based on at least a █% reduction in price together with acceptance of a Risk Sharing Arrangement (para 7.10)	-

Source: Compiled during preparation of the Overview

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; BCC = basal cell carcinoma; DPMQ = Dispensed Price for Maximum Quantity; EOC = episode of care; ICER = incremental cost-effectiveness ratio; NEP = National Efficient Price; PBAC = Pharmaceutical Benefits Advisory Committee; para = paragraph; PBS = Pharmaceutical Benefits Scheme; PSCR = Pre-Sub-Committee Response; RSA = Risk Sharing Agreement; SCC = squamous cell carcinoma; SPA = Special Pricing Arrangement

For more detail on PBAC’s view, see section 5 “PBAC outcome”

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the clinical place for vismodegib, namely in patients with advanced BCC who are not eligible for surgery. One comment noted that treatment with vismodegib would be intermittent due to treatment-related side effects. Comments indicated that treatment with vismodegib was effective and leads to less serious disfigurement.
- 4.3 The PBAC noted the advice received from Rare Cancers Australia highlighting the impact of the delay in listing vismodegib since the PBAC recommendation in March 2016.

Clinical data

- 4.4 The resubmission provided new information regarding two clinical inputs into the economic evaluation:
- Updated data from the STEVIE study. This was used to justify the vismodegib overall response rate used in the economic evaluation.
 - Survey responses from two clinicians. This was used to justify the disfigurement rate with vismodegib.
- 4.5 Details of the studies presented in the resubmission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Vismodegib		
STEVIE	A single-arm, open-label, phase II, multicentre study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma.	December 2015
	Basset-Seguín, Hauschild, Grob, <i>et al</i> (2015) Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial	<i>The Lancet</i> 2015; 16(6):729-736
Surgery		
Schwipper (2011)	Schwipper (2011) Invasive basal cell carcinoma of the head and neck (basalioma terebrans)	<i>Facial Plastic Surgery</i> 2011; 27:3 (258-265).

Source: Table 1, p6 of the Vismodegib March 2016 PBAC PSD; "Updated STEVIE analysis" provided in the resubmission

- 4.6 The key features of the non-randomised, single-arm studies used in the resubmission are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Used in modelled evaluation
Vismodegib						
STEVIE	1,161 vs 482 in previous submission ^a	OL, MC, SA Duration of follow-up not provided (median 9.3 months in previous submission)	High	mBCC or laBCC not suitable for surgery	AE, ORR, PFS, OS	Yes
Surgery						
Schwipper (2011)	118	SA, Cohort study 9 years	High	Invasive BCC of the head and neck	CR, PFS, OS	Yes

Source: Compiled during preparation of the Overview

AE = adverse events; BCC = basal cell carcinoma; CR = complete response; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; MC = multi-centre; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SA = single-arm

^a Based on the "efficacy evaluable population". The intention-to-treat population was 1,192 in the resubmission versus 501 in the previous submission.

Overall response rate with vismodegib

- 4.7 The resubmission provided updated data from the STEVIE study. This was a single-arm, open-label, multi-centre study of patients with metastatic or locally advanced BCC who were not suitable for surgery. No new data were provided for the surgery arm of the naïve comparison.
- 4.8 The updated data were from the 16 March 2015 data-cut while the previous submission was based on the 6 November 2013 data-cut. The more recent data-cut was based on 1,161 patients, compared with 482 patients in the previous data-cut. The resubmission did not state the median duration of follow-up for the updated data-cut (there was 9.3 months median follow-up in the previous data-cut).
- 4.9 Table 4 presents the objective response rates from the previous submission and the resubmission for both the metastatic and locally advanced BCC subgroups.

Table 4: Objective response rate per the previous submission and the resubmission

	Previous submission			Resubmission		
	mBCC	laBCC	All patients	mBCC	laBCC	All patients
Objective response rate (investigator assessed), n/N (%)						
STEVIE	6 November 2013 data-cut			16 March 2015 data-cut		
	11/29 (37.9%)	302/453 (66.7%)	313/482 (64.9%)	████████	██████	██████
ERIVANCE ^a	16/33 (48.5%)	38/63 (60.3%)	54/96 (56.2%)	-	-	-
Chang <i>et al</i> 2014 ^b	12/39 (30.8%)	26/56 (46.4%)	38/95 (40.0%)	-	-	-

Source: Table A.2, p2 of the resubmission; Table 3 of the March 2016 PBAC PSD

laBCC = locally advanced BCC; mBCC = metastatic BCC

^a Based on the 30 month update, which was provided in the previous submission

^b Investigator assessed for a median follow up of 6.5 months due to early ending of the trial

- 4.10 The vismodegib overall response rate in the updated STEVIE data-cut was ██████████ versus 64.9% reported in the previous data-cut.
- 4.11 The March 2016 PBAC considered that the most plausible estimate of the vismodegib overall response rate was 50%, which was a key parameter on which the

PBAC based its recommendation. The resubmission argued that the rate used in the previous submission was supported by more recent data from the STEVIE study and also that the rate proposed by the PBAC was not based on clinical evidence. Therefore, the resubmission maintained the vismodegib response rate in the economic model at 64.9%, rather than 50% as recommended by the March 2016 PBAC.

- 4.12 While the updated STEVIE data was based on more patients than previously, it did not address the March 2016 PBAC's concerns about relying only on the STEVIE study (rather than ERIVANCE and Chang *et al* 2014), which were:
“The PBAC noted that the use of the STEVIE trial to populate the model was the most optimistic in terms of benefits from treatment of all the provided trials of vismodegib. The STEVIE trial reported a higher response compared to the other studies, had the lowest proportion of participants with metastatic disease, and used investigator rather than independent response assessment” (Paragraph 6.24, March 2016 PBAC PSD).

The pre-PBAC response (p1) noted that the investigator assessed objective response rate more appropriately classified patients with residual scar or tissue defects as complete responders, taking into account the cosmetic and clinical improvement associated with vismodegib; these would have been classified as a stable response by the protocol for independent response assessment.

Disfigurement rate with vismodegib

- 4.13 The resubmission provided survey responses (narrative text) from two clinicians experienced in the use of vismodegib (the total number of clinicians surveyed was not reported). The clinicians were asked about disfigurement rates with vismodegib. The responses included: “0% of the patients who respond to treatment would encounter further disfigurement”;
- “I think less than 1% of patients would have further disfigurement after vismodegib”; and
 - “In the patients I had in the clinical trial, all responding lesions had less disfigurement. The patients that ceased the treatment due to side effects had further disfigurement due to the progression of the tumour.” (Note the response refers to less disfigurement, rather than no disfigurement)
- Based on these responses, the resubmission changed the disfigurement rate in the economic evaluation from 0% to 10% (rather than 20% requested by the PBAC) to “reflect both the clinical uncertainty and clinician advice”.
- 4.14 However, in stating the disfigurement free rate would be 0% or less than 1%, the clinicians appeared to have referred to patients currently responding to vismodegib. No information was provided about patients who progressed after an initial response who would not be captured elsewhere. It was likely that these patients would need further local treatment that might include surgery and/or radiotherapy, which might be associated with disfigurement. The pre-PBAC response (p2) noted that a number of patients who respond to treatment with vismodegib may become eligible for curative surgery or radiotherapy that was not previously possible and that there is a potential for patients to undergo retreatment with vismodegib. The PBAC noted that neither of these options were included in the costings of the revised model.

Economic analysis

- 4.15 The previous submission presented a cost-effectiveness analysis using the cost per disfigurement-free responder versus surgery. The resubmission did not alter the economic model structure but sought to respecify the best estimate of the base case ICER by adding a disfigurement rate with vismodegib of 10% (versus 0% in the previous submission) and including a ■% rebate on the ex-manufacturer price of vismodegib (versus no rebate in the previous submission). The respecified base case ICER was verified during preparation of the Overview.
- 4.16 Table 5 summarises the model inputs in the resubmission versus the previous submission.

Table 5: Summary of model inputs in the resubmission versus the previous submission

Parameter	Previous consideration		Resubmission	
	Previous submission	PBAC requested	Resubmission	Basis/comment
Vismodegib: response rate	64.9%	50%	64.9%	Unchanged despite PBAC request. Based on updated data-cut from STEVIE study.
Vismodegib: disfigurement rate	0%	20%	10%	Mid-way between previous submission and PBAC request. Based on a survey of 2 clinicians and to reflect the clinical uncertainty.
Surgery: response rate	90.7% (PSCR's revised base case; 53.4% in original submission)	90.7%	90.7%	Appropriate
Rebate on vismodegib ex-manufacturer price	0% (i.e. no SPA requested)	■%	■%	
Effective DPMQ	\$ ■		\$ ■	Includes ■% rebate, plus appropriately updated to reflect 1 July 2016 dispensing fees and mark-ups.
Unit cost of serious pneumonia AEs: vismodegib arm (public setting)	\$ ■ per separation X 1.8% incidence = \$ ■/pt treated		\$ ■ per separation X 1.8% incidence = \$ ■/pt treated	Appropriately updated to reflect current values (using AR-DRG v.7.0 Round 18, NEP 2014-15).
Unit cost of surgery (public setting)	\$10,057 per surgery patient		\$11,248 per surgery pt	

Source: Tables B.1 and B.2 pp4-5 of the resubmission, compiled during preparation of the Overview

AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; DPMQ = Dispensed Price for Maximum Quantity; NEP = National Efficient Price; PBAC = Pharmaceutical Benefits Advisory Committee; PSCR = Pre-Sub-Committee Response; pt = patient; SPA = Special Pricing Arrangement

- 4.17 Overall, the disfigurement-free response rate with vismodegib (the overall response rate, adjusted for the disfigurement rate) was 58.4% in the resubmission, versus 64.9% in the previous submission. This was higher than the 40% requested by the PBAC (based on 50% response adjusted for the 20% disfigurement rate) on which the March 2016 recommendation was based. The resubmission's disfigurement-free response rate may not have been appropriate because: the vismodegib response rate was based only on data from the STEVIE study; and the disfigurement rate

appeared to relate only to patients currently responding to vismodegib and not those that may initially respond and then relapse.

- 4.18 Table 6 presents the results of the cost-effectiveness evaluation.

Table 6: Results of the modelled economic evaluation

Step and component	Previous submission ^a			Resubmission		
	Vismodegib	Surgery	Increment	Vismodegib	Surgery	Increment
Modelled evaluation						
Costs (with EOC) ^b	\$ [REDACTED]	\$10,057	\$ [REDACTED]	\$ [REDACTED]	\$11,248	\$ [REDACTED]
Disfigurement-free response rate	64.9%	16.1%	48.8%	58.4% ^c	16.1%	42.3%
Incremental cost/extra disfigurement-free responder with EOC cap			\$ [REDACTED]	\$ [REDACTED]		
ICER without EOC cap			\$ [REDACTED]	\$ [REDACTED]		

Source: Table B.4, p6 of the resubmission; Table 9, p13 of the March 2016 PBAC PSD; "Economic Evaluation.xlsx" from the previous submission

EOC = episode of care; ICER = incremental cost-effectiveness ratio

^a The ESC and PBAC considered this as the new base case, per paragraph 6.26 of the March 2016 PBAC PSD.

^b The EOC cap was based on the Commonwealth subsidising a maximum of [REDACTED] of vismodegib per patient.

^c Based on response rate of 64.9% and a disfigurement rate of 10%.

- 4.19 The economic evaluation resulted in an ICER per disfigurement-free responder of \$ [REDACTED] for vismodegib versus surgery based on the EOC cap. This was less than in the previous submission due to the reduced price of vismodegib ([REDACTED]% rebate), despite the reduction in the disfigurement-free response rate for vismodegib (from 64.9% to 58.4%). The ICER may have been underestimated due to the inclusion of a higher response rate and lower disfigurement rate for vismodegib than requested by the PBAC in its previous consideration.
- 4.20 The economic evaluation did not include any additional AEs in the updated analysis despite this being noted in the March 2016 PBAC PSD (Paragraph 7.7).
- 4.21 Table 7 provided the results of univariate and multivariate sensitivity analyses conducted during the preparation of the overview.

Table 7: Results of univariate and multivariate sensitivity analyses

	Incremental effectiveness	With EOC ^a cap		Without EOC cap	
		Incremental costs	ICER	Incremental costs	ICER
Base case	█%	\$█	\$█	\$█	\$█
Univariate sensitivity analyses					
Vismodegib response rate (base case: 64.9%) • 50% (requested by PBAC March 2016)	█%	\$█	\$█	\$█	\$█
Vismodegib disfigurement rate (base case 10%) • 20% (requested by PBAC March 2016)	█%	\$█	\$█	\$█	\$█
Vismodegib rebate (base case: █%) • █%	█%	\$█	\$█	\$█	\$█
Multivariate sensitivity analyses					
March 2016 PBAC PSD (Para 6.28) • response rate 50% (base case 64.9%) • disfigurement rate 20% (base case 10%) (i.e. disfigurement-free response rate of 40%, versus base case of 58.4%)	█%	\$█	\$█	\$█	\$█
March 2016 PBAC PSD (Para 6.28) • response rate 50% (base case 64.9%) • disfigurement rate 20% (base case 10%) • █% rebate (base case: █%)	█%	\$█	\$█	\$█	\$█

Source: Compiled during preparation of the Overview based on "Updated Economic Evaluation.xlsx" worksheet
EOC = episode of care; ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee
^a The EOC cap was based on the Commonwealth subsidising a maximum of █ packs of vismodegib per patient.

4.22 Based on the effectiveness estimates that the March 2016 PBAC considered to be most plausible, the ICER per disfigurement-free responder would be \$105,000 - \$200,000 for vismodegib versus surgery with the EOC cap (that is, a vismodegib response rate and disfigurement rate of 50% and 20%, respectively), using the proposed █% rebate. With a █% rebate, the ICER per disfigurement-free responder would be \$█, which is outside the ICER range of \$45,000 - \$75,000 outlined in the March 2016 PBAC PSD (Paragraph 6.28).

Drug cost/patient/course: \$█ with EOC cap; \$█ without EOC cap.

4.23 With the EOC cap, the estimated average cost per patient per course was \$█ based on an average treatment duration of █ weeks, a 92% compliance rate, an effective Dispensed Price for Maximum Quantity of \$█ per pack, and an average of █ packs per patient per week. Without the EOC cap, the average cost per patient per course was \$█ based on an average treatment duration of 50.62 weeks and a 92% compliance rate. The March 2016 PBAC noted that the uncertainty surrounding the assumptions in the model for average treatment duration, compliance and dose intensity strongly favoured vismodegib. In its previous consideration, the PBAC did not consider that the average treatment duration of 50.62 weeks was realistic, with patients more likely to discontinue treatment early due to an adverse event (March 2016 PBAC PSD, Paragraph 6.29).

Estimated PBS usage & financial implications

- 4.24 The financial estimates were updated to reflect:
- the █% rebate to the price of vismodegib;
 - current PBS dispensing fees and mark-ups and Australian Refined Diagnosis Related Groups data (see Table 5);
 - current PBS patient co-payments based on the updated proportion of general, concessional and safety net patients who received memantine for Alzheimer disease from July 2014 to June 2016.

Note that the number of patients treated and the total number of scripts were unchanged.

- 4.25 The estimated net cost to the PBS, RPBS and MBS are summarised in Table 8.

Table 8: Estimated PBS usage & financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Scripts ^a					
Estimated net cost to PBS/RPBS/MBS - without episode of care cap					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$
Estimated total net cost - without episode of care cap					
Net cost to PBS/RPBS/MBS - resubmission	\$	\$	\$	\$	\$
Net cost to PBS/RPBS/MBS - March 2016	\$	\$	\$	\$	\$
Changes with an episode of care cap of █ packs per patient					
Scripts paid for by PBS/RPBS					
Net cost to PBS/RPBS ^b	\$	\$	\$	\$	\$
Net cost to PBS/RPBS/MBS - resubmission	\$	\$	\$	\$	\$
Net cost to PBS/RPBS/MBS - March 2016	\$	\$	\$	\$	\$

Source: Tables C.1-C.3, pp7-8 of the resubmission; Table 10 of the March 2016 PBAC PSD; Values in italics were calculated during preparation of the Overview based on "Updated Financial Cost to PBS.xlsx" spreadsheet

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming 11.64 prescriptions per patient per year as estimated by the submission.

^b The resubmission stated that this amount "directly correspond to the updated subsidisation caps with █% rebate for any expenditure above the caps".

- 4.26 The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.
- 4.27 The minor resubmission estimated a net cost to the PBS/RPBS of less than \$10 million in Year 5 of listing, with a total net cost to the PBS/RPBS of \$20 - \$30 million over the first 5 years of listing with the EOC cap. In the previous submission the total net cost to the PBS/RPBS was estimated to be \$20 - \$30 million over the first 5 years of listing. The difference was primarily due to the █% rebate offered in the resubmission.
- 4.28 Without the EOC cap, the total net cost to the PBS/RPBS was estimated to be \$30 - \$60 million over the first 5 years of listing.

Financial Management – Risk-sharing Arrangements

- 4.29 In its previous consideration, the March 2016 PBAC stated that “a total financial cap should be based on the submission’s estimated patient numbers, the estimated average cost per patient per course under the EOC, after taking into account PBAC’s requested price reduction. Beyond the financial cap a total rebate of ■■■% of expenditure above the cap would be rebated to Government” (Paragraph 6.36). The resubmission addressed this by offering updated subsidisation caps based on the net cost to the PBS/RPBS with the EOC cap applied and a ■■■% rebate for any expenditure above the cap. This was based on a ■■■% rebate, rather than at least ■■■% as requested by the March 2016 PBAC. In the pre-PBAC response (p3), the sponsor proposed a fixed total financial cap based on the calculations used in the EOC cap.

For more detail on PBAC’s view, see section 5 “PBAC outcome”

5 PBAC Outcome

- 5.1 The PBAC updated the advice that it provided in March 2016 when recommending an Authority Required listing of vismodegib for the treatment of metastatic or locally advanced BCC inappropriate for surgery and curative radiotherapy.
- 5.2 The PBAC confirmed its March 2016 advice that there was a continued unmet clinical need for vismodegib and that there was a likely benefit for a highly selected patient group.
- 5.3 The PBAC noted that there was significant toxicity associated with vismodegib and no improvement in quality of life.
- 5.4 The PBAC noted the use of a non-standard ICER per ‘disfigurement-free responder’ and considered that the cost-effectiveness of vismodegib remained uncertain with the proposed higher response rate and lower disfigurement rate inputs within the revised model.
- 5.5 The PBAC considered that it was not appropriate to rely solely on data from the STEVIE trial to inform the vismodegib response rate, as that study reported a higher response compared to the other studies, had the lowest proportion of participants with metastatic disease, and used investigator rather than independent response assessment. A less optimistic interpretation of the total data, giving more weight to response rates from the other studies, independent assessment, and response rates in metastatic disease, would suggest a vismodegib response rate substantially less than 50%. The PBAC reaffirmed that it considered a response rate of 50% for vismodegib as appropriate as per its recommendation in March 2016. In terms of the model input for disfigurement rate, the PBAC considered a revised 10% disfigurement rate may be reasonable.
- 5.6 The PBAC noted that this submission is not eligible for an Independent Review as this was a request to change an existing recommendation.

Outcome:

Advice provided.

6 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.

7 Sponsor's Comment

Roche welcomes the advice provided by the PBAC and look forward to working with the Department of Health to ensure the earliest possible access for patients with advanced BCC who are currently without suitable treatment alternatives