

5.13 VISMODEGIB, 150 mg capsule, Erivedge®, Roche Products Pty Ltd

1 Purpose of Application

- 1.1 To seek General Schedule, Authority Required listing for vismodegib for treatment of adult patients with metastatic or locally advanced basal cell carcinoma (BCC) where surgery and radiotherapy are not appropriate.

2 Requested listing

- 2.1 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 form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
VISMODEGIB 150 MG CAPSULE, 28	1	2	\$ [REDACTED]	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 <i>curative</i> 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><i>Special Pricing Arrangements apply.</i></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

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<p>Restriction Method:</p>	<p> <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 </p>
<p>Clinical criteria:</p>	<p> The treatment must be for patients who have previously received PBS-subsidised treatment with vismodegib <i>Patient must have previously been issued with an authority prescription for this drug for this condition</i> AND Patient must not have progressive disease AND The patient must remain inappropriate for surgery and radiotherapy </p>
<p>Prescriber Instructions</p>	<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>
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- 2.2 The ESC considered that the definition in the restriction for ‘inappropriate for surgery and curative radiotherapy’ could be subjective and that this may lead to leakage to a broader patient population, or to the use of vismodegib as a neoadjuvant therapy. The PBAC considered that the definition of condition in the restriction was acceptable
- 2.3 The submission requested listing on the basis of relative cost-effectiveness compared with surgery.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

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 has not been considered by PBAC previously for this indication.

4 Clinical place for the proposed therapy

- 4.1 The proposed clinical treatment algorithm is simplified and does not encompass the complexity of metastatic and locally advanced BCC, and placed vismodegib as the only treatment for all patients with BCC who are ineligible for radiotherapy and surgery. Whilst the definition of locally advanced BCC is being ineligible for surgery and radiotherapy, a metastatic disease definition is not specified.
- 4.2 The proposed clinical algorithm was not consistent with PBS restriction proposed by the submission. The submission placed vismodegib as the only treatment for adult patients with metastatic or locally advanced BCC where surgery and radiotherapy are not appropriate.
- 4.3 The proposed PBS restriction was not consistent with the TGA registration. The proposed PBS restriction was for patients who were inappropriate for surgery AND radiotherapy; whereas, the TGA registration is for patients that were inappropriate for surgery AND/OR radiotherapy. The Pre-Sub-Committee Response (PSCR) clarified that the requested listing is correct. The sponsor noted that this is a narrower listing than the TGA registration, requiring both surgery and radiotherapy to have been considered for the patient, and that this is consistent with the trial population.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

5 Comparator

- 5.1 The submission nominated two comparators: surgery and best supportive care. The ESC agreed that these were appropriate comparators. The PBAC was made aware that another oral sonic hedgehog (HH) pathway inhibitor sonidegib was a potential comparator. Sonidegib is TGA approved, but not PBS listed, for the treatment of adult patients with locally advanced BCC who are not amenable to curative surgery

or radiotherapy and adult patients with metastatic BCC. The ESC and PBAC noted that the submission did not consider radiotherapy or the combination of radiotherapy and surgery as potential comparators.

- 5.2 While best supportive care was identified as a comparator in Sections A, C and E of the submission, the submission did not compare the clinical efficacy of vismodegib versus best supportive care. Surgery was used as the main clinical and economic comparator throughout the submission. This was an appropriate comparator, though due to the complex nature of current treatment for this patient group, other comparators, such as radiotherapy or supportive care should also have been considered because clinical guidelines recommend consultation with a multidisciplinary tumour board.

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 (5), health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with vismodegib including the shrinkage of tumours and avoidance of surgery, despite side effects.
- 6.3 The PBAC noted the input received from Rare Cancers Australia supporting the use of vismodegib in clinical practice. The PBAC specifically noted the advice that the use of vismodegib may, in patients with Gorlin's Syndrome who undergo many surgeries, offer relief from these multiple surgeries. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.4 The submission was based on three non-randomised, open-label, single-arm studies for vismodegib and one retrospective cohort study for surgery.
- 6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Study	Protocol title/ Publication title	Publication citation
Vismodegib		
<i>Non-randomised studies</i>		
ERIVANCE	A pivotal phase II, multicentre, single-arm, two-cohort trial evaluating the efficacy and safety of GDC 0449 in patients with advanced basal cell carcinoma.	2011
	Interim Clinical Study Report – SHH4476g: Clinical Study Report – A Pivotal Phase II, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients With Advanced Basal Cell Carcinoma	2014
	Sekulic, Migden, Lewis. <i>et al</i> (2015) Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC	<i>Journal of the American Academy of Dermatology</i> 2015; 72(6):1021-26.e8.
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.	2014
	Basset-Seguin, 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
Chang <i>et al</i> (2014)	Chang, Solomon, Hainsworth, <i>et al</i> (2014) Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib.	<i>Journal of the American Academy of Dermatology</i> 2014; 70(1):60-69.
Surgery		
Schwippen (2011)	Schwippen (2011) Invasive basal cell carcinoma of the head and neck (basalioma terebrans)	<i>Facial Plastic Surgery</i> 2011; 27:3 (258-265).

Source: Table B.2.4, pp7-8 of Section B; and Attachment 1 of the submission

- 6.6 The key features of the non-randomised, single-arm studies are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Used in modelled evaluation
Vismodegib						
STEVIE	501	OL, MC, SA 9.3 months median follow up – still ongoing	High	mBCC or laBCC not suitable for surgery	AE, ORR, PFS, OS	Yes
ERIVANCE	104	OL, MC, SA 14.5 months median follow up	High	mBCC or laBCC not suitable for surgery	ORR, PFS, OS, AE	No
Chang et al (2014)	119	OL, MC, SA 6.5 months median follow up	High	mBCC or laBCC not suitable for surgery	ORR, PFS, OS, AE	No
Surgery						
Schipper (2011)	118	SA, Cohort study 9 years	High	Invasive BCC of the Head and Neck	CR, PFS, OS	Yes

Source: *Compiled during the evaluation*

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

- 6.7 The STEVIE study was identified by the submission as the pivotal study for the economic evaluation and financial estimates.

Comparative effectiveness

- 6.8 The submission highlighted objective response rate as the key outcome variable. An objective response was defined as a complete or partial response determined on two consecutive assessments at least four weeks apart. In turn, a complete response was where the target lesion(s) were no longer visible and this was maintained for at least four weeks and a partial response was where the target lesion obtained a decrease of 30% or greater that was maintained for at least four weeks. In the surgery study, the outcome was the surgical response rate defined as the proportion of patients considered 'cured' after an average post-operative follow-up period of 5 years. Table 3 presents the results of the main outcomes across the non-randomised studies.

Table 3: Results of response across the non-randomised studies

Trial ID	Vismodegib			Surgery
	mBCC n/N (%)	laBCC n/N (%)	All patients n/N (%)	All patients n/N (%)
Objective response (ORR)				
STEVIE ^a	11/29 (37.9)	302/453 (66.7)	313/482 (64.9)	-
ERIVANCE ^a	15/33 (45.5)	38/63 (60.3)	53/96 (55.2)	
Chang <i>et al</i> 2014 ^b	12/39 (30.8)	26/56 (46.4)	38/95 (40.0)	-
Patients considered 'cured' after an average post-operative follow up period of 5-years				
Schwipper 2011				63/118 (53.4)
Patients with resection within healthy tissue margin				
Schwipper 2011				107/118 (90.7)

Source: Table B.6.1, p33; Table B.6.3, p35; Table B.6.5, p38 of Section B of the submission; and Schwipper (2011)

BCC = basal cell carcinoma; mBCC = metastatic BCC; laBCC = locally advanced BCC; ORR = objective response rate

^a Investigator assessed

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

- 6.9 The surgical complete response rate after five years was compared with the objective response rate for the vismodegib studies; this was inappropriate. This comparison was based on three single-arm studies with substantial baseline heterogeneity and somewhat different outcome measures that should be considered when interpreting this result. In the STEVIE and ERIVANCE studies vismodegib had a lower objective response rate (63.3%) compared with resected BCC within historically controlled healthy safety margins in patients who received surgical excision (90.7%). The PBAC considered that the complete response rate for surgery was 90.7% with a cure rate of 53.4%.
- 6.10 The three vismodegib studies reported vismodegib was more effective in a locally advanced population than in a metastatic population. However, the incremental benefit of vismodegib between the two sub-populations was not estimable as the Schwipper (2011) data do not sub-divide by metastatic versus locally advanced disease.
- 6.11 Table 4 presents the duration of response across the non-randomised studies.

Table 4: Results of duration of response across the non-randomised studies

Trial ID	mBCC Months (95% CI)	laBCC Months (95% CI)	All patients Months (95% CI)
Median duration of objective response – vismodegib studies			
STEVIE ^a	10.0 (5.7, NE)	22.7 (16.8, NE)	22.7 (16.8, NE)
ERIVANCE			
Investigator assessed	12.9 (5.6, 12.9)	7.6 (7.4, NE)	9.5 (7.4, 12.9)
Independent review	7.6 (5.6, NE)	7.6 (5.7, 9.7)	7.6 (5.7, 9.7)
30 month update	14.8 (5.6, 17.0)	26.2 (9.0, 37.6)	16.1 (9.5, 26.2)
Mean period free from recurrence – surgery study			
Schwipper 2011			25.6 (NR, NR)

Source: Table B.6.6-B.6.8, pp39-40; text, p44 of Section B of the submission; and Schwipper (2011)

BCC = basal cell carcinoma; mBCC = metastatic BCC; laBCC = locally advanced BCC; CI = confidence intervals; NR = not reported; NE = not estimable

^a Investigator assessed

- 6.12 The duration of response was similar between vismodegib and surgery; however, this comparison was based on different outcome measures (objective response in the

vismodegib studies and complete response in the surgical study). The comparison was also based on single-arm studies with substantial baseline heterogeneity (year of treatment, disease inclusion criteria, age, location) that should be considered when interpreting the result. The PBAC did not accept the equivalence of treatment with vismodegib to surgery and noted that no comparison was made to radiotherapy or best supportive care.

Comparative harms

- 6.13 The submission did not present comparative harms for vismodegib compared with surgery. Vismodegib resulted in Grade 3 or greater adverse events including muscle spasms and weight loss in 29 to 42% of patients in the non-randomised studies, while muscle spasms, taste disturbances, alopecia and weight loss were frequent adverse events reported in the Periodic Safety Update Report (PSUR). The submission suggested that pneumonia was the only adverse event for vismodegib that resulted in increased costs and utilised this in the economic evaluation. Only 1.8% of patients in the STEVIE study reported pneumonia. The PBAC noted in JAMA Dermatology that there was an increased risk of further neoplastic lesions in BCC patients treated with vismodegib, HR 6.37 (95% CI, 3.39-11.98) for non-BCC malignancy and 8.12 (3.89-16.97) for cutaneous squamous cell carcinoma (SCC). It was noted that the SCC can arise within the advanced BCC. Approximately 50% of the non-BCC malignancies in cases were diagnosed within 1 year (Mohan et al., JAMA dermatology, on line Feb 24 2016).
- 6.14 In the surgery cohort (Schwipper 2011), 97/118 patients (82.2%) lost one or more facial organs. This was used in the submission to describe disfigurement and deformity and it was assumed that patients in the vismodegib studies did not have disfigurement and deformity. This might not have been appropriate as no information was provided on those patients that progressed in the vismodegib studies. It was likely that these patients would need further local treatment that might have included surgery and or radiotherapy.

Benefits/harms

- 6.15 A summary of the comparative benefits and harms for vismodegib versus surgery is presented in the table below.

Table 5: Summary of comparative benefits and harms for vismodegib and surgery

Trial	Vismodegib	Surgery	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Vismodegib	Surgery	
Benefits						
Objective response						
	Vismodegib	Surgery	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Vismodegib	Surgery	
STEVIE	313/482	-	-	65	-	-
ERIVANCE	53/96	-	-	55	-	-
Chang <i>et al</i> 2014	38/95	-	-	40	-	-
Schwipper 2011	-	NR	-	-	NR	-

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Trial	Vismodegib	Surgery	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Vismodegib	Surgery	
Complete response^a						
	Vismodegib	Surgery	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Vismodegib	Surgery	
STEVIE	155/482	-	-	32	-	-
ERIVANCE	20/96	-	-	21	-	-
Chang <i>et al</i> 2014	8/95	-	-	8	-	-
Schwippen 2011	-	95/118	-	-	81	-
Progression free survival; Median months (95% CI)						
	Vismodegib	Surgery	Absolute Difference		HR (95% CI)	
STEVIE	20.2 (19.3; NE)	-	-		-	
ERIVANCE	12.8 (9.46; 17.97)	-	-		-	
Schwippen 2011	-	25.6 (NR, NR)	-		-	
Harms						
	Vismodegib	Surgery	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Vismodegib	Surgery	
Any adverse event						
STEVIE	492/500	-	-	98	-	-
ERIVANCE	104/104	-	-	100	-	-
Chang <i>et al</i> 2014	116/119	-	-	98	-	-
Schwippen 2011	-	NR	-	-	NR	-
Grade ≥3 adverse event						
STEVIE	210/500	-	-	42	-	-
ERIVANCE	44/104	-	-	42	-	-
Chang <i>et al</i> 2014	35/119	-	-	29	-	-
Schwippen 2011	-	NR	-	-	NR	-
Treatment related SAEs						
STEVIE	33/500	-	-	7	-	-
ERIVANCE	4/104	-	-	4	-	-
Chang <i>et al</i> 2014	1/119	-	-	1	-	-
Schwippen 2011	-	NR	-	-	NR	-
Disfigurement						
STEVIE	NR	-	-	-	-	-
ERIVANCE	NR	-	-	-	-	-
Chang <i>et al</i> 2014	NR	-	-	-	-	-
Schwippen 2011	-	97/118	-	-	82	-

Median duration of follow-up): STEVIE = 9.3 months; ERIVANCE = 14.5 months; Chang *et al* (2014) = 6.5 months; Schwippen (2011) = 5 years

Source: *Compiled during the evaluation*

RD = risk difference; RR = risk ratio; NE = not estimable; NR = not reported; CI = confidence interval

^a Complete response in Schwippen (2011) was patients whose BCCs were resected within historically controlled healthy safety margins; whereas, complete response in the vismodegib studies was determined on two consecutive assessments ≥ 4 weeks apart and could not be directly compared.

- 6.16 The ESC noted that on the basis of single-arm study evidence presented by the submission, a comparison of vismodegib and surgery was not possible. This was supported by the PBAC.
- 6.17 The PBAC considered that the data for the surgical comparator from a published retrospective study (Schwippen) most likely overestimated the disfigurement rate due to the age of the data and the subsequent advancements in surgical procedures. The

PBAC acknowledged that this was a rare subgroup of the disease and that no better data would be expected.

Clinical claim

- 6.18 Based on a naïve indirect comparison with no common comparator, the submission described vismodegib as equivalent in terms of comparative effectiveness and superior in terms of comparative safety over surgery. This claim was not adequately supported.
- The evidence presented in the submission for vismodegib and surgery was not comparable.
 - The disfigurement rate associated with surgery was likely to be over-estimated. The surgical study was based on data collected from surgical cases greater than or equal to 18 years ago; more effective surgical techniques and improved health care might have been available when the vismodegib data was collected. The PSCR (p.2) argued that there have been no advances in surgical treatment during this time, noting that Mohs surgery, which is now the standard of care, was available at the time of data collection. The ESC noted that the use of Mohs surgery has greatly increased since the time of the data collection and consider this an area of uncertainty, increased use of Mohs surgery because it was better will favour vismodegib.
 - Using the available evidence, it was likely that surgery had superior efficacy in terms of response rate.
- 6.19 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data. The PBAC indicated that there was a clinical place for vismodegib in a highly selected patient group with very large destructive BCCs in very difficult anatomical locations that would not be suitable for surgery and radiotherapy.
- 6.20 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data. The PBAC noted the high incidence of serious AEs, the increased risk of further malignancies, and the teratogenic nature of vismodegib.

Economic analysis

- 6.21 The submission presented a modelled cost-effectiveness analysis using cost per disfigurement-free responder for the economic evaluation. The submission provided two economic evaluations in parallel; one without any risk-sharing agreement, and one with a risk-sharing agreement capping the number of PBS-subsidised packs of vismodegib (to [REDACTED] packs) per episode of care (EOC).

Table 6: Summary of model structure and rationale

Component	Summary
Time horizon	4 years in the model base case versus 12.7 months in trial
Outcomes	Disfigurement-free responder = disfigurement rate x responder rate
Methods used to generate results	Kaplan Meier estimates
Cycle length	1 week
Transition probabilities	None

Source: Compiled during the evaluation

6.22 Table 7 presents the key drivers for the economic model.

Table 7: Key drivers of the model

Description	Method/Value	Impact
Response rate	<u>Vismodegib</u> : based on objective response rate from the STEVIE study; <u>Surgery</u> : based on the proportion of patients considered 'cured' after an average post-operative follow up period of 5-years.	High, favours vismodegib
Proportion of patients receiving vismodegib	The proportion of patients receiving vismodegib is based on time to off-treatment from the STEVIE study and modelled beyond 18.7 months. The data was immature and might have been affected by the study protocol.	High, favours vismodegib
Proportion free of further disfigurement	<u>Vismodegib</u> : Not reported and was assumed that patients on vismodegib would not have any disfigurement.	High, favours vismodegib

Source: Compiled during the evaluation

6.23 Table 8 presents the results of the economic model.

Table 8: Results of the modelled economic evaluation

Step and component	Vismodegib	Surgery	Increment
Modelled evaluation			
Costs	\$ [REDACTED]	\$10,057	\$ [REDACTED]
Disfigurement-free response rate	[REDACTED] %	[REDACTED] %	[REDACTED] %
Incremental cost/extra disfigurement-free responder (without EOC^a cap)			\$ [REDACTED]
ICER under EOC cap from Section F			\$ [REDACTED]

Source: Table D.2.1-D2.2, p4 of Section D of the submission

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

^a The EOC cap was [REDACTED] packs per patient treated with vismodegib

6.24 The economic evaluation resulted in an incremental cost-effectiveness ratio (ICER) of \$45,000 - \$75,000 per extra disfigurement-free responder for vismodegib versus surgery with the EOC cap and \$105,000 - \$200,000 without the EOC cap. The cost-effectiveness of vismodegib was highly uncertain, due to:

- The submission used disfigurement-free response rate, based on the response rate multiplied by the proportion of patients free of further disfigurement. This was not appropriate as:
 - additional disfigurement-free responder was not a clinically meaningful efficacy outcome;
 - loss of an organ as a measure of disfigurement might have been inappropriate as other disfigurement from the disease and treatment process might exist;
 - the submission assumed that all patients who responded to vismodegib were free of further disfigurement; though this was not measured in the vismodegib

- studies, the PBAC considered that this rate would be 20% - 40% encountering disfigurement; and
 - the submission used an inappropriate response rate for surgery.
- The short follow up of the STEVIE study might have led to an underestimate of treatment duration (50.6 weeks), as the longer follow-up ERIVANCE study had a treatment duration of approximately 73 weeks;
- The response outcome used for vismodegib (complete or partial response maintained for four weeks or more) was different to that of surgery (patients considered 'cured' after an average post-operative follow up period of 5-years); and
- The cost estimates for surgery were uncertain due to the processes used to estimate them.
- No analysis compared to best supportive care was undertaken.
-
- 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.

6.25 Table 9 provides the results of the univariate sensitivity analyses presented by the submission and additional analyses conducted during the evaluation.

Table 9: Results of univariate sensitivity analyses

Univariate analyses	Incremental effectiveness	EOC ^b cap applied		Without EOC cap	
		Incremental costs	ICER	Incremental costs	ICER
Base case	█%	\$█	\$█	\$█	\$█
Equivalent response rate	█%	\$█	\$█	\$█	\$█
Surgery response rate (90.7%)	█%	\$█	\$█	\$█	\$█
PSCR (p, 5) calculated					
Surgery response rate (90.7%)^c					
New base case	█%	\$█	\$█		
Proportion free of further disfigurement in vismodegib (80%)	█%	\$█	\$█	\$█	\$█
All patients starting treatment receive █ packs at 100% dose intensity	█%	\$█	\$█	\$█	\$█

Source: Table D.2.3, p6 of Section D of the submission; and compiled during evaluation

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

^a \$█ when checked in the Economic Evaluation.xls of the submission

^b The EOC cap was █ packs per patient treated with vismodegib

^c Calculated by the sponsor in the PSCR (p, 5) the ICER is slightly higher than that calculated during the evaluation.

6.26 The PSCR acknowledged that in terms of the different definitions of response rate used in the vismodegib and surgery studies, Roche recognised the uncertainty associated with the clinical comparison presented in the submission and was willing to accept the modification to the surgical response rate, to 90.7% as noted in Table 9. This was considered the new base case by the ESC and PBAC.

6.27 The univariate sensitivity analyses conducted by the submission (i.e. on the result reported as the base case in Table 9, rather than the new base case) resulted in an

ICER ranging from \$45,000 - \$75,000 per disfigurement-free response taking into account the EOC cap and a range from \$105,000 - \$200,000 per disfigurement-free response when no EOC cap was in place. Analyses performed during evaluation, resulted in higher ICERs of up to \$75,000 - \$105,000 (with EOC cap) and \$105,000 - \$200,000 (no EOC cap) per disfigurement-free response with the key drivers being response rate, the proportion of patients receiving vismodegib, and the proportion free of further disfigurement. The ESC considered that the response rates differ a lot between metastatic and locally advanced disease. While the proposed listing treats these as one population, the ESC considered that the ICER would most likely be quite different in the two groups; however, it was not possible to show this clearly.

- 6.28 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 [REDACTED]% reduction in drug price would be required to achieve an ICER between \$45,000 - \$75,000 per disfigurement-free responder using the average treatment duration of [REDACTED] weeks, as proposed in the EOC cap.

Drug cost/patient/course

- 6.29 The estimated average cost per patient per course was \$[REDACTED] based on an average treatment duration of 50.62 weeks and a 92% compliance rate. Using the EOC cap the estimated average cost per patient per course was \$[REDACTED] based on an average treatment duration of [REDACTED] weeks and a 92% compliance rate. The average treatment length was based on the modelled time to off-treatment from the STEVIE study, treatment was considered to be ongoing until disease progression or intolerable toxicity was reached in the trial. There was potential for this to be higher in the PBS population as intolerable toxicity was not included in the PBS restriction but was a stopping rule in the STEVIE study. In addition, the STEVIE study data was immature and the average length of treatment may be longer. The PSCR identified that in the commentary, the average cost per patient per course was originally calculated based on [REDACTED] weeks of treatment. The treatment duration of [REDACTED] weeks has now been used in Paragraph 6.28 to calculate the average cost per patient per course. The PBAC noted that the uncertainty surrounding the assumptions in the model for average treatment duration, compliance and dose intensity strongly favoured vismodegib. 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 AE.

Estimated PBS usage & financial implications

- 6.30 The submission was considered by DUSC.
- 6.31 The submission took an epidemiological approach to estimate the utilisation and financial implications associated with the requested PBS listing of vismodegib for advanced BCC.

Table 10: 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					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$
Changes made based on episode of care cap of 8 packs					
Scripts paid for by PBS/RPBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

Source: Table E.2.1-E.2.2, p9; E.5.5 – E.5.6, p17 of Section E of the submission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; MBS = Medical Benefits Scheme. ^a Assuming 11.64 prescriptions per patient per year as estimated by the submission.

The redacted table above shows that at year 5, the estimated number of scripts was less than 10,000 and the net cost to PBS would be less than \$10 million.

- 6.32 DUSC considered the estimates presented in the submission may be accurate, if use is limited to the severe patients intended by the sponsor. The main issues were:
- BCC is not required to be reported to cancer registries, so there is limited information regarding the incidence and prevalence of the disease.
 - It is likely overseas data of the incidence of the disease underestimates the rate of BCC in Australia.
 - The uncertainty around the definition of 'locally advanced BCC' and 'inappropriate for surgery' in the restriction would affect selection of potential patients and could allow patients with less severe disease to be treated with vismodegib. Additionally, it is common for patients with BCC to be affected by multiple lesions on highly visible areas of the head and neck. The number of treated patients could be higher if vismodegib is used to treat milder disease in patients with multiple re-occurring lesions.
 - However, as surgery is curative, and vismodegib is associated with significant adverse reactions, the risk of this leakage may be low as most BCC will continue to be treated with surgery.
 - The subsidisation caps and % reimbursement of expenditure over the caps, which were proposed by the sponsor, protect the Commonwealth against higher than expected use.

Quality Use of Medicines

- 6.33 DUSC commented vismodegib is a toxic drug and several adverse drug reactions were reported to be very common (≥10%) in the clinical studies. Additionally, sonic hedgehog pathway inhibitors such as vismodegib have been demonstrated to be embryotoxic and/or teratogenic. Teratogenic effects include severe midline defects, missing digits, and other irreversible malformations. Vismodegib exposure through semen can also be embryotoxic and/or teratogenic.

Financial Management – Risk-sharing Arrangements

- 6.34 The submission proposed a Risk Sharing Arrangement in the form of an EOC cap for vismodegib. The submission proposed that the EOC cap of [REDACTED] packs be operationalised as a subsidisation cap taking into account the estimated number of patients treated with vismodegib per year. The submission stated that [REDACTED]% of expenditure above the subsidisation caps will be rebated to Government.
- 6.35 The PBAC considered that the financial implications to the Commonwealth were unacceptable as presented in the submission. The proposed price was too high, given the uncertainties regarding incremental effectiveness and harms, the uncertainties regarding incremental cost per extra disfigurement-free responder, and the unknown but potentially very high and unacceptable incremental cost per QALY gained. The use of a fixed total financial cap was proposed by the PBAC to mitigate the uncertainty around the cost effectiveness and total financial impact of vismodegib in these patients.
- 6.36 Rather than accept the subsidisation caps proposed by the submission, the PBAC recommended 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 [REDACTED]% of expenditure above the cap would be rebated to Government. This was a pragmatic decision taking into account the high clinical need for an alternative to surgery, but noting the high toxicity and discontinuation rates associated with use of vismodegib, and the limitations of the clinical data in this rare population.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing of vismodegib for the treatment of metastatic or locally advanced BCC inappropriate for surgery and curative radiotherapy.
- 7.2 The PBAC was satisfied that vismodegib provides, for a highly selected patient group, a significant improvement in efficacy over best supportive care.
- 7.3 The PBAC considered that the clinical place for vismodegib is in metastatic or locally advanced BCC that is inappropriate for surgery and curative radiotherapy.
- 7.4 The PBAC considered that the wording of the restriction, to exclude patients who should have access to surgery or radiotherapy instead of vismodegib, was sufficient to limit access to vismodegib to the target population. There was considered only a small risk of leakage to patients for whom surgery was an option based mainly on the safety profile of the drug.
- 7.5 The PBAC considered that appropriate comparators included surgery and best supportive care. Vismodegib was not considered equivalent in terms of comparative effectiveness to surgery, as vismodegib was not considered to be curative for BCC.

- 7.6 The PBAC did not accept that vismodegib was superior in safety to best supportive care, noting the high frequency of adverse events, and the potentially teratogenic and mutagenic nature of vismodegib. The PBAC noted that most patients discontinued due to AEs. The PBAC also noted that a significantly increased risk of cutaneous SCC in patients exposed to vismodegib had been reported.
- 7.7 The PBAC did not consider that the model as presented in the submission was either reasonable or acceptable, as the inputs were overly optimistic in favour of treatment with vismodegib. The resultant ICER was not considered to be representative of the actual ICER due to the inputs selected, the lack of any costs associated with AEs and the use of 100% offset of disfigurement from treatment. However, the PBAC considered that there was an unmet clinical need for vismodegib to be PBS listed for the treatment of metastatic or locally advanced BCC in a highly restricted sub-population with the following conditions to be met by the sponsor before listing could occur.
- 7.8 The PBAC considered that the patient estimates were reasonable when restricted to the clinical criteria in the restriction.
- 7.9 The PBAC considered that the financial implications to the Commonwealth were unacceptable as presented in the submission, at the price proposed by the sponsor.
- 7.10 The PBAC considered that a price reduction of at least ■■■% was required to achieve a high but acceptable ICER per disfigurement-free responder. The PBAC recommendation to list is based on a corresponding reduction in price together with acceptance of a Risk Sharing Arrangement.
- 7.11 The PBAC recommended a total financial cap of beyond which ■■■% of expenditure above the cap would be rebated to Government.
- 7.12 The PBAC advised that vismodegib is not suitable for prescribing by nurse practitioners.
- 7.13 The PBAC recommended that vismodegib should not be treated as interchangeable on an individual patient basis with any other drug.
- 7.14 The PBAC recommended that the Early Supply Rule should apply as the requested maximum quantity is sufficient supply for 28 days of treatment.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as the submission was recommended.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
VISMODEGIB 150 MG CAPSULE, 28	1	2	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
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>

Public Summary Document – March 2016 PBAC Meeting

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>
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Public Summary Document – March 2016 PBAC Meeting

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:	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
Prescriber Instructions	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 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 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

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>
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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

Roche welcomes the PBACs pragmatism in its decision to enable access to vismodegib for patients with advanced BCC who are currently without suitable treatment alternatives.