

5.14 SONIDEGIB, capsule 200 mg, Odomzo[®], Sun Pharma Limited

1 Purpose of application

- 1.1 The submission requested a Section 85 (Authority Required) listing for sonidegib for the treatment of locally advanced basal cell carcinoma (laBCC) or metastatic BCC (mBCC), who are inappropriate for surgery and curative radiotherapy due to the type, size, location, depth of penetration of the lesions and extent of the disease.
- 1.2 The requested listing was based on a cost-minimisation analysis of sonidegib compared with vismodegib for patients with laBCC or mBCC.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	laBCC or mBCC patients where surgery and radiation therapy are not appropriate
Intervention	Sonidegib 200 mg capsules, daily oral administration
Comparator	Vismodegib 150 mg capsules, daily oral administration
Outcomes	Objective response rate, duration of response, progression-free survival and safety
Clinical claim	In patients with mBCC or with laBCC who are not amenable to curative surgery or radiation therapy, sonidegib 200 mg is as effective as vismodegib 150 mg at improving objective response rates and reducing treatment related adverse events.

laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma
Source: Table 1.1-1, p2 of the main submission.

2 Requested listing

- 2.1 The PBAC advised that the restriction for sonidegib should be the same as the current listing for vismodegib. The changes to the requested listing to match the vismodegib listing along with those requested by the PBAC are updated below with additions in italics and deletions in strikethrough.

Public Summary Document – November 2017 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SONIDEGIB Capsule 200 mg, 30	1	3	\$ [REDACTED]	Odomzo Sun Pharma Ltd.

* requested published price, adjusted using the mark-ups and dispensing fee as updated in July 2017, with a Special Pricing Arrangement requested.

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 treatment
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:	The condition must be inappropriate for surgery, AND The condition must be inappropriate for curative radiotherapy, AND <i>Patient must not have received previous PBS-subsidised treatment with another hedgehog (Hh) inhibitor; OR</i> <i>Patient must have developed intolerance to another hedgehog (Hh) inhibitor of a severity necessitating permanent treatment withdrawal,</i> AND Patient must not receive more than 16 weeks of treatment under this restriction.

<p>Prescriber Instructions</p>	<p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> a) A completed authority prescription form; and b) A completed Basal Cell Carcinoma Initial PBS Authority Application Form - Supporting Information Form; and c) A histological confirmation of BCC <i>and whether the condition is metastatic or locally advanced</i> ; and d) A letter from a surgically qualified clinician demonstrating inappropriateness for surgery <i>for patients with locally advanced BCC</i>; and e) A letter from a radiation oncologist demonstrating inappropriateness for curative radiotherapy <i>for patients with locally advanced BCC</i>; and f) A signed patient acknowledgement. <p>The assessment of the patient's response to this PBS-subsidised course of therapy must be made within the 4 weeks prior to completion of the course of treatment. It is recommended that an application is submitted to the Department of Human Services no less than 2 weeks prior to the date the next dose is due in order to ensure continuity of treatment for those patients who meet the continuation criteria.</p> <p>Inappropriate for surgery is defined as:</p> <ul style="list-style-type: none"> i/ Curative resection is unlikely, such as where BCC has recurred in the same location after two or more surgical procedures; or ii/ Anticipated substantial morbidity 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); or iii/ Medical contraindication to surgery <p>Inappropriate for curative radiotherapy is defined as:</p> <ul style="list-style-type: none"> i / Hypersensitivity to radiation due to genetic syndrome such as Gorlin Syndrome; or ii/ Limitations due to location of tumour; or iii/ Limitations due to cumulative prior radiotherapy dose; or iv/ Progressive disease despite prior irradiation of locally advanced BCC.
<p>Administrative Advice</p>	<p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p> <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 Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p>
<p>Cautions</p>	<p><i>Sonidegib is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 9 months and 2 months period after cessation of treatment for female and male patients respectively, as according to the TGA approved Product Information.</i></p>

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Severity:	Metastatic or locally advanced
Condition:	Basal cell carcinoma
PBS Indication:	Metastatic or locally advanced basal cell carcinoma
Treatment phase:	Continuing treatment
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 received an authority prescription for this condition with this drug,</p> <p>AND</p> <p>The condition must not have progressed,</p> <p>AND</p> <p>The condition must remain inappropriate for surgery,</p> <p>AND</p> <p>The condition must remain inappropriate for curative radiotherapy,</p> <p>AND</p> <p>Patient must not receive more than 16 weeks of treatment per continuing treatment under this restriction.</p>
Prescriber Instructions:	<p>The authority application must be made in writing and must include:</p> <p>a) A completed authority prescription form; and</p> <p>b) A completed Basal Cell Carcinoma Continuing PBS Authority Application Form - Supporting Information Form; and</p> <p>c) <i>A confirmation statement from the treating doctor that the disease has not progressed; and</i></p> <p>d) <i>In patients with locally advanced BCC, a A letter from a surgically qualified clinician demonstrating that the condition remains inappropriate for surgery; and-or</i></p> <p>A a letter from a radiation oncologist demonstrating that the condition remains inappropriate for curative radiotherapy; and</p> <p>A confirmation statement from the treating doctor that the disease has not progressed</p> <p>The assessment of the patient's response to this PBS-subsidised course of therapy must be made within the 4 weeks prior to completion of the course of treatment. It is recommended that an application is submitted to the Department of Human Services no less than 2 weeks prior to the date the next dose is due in order to ensure continuity of treatment for those patients who meet the continuation criteria.</p> <p>Inappropriate for surgery is defined as:</p> <p>i/ Curative resection is unlikely, such as where BCC has recurred in the same location after two or more surgical procedures; or</p> <p>ii/ Anticipated substantial morbidity 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); or</p> <p>iii/ Medical contraindication to surgery</p>

	<p>Inappropriate for curative radiotherapy is defined as: i/ Hypersensitivity to radiation due to genetic syndrome such as Gorlin Syndrome; or ii/ Limitations due to location of tumour; or iii/ Limitations due to cumulative prior radiotherapy dose; or iv/ Progressive disease despite prior irradiation of locally advanced BCC</p>
<p>Administrative advice</p>	<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 Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p>

- 2.2 A special pricing arrangement (SPA) and a risk sharing arrangement (RSA) are currently in place for the comparator, vismodegib. The Pre-Sub-Committee Response (PSCR) acknowledged that cost minimisation would be calculated using the effective AEMP price of vismodegib and that if sonidegib was recommended for listing on the PBS, it would join the existing RSA with vismodegib.
- 2.3 The submission also proposed a grandfathering provision to allow those patients who are currently receiving sonidegib treatment (i.e. prior to it being available on the PBS) to continue with PBS-subsidised treatment. No details for the requested grandfathering restriction or the expected number of patient qualifying under this restriction were provided in the submission. The PSCR indicated that 20 to 30 patients would seek access to sonidegib on the PBS through a grandfathering provision. The PBAC recommended that patients currently being treated with sonidegib who would have met the PBS initial restriction criteria when they started treatment and who have not experienced disease progression whilst on treatment are grandfathered to PBS-subsidised treatment. The PBAC considered that these patients would meet the criteria of the initial PBS restriction and hence that a separate grandfather restriction would not be required.
- 2.4 The PBAC noted that there was no evidence to support sequential use of vismodegib and sonidegib and considered the restrictions for vismodegib and sonidegib should prevent use with another hedgehog (Hh) inhibitor after progression on a prior Hh inhibitor, except in the case of intolerance.

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

3 Background

Registration status

- 3.1 Sonidegib was TGA registered on 10 August 2015 for the treatment of adult patients with laBCC who are not amenable to curative surgery or radiation therapy; and

mBCC. Vismodegib (the main comparator) was TGA registered in December 2013 for the treatment of adult patients with metastatic or locally advanced BCC where surgery and/or radiotherapy are not appropriate.

- 3.2 International status: Sonidegib was approved by the European Medicines Association (EMA) and US Food and Drug Administration (FDA) only for laBCC patients who are not candidates for surgery or radiation therapy. Vismodegib was approved by the European Medicines Association (EMA) and US Food and Drug Administration (FDA) for both laBCC and mBCC where surgery or radiation therapy is not appropriate.

Previous PBAC consideration

- 3.3 This is the first PBAC submission for sonidegib.
- 3.4 The comparator, vismodegib, was recommended at the March 2016 PBAC meeting for the treatment of mBCC or laBCC. This recommendation was based on a number of parameters that remained to be addressed such as efficacy inputs, costs associated with adverse events (AEs) and the assumed disfigurement rate. The PBAC considered a minor resubmission for vismodegib addressing these parameters in November 2016. Vismodegib is currently listed on the PBS for mBCC and laBCC patients who are inappropriate for surgery and curative radiotherapy.

4 Population and disease

- 4.1 Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer. BCCs are effectively cured with surgery and radiotherapy with 5-year cure rates of greater than 90%. However, a small proportion of patients will develop recurrent disease and progress to laBCC or mBCC. The treatment of laBCC or mBCC are more challenging due to the nature and the extent of the disease. Importantly, many patients with laBCC and mBCC are not amenable to curative surgery or radiation therapy.
- 4.2 Sonidegib was proposed as an alternative to vismodegib for the treatment of laBCC and mBCC patients who are not amenable to curative surgery or radiation therapy.

5 Comparator

- 5.1 The submission nominated vismodegib as the main comparator. The justification was that vismodegib is a pharmacological analogue to sonidegib, belongs to the same therapeutic class, has the same mechanism of action and mode of administration and is the only PBS listed treatment for the proposed population. The PBAC considered that the nominated comparator was appropriate.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented information based on his personal experience in treating patients with both sonidegib and the comparator vismodegib including switching between the drugs due to idiosyncratic side effects, and addressed other matters in response to the Committee's questions.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical studies

6.3 The submission was based on a naïve indirect comparison between sonidegib and vismodegib using one sonidegib study (BOLT) and three vismodegib studies (ERIVANCE, STEVIE and EAS) conducted in patients with laBCC or mBCC. BOLT has not been previously considered by the PBAC. The three vismodegib studies have previously been considered by the PBAC (all three studies in March 2016 and updated data from STEVIE in November 2016).

- Sonidegib: the BOLT study is a randomised controlled trial that compared the TGA approved 200 mg once daily dose of sonidegib with the 800 mg once daily dose. The 800 mg dose is not considered relevant to the current submission and therefore BOLT represents a single arm study of the recommended dose of 200 mg sonidegib. Primary efficacy analysis set (pEAS) N = 55 (laBCC 42, mBCC 13). Full analysis set (FAS) N = 79 (laBCC 66, mBCC 13).
- Vismodegib (the three studies were single arm and assessed the recommended 150 mg once daily dose):
 - ERIVANCE: N = 96 (laBCC 63, mBCC 33);
 - STEVIE: Interim N = 482 (laBCC 453, mBCC 29). An independent literature search identified updated final analysis for STEVIE¹: N = 1,161 (laBCC 1,119, mBCC 96).
 - Expanded access study (EAS) or Chang et al (2014): N=95 (laBCC 56, mBCC 39). There was early termination of the study by the sponsor due to FDA approval when patients were transitioned to commercially available vismodegib.

6.4 Details of the studies presented in the submission are provided in the table below.

¹ Hansson J, Hauschild A, Kunstfeld R, Grob JJ, Dréno B, Mortier L, et al. Vismodegib (VISMO), a hedgehog pathway inhibitor (HPI), in advanced basal cell carcinoma (aBCC): STEVIE study primary analysis in 1215 patients (pts). *American Society of Clinical Oncology*; 2016.

Table 2: Single arm studies and associated reports included in the submission

Study	Protocol title/ Publication title	Publication citation
Proposed medicine sonidegib		
BOLT	<p data-bbox="360 302 874 333"><u>Clinical study reports</u></p> <p data-bbox="360 333 874 488">A phase II, randomised, double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma (BOLT): 18-month analysis (24 February 2015)</p> <p data-bbox="360 510 874 600">Addendum 3 to Module 2.7.4 summary of clinical safety in advanced basal cell carcinoma: 30-month analysis</p> <p data-bbox="360 622 874 712">Addendum 3 to Module 2.7.3 summary of clinical efficacy in advanced basal cell carcinoma: 30-month analysis</p> <p data-bbox="360 734 874 824">Appendix 1 (Integrated summary of efficacy, data analyses)</p> <p data-bbox="360 824 874 913">Appendix 2 (Composite overall response in Study A2201: mRECIST criteria vs. ERIVANCE-like criteria).</p> <p data-bbox="360 936 874 967">ClinicalTrials.gov: NCT01327053</p> <p data-bbox="360 990 874 1021"><u>Publications</u></p> <p data-bbox="360 1021 874 1133">Migden, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial.</p> <p data-bbox="360 1133 874 1290">Dummer, et al. The 12-month analysis from basal cell carcinoma outcomes with LDE225 treatment (BOLT): A phase II, randomised, double-blind study of sonidegib in patients with advanced basal cell carcinoma.</p> <p data-bbox="360 1290 874 1357">Casey, et al. FDA approval summary: Sonidegib for locally advanced basal cell carcinoma.</p> <p data-bbox="360 1357 874 1469">Chen, et al. Sonidegib for the treatment of advanced basal cell carcinoma: A comprehensive review of sonidegib and the BOLT trial with 12-month update.</p> <p data-bbox="360 1469 874 1581">Zhou, et al. Exposure-response analysis of sonidegib (LDE225), an oral Inhibitor of the hedgehog signalling pathway, for effectiveness and safety in patients with advanced solid tumours.</p>	<p data-bbox="874 333 1398 365">24 February 2015</p> <p data-bbox="874 519 1398 551">7 March 2016</p> <p data-bbox="874 640 1398 672">29 March 2016</p> <p data-bbox="874 1012 1398 1070">Lancet Oncology 2015; 16(6):716-728</p> <p data-bbox="874 1133 1398 1191">Journal of the American Academy of Dermatology 2016; 75(1):113-125.e5</p> <p data-bbox="874 1290 1398 1348">Clinical Cancer Research; Ahead of print Jan 10th 2017</p> <p data-bbox="874 1348 1398 1379">Future Oncology 2016; 12(18):2095-2105</p> <p data-bbox="874 1469 1398 1500">Journal of Clinical Pharmacology 2016; 1406-1415</p>

Study	Protocol title/ Publication title	Publication citation
Comparator vismodegib		
ERIVANCE	<p>Sekulic, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma.</p> <p>Sekulic, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC.</p> <p>Sekulic, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study.</p> <p>Axelson, et al. U.S. Food and Drug Administration approval: Vismodegib for recurrent, locally advanced, or metastatic basal cell carcinoma.</p> <p>Dessinioti, et al. Vismodegib for the treatment of basal cell carcinoma: Results and implications of the ERIVANCE BCC trial.</p> <p>Dreno, et al. Clinical benefit assessment of vismodegib therapy in patients with advanced basal cell carcinoma.</p>	<p>New England Journal of Medicine 2012; 366:23 (2171-2179).</p> <p>Journal of the American Academy of Dermatology 2015; 72(6):1021-1026.e8</p> <p>BioMed Central Cancer 2017; 17:332</p> <p>Clinical Cancer Research 2013; 19(9):2289-2293</p> <p>Future Oncology 2014; 10 (6):927-936</p> <p>Oncologist 2014; 19 (8):790-796</p>
STEVIE	<p>Basset-Seguin, Hauschild, Grob, et al (2015) Vismodegib in patients with advanced basal cell carcinoma (STEVIE): A pre-planned): a pre-planned interim analysis of an international, open-label trial</p> <p><u>Updated STEVIE data</u></p> <p>Abstract 9532: Hanson, et al. Vismodegib (VISMO), a hedgehog pathway inhibitor (HPI), in advanced basal cell carcinoma (aBCC): STEVIE study primary analysis in 1215 patients (pts)</p>	<p>The Lancet 2015; 16(6):729-736</p> <p>Journal of Clinical Oncology/American Society of Clinical Oncology 2016 (http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.9532)</p>
Chang et al (2014)	<p>Chang, Solomon, Hainsworth, et al (2014) Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib.</p>	<p>Journal of The American Academy of Dermatology 2014; 70(1):60-69.</p>

Source: Table 2.2-3, pp35-6 of the main body of the submission and an independent search of the literature.

6.5 The key features of the studies included in the naïve indirect comparison are summarised in the table below.

Table 3: Key features of the included evidence – indirect comparison

Study	N	Design/ duration of follow-up ^e	Risk of bias	Patient population	Outcome(s)
Sonidegib study (200 mg once daily arm)					
BOLT	pEAS ^a N=55 FAS ^b N=79	SA ^c Central and Investigator review 12, 18 and 30 mths	High	laBCC and mBCC who are ineligible/contraindicated for curative surgery or radiotherapy	ORR, TTR, DOR, PFS, AEs
Vismodegib single arm studies					
ERIVANCE	96	SA, OL 12 and 30 mths	High	As above	ORR, DOR, PFS, AEs
STEVIE	482 ^{d, f}	SA, OL 12 mths	High	As above	ORR, TTR, DOR, PFS, AEs
EAS (Chang 2014)	95 ^f	SA, OL unclear	High	As above	ORR, TTR, DOR, PFS, AEs

AEs = adverse events; DOR = duration of response; OL=open label; ORR = objective response rate; PFS=progression-free survival; SA = single arm; TTR = time to tumour response.

^a Primary efficacy analysis set

^b Full analysis set

^c BOLT is a RCT assessing the recommended (200 mg once daily) and non-recommended (800 mg once daily) doses of sonidegib. The evaluation considers BOLT as a single arm study of 200 mg sonidegib.

^d An independent literature search identified updated final analysis for STEVIE²: N = 1,161 (laBCC 1,119, mBCC 96).

^e The submission stated that the median duration of follow-up varied among the studies and “the difference in follow-up can be attributed to the study design where treatment was continuous until disease progression or until unacceptable toxicity developed. This meant that there were no predefined follow-up time points rather a treatment cut-off time point was specified where the data was collected up to that point and then analysed”. The submission further stated (p54) that BOLT and ERIVANCE had four and three data cuts, respectively (BOLT: primary, 12-month, 18-month and 30-month time points; ERIVANCE: primary, 12-month and 30-month time points), and STEVIE and EAS had one cut-off point (STEVIE: When approximately 1,200 patients had been followed for at least one year; EAS (Chang, 2014): No pre-specified efficacy analysis time point could be verified for this study). These “time points” were used in the submission for naïve indirect comparisons between sonidegib and vismodegib on the basis that they represent “comparable” periods for efficacy and safety analyses across the single arm studies. These time points are arbitrary and should be interpreted with caution.

In terms of missing data, the submission noted that BOLT and ERIVANCE were the only studies that stipulated the method for imputation of missing data. An overall response of “Unknown” was treated as a non-responder when estimating objective response rates (ORR) and complete response (CR) in both BOLT and ERIVANCE.

^f These are the analysis sets used for effectiveness. Baseline data were provided for a larger dataset for STEVIE (N = 499) and EAS (N = 119)

Source: Compiled during the evaluation using information from Sections 2.2, 2.3 and 2.4.

6.6 The mean or median treatment durations provided in the submission were based on multiple arbitrary analysis time points rather than on a complete follow-up time point. Approximately [REDACTED] % of participants in BOLT were still on sonidegib at the latest data cut-off ([REDACTED]).

6.7 The single arm nature of the studies introduces a high risk of measurement bias. The sonidegib and vismodegib studies differed in terms of design (use of different criteria for measuring overall response in BOLT such as modified RECIST (mRECIST)³ criteria for laBCC patients and the use of different analysis sets). mRECIST criteria (non-existent during the conduct of the vismodegib studies) were developed to adequately assess response in patients with laBCC that were associated with features which were not adequately covered by RECIST 1.1 criteria, such as

² Hansson J, Hauschild A, Kunstfeld R, Grob JJ, Dréno B, Mortier L, et al. Vismodegib (VISMO), a hedgehog pathway inhibitor (HPI), in advanced basal cell carcinoma (aBCC): STEVIE study primary analysis in 1215 patients (pts). American Society of Clinical Oncology; 2016

³ A protocol-specific modified RECIST (mRECIST) was used for assessing response in patients with laBCC. The mRECIST criteria were based on evaluation of multiple modalities including localized MRI scans, digital colour photography and histopathology from tumour biopsy specimens, to derive a composite endpoint of “composite overall response”.

scarring/fibrosis and ulceration and would be expected to be more stringent compared to the criteria used in the vismodegib studies. The BOLT study protocol also pre-specified that response would be reassessed using ERIVANCE-like criteria. ERIVANCE used a composite response to incorporate both clinical and RECIST criteria.

- 6.8 Baseline data varied considerably across the studies and this raised concerns regarding the validity of the naive indirect comparison.
- There was a lower proportion of mBCC patients in STEVIE (6%) and BOLT (16%) compared to ERIVANCE (34%) and EAS (48%). Therefore, a comparison of sonidegib and vismodegib using response rates for the whole study populations are potentially confounded.
 - BOLT had a lower proportion of patients with basal cell naevus syndrome (BCNS) (4%) compared to the vismodegib studies (20%). The impact of this difference on the comparative clinical benefit of sonidegib relative to vismodegib is unclear.
 - No patients in the BOLT study had prior systemic therapy compared to 18% and 26% in the ERIVANCE and EAS studies, respectively.
- 6.9 Overall, the risk of bias associated with the indirect comparison was high.
- 6.10 Data to support the effectiveness of sonidegib in mBCC were limited with only 13 patients enrolled in the 200 mg sonidegib arm of the BOLT study making the results unreliable.
- 6.11 The key outcome measure considered for the cost minimisation analysis was the objective response rate (ORR) that was the primary outcome in the single arm studies. The submission did not nominate a minimal clinically important difference (MCID) for ORR for the naïve indirect comparison. The lack of a MCID makes it difficult to assess a claim of non-inferiority.
- 6.12 Determination of ORR differed across the sonidegib and vismodegib studies. In BOLT, ORR was confirmed according to RECIST version 1.1 in patients with mBCC and a protocol-specific, modified RECIST (mRECIST) for patients with laBCC. Although the vismodegib ERIVANCE study assessed ORR separately for patients in the laBCC and mBCC cohorts (as in BOLT), the criteria differed for laBCC patients. As the mRECIST criteria had not yet been developed, ERIVANCE used a composite response to incorporate both clinical and RECIST criteria. The STEVIE and EAS studies only used RECIST criteria for both mBCC or laBCC patients (v1.1 and 1.0, respectively⁴). The submission noted that the mRECIST criteria used in BOLT are more stringent compared to the criteria used in the vismodegib studies. For example, all lesions must have disappeared to qualify for a complete response (CR) in BOLT, whereas in ERIVANCE and STEVIE, only the target lesion was required to be no longer visible. While partial response (PR) was defined as a $\geq 30\%$ decrease from baseline in the sum of longest diameters (SLD) of target lesions in all the studies, BOLT also incorporated colour photographs and required a $\geq 50\%$ decrease in the sum of the product of perpendicular diameters (SPD) of lesions (WHO criteria). A sensitivity

⁴ A key difference between RECIST version 1.1 and version 1.0 is the inclusion of lymph node assessment in regard to the definition of complete response in version 1.1, whereas lymph node assessment is not conducted for version 1.0.

analysis was pre-specified in the sonidegib BOLT clinical study report (CSR) to assess ORR using “ERIVANCE like” criteria.

- 6.13 Central versus investigator review: BOLT and ERIVANCE presented primary analyses using a central-review assessment of ORR as well as secondary analyses based on investigator review, while STEVIE and EAS only reported ORR as assessed by investigators. The submission stated that investigator-assessed ORR is usually higher than central review.
- 6.14 FAS versus pEAS: In BOLT, the pEAS was planned to be the primary analysis set. pEAS was a subset of the FAS which included laBCC patients whose tumours were adequately assessed according to mRECIST by MRI or photography or both, and all patients with mBCC. The key difference between these analysis sets is that mRECIST criteria were implemented in amendment 2 of the BOLT protocol and the majority of patients with laBCC who were enrolled prior to this amendment, were not evaluable for response according to mRECIST due to lack of baseline MRI or annotated photography. Protocol amendment 4 introduced the pEAS as the primary analysis set.
- 6.15 The submission argued that despite the differences across the studies, comparisons at the 9-month, 12-month and 30-month “analysis time-points” can be conducted using the BOLT, ERIVANCE AND STEVIE studies.
- 6.16 The table below summarises the indirect comparisons presented in the submission and those undertaken during the evaluation.
- The analysis time-points in the submission were based on time since enrolment of the last patient at a particular data cut. For example, the 12-month analysis was conducted at 50 weeks following enrolment of the last patient (data cut 31 December 2013). Thus these analysis time-points represent minimum follow-up periods by data cut. These time-points do not necessarily represent comparable median durations of follow-up across the studies.
 - The submission presented additional analyses combining ERIVANCE and STEVIE. Due to differences between these studies in terms of measurement for response rates, the evaluation did not consider this to be appropriate.
 - An alternative approach is to compare sonidegib with vismodegib using the “most similar” median durations of follow-up from BOLT, ERIVANCE and STEVIE. A comparison using the EAS study was not possible due to the shorter median duration of follow-up (6.5 months).
 - There remain substantial concerns with these comparisons relating to a lack of transitivity and as such they should be interpreted with a high degree of caution.

Table 4: Time-points chosen for the indirect comparisons presented in the submission and in the Commentary

Analysis Time-point	Sonidegib study	Vismodegib studies
Indirect comparisons presented in the submission		
Minimum duration of follow-up	Median duration of exposure as presented in the submission	
9 months	BOLT: 8.9 months	ERIVANCE: 9.9 months STEVIE 8.4 months
12 months	BOLT: 11.0 months	ERIVANCE: 13.0 months
30 months		ERIVANCE: 12.9 months
Indirect comparisons presented in the Commentary		
Median duration of follow-up	Median duration of exposure as presented in the submission	
20-21 months (ORR as assessed by central review using ERIVANCE-like criteria)	BOLT: 11.0 months	ERIVANCE: 9.9 months (ERIVANCE criteria)
13-14 months (ORR as assessed by investigator review, BOLT mRECIST vs. STEVIE RECIST v1.1)		STEVIE: 8.4 months

ORR = objective response rate

NOTE: BOLT and ERIVANCE presented both central assessed and investigator assessed ORR. STEVIE only presented investigator assessed ORR.

ORR = objective response rate; mRECIST = Modified RECIST criteria

Source: Compiled during the evaluation from Sections 2.4 and 2.6 and Attachments 2 and 3 of the main submission.

6.17 The statistical analyses presented in the submission were not considered reliable given the transitivity concerns and lack of a common comparator. These analyses were not considered during the evaluation.

Comparative effectiveness

6.18 Tables 5 and 6 summarise the naïve indirect comparison of ORR, between sonidegib (BOLT) and vismodegib (ERIVANCE), and between sonidegib (BOLT) and vismodegib (STEVIE).

Table 5: BOLT (ERIVANCE - like criteria, median duration of follow-up 20 months) versus ERIVANCE (median duration of follow-up 21 months), central review assessed ORR, FAS

Population	BOLT Sonidegib Data cut Dec 2013 (Median follow-up 20 months) n/N (%)	ERIVANCE Vismodegib Data cut Nov 2010 (Median follow-up 21 months) ^a n/N (%)
Whole study arm (Advanced BCC)	42/79 (53.2)	37/96 (38.5)
laBCC cohort (ERIVANCE LIKE criteria)	41/66 (62.1) (95%CI: 49.3, 73.8)	27/63 (42.9)
mBCC cohort	1/13 (7.7%) ^b RECIST v1.1	10/33 (30.3) RECIST v1.0
Complete response	13/79 (16.5)	13/96 (13.5)
Partial response	29/79 (36.7)	24/96 (25.0)
Stable disease	30/79 (38.0)	45/96 (46.9)
Progressive disease	1/79 (1.3)	9/96 (9.4)
Unavailable/missing	6/79 (7.6)	5/96 (5.2)

CI = confidence interval; FAS = full analysis set; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; mRECIST = Modified Response Evaluation Criteria In Solid Tumours; ORR = objective response rate

^a Inferred by study start (February 10, 2009). Median duration of follow-up up to 21 months as described in Table 2.4-1, p55 of the main submission.

^b There were 2 patients out of 13 with an objective response at the June 2013 data cut. However, at the December 2013 data cut, one patient's response status was removed from the partial response category during central re-review due to a new lesion identified in the photo image (Table 2-14, p38 of the sonidegib CSR_efficacy_addendum 3 report).

Source: Tables 2.6-3 and 2.6-6 of the main submission and sonidegib clinical study reports.

Table 6: BOLT (median duration of follow-up of 13.9 months) versus STEVIE (median duration of follow-up of 12.8 months), investigator assessed ORR, FAS

Population	BOLT Sonidegib Data cut June 2013 (Median follow-up 13.9 months) n/N (%)	STEVIE Vismodegib Data cut Nov 2013 (Median follow-up 12.8 months) n/N (%)
Whole study arm (Advanced BCC)	33/79 (41.8%) (95% CI: 30.8%, 53.4%)	313/482 (64.9) (95% CI: 60.5%, 69.2%)
laBCC cohort	31/66 (47.0) mRECIST	302/453 (66.7) RECIST v1.1
mBCC cohort	2/13 (15.4%) ^a RECIST v1.1	11/29 (37.9) RECIST v1.1
Whole study arm (Advanced BCC)		
Complete response	2/79 (2.5)	155/482 (32.2)
Partial response	31/79 (39.2)	158/482 (32.8)

BCC = basal cell carcinoma; CI = confidence interval; FAS = full analysis set; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; mRECIST = Modified Response Evaluation Criteria In Solid Tumours; ORR = objective response rate

^a There were 2 patients out of 13 with an objective response at the June 2013 data cut. However, at the December 2013 data cut, one patient's response status was removed from the partial response category during central re-review due to a new lesion identified in the photo image (Table 2-14, p38 of the sonidegib CSR_efficacy_addendum 3 report).

Source: Tables 2.6-3 and 2.6-6 of the main submission

- 6.19 The naïve indirect comparison between BOLT and EVIRANCE indicates the ORR results numerically favour sonidegib over vismodegib in the laBCC cohort and vice versa in the mBCC cohort.
- 6.20 The naïve indirect comparison between BOLT and STEVIE indicates the ORR results numerically favour vismodegib over sonidegib in both the laBCC and mBCC cohorts. Different criteria (mRECIST vs. RECIST v1.1) were used to assess response in the laBCC cohort.
- 6.21 The PBAC in both its March and November 2016 considerations of vismodegib considered that a response rate of 50% was the more appropriate estimation of effectiveness of vismodegib. The PBAC noted that the STEVIE study reported a higher response compared to the other vismodegib studies. This study had the lowest proportion of participants with metastatic disease (6.2% vs 16.5% in BOLT vs 34.4%-47.9% in ERIVANCE and EAS) and used investigator rather than independent response assessment (vismodegib public summary documents, March 2016 and November 2016 PBAC meetings).
- 6.22 The ESC noted that the Pre-Sub-Committee Response (PSCR) provided additional analysis of the BOLT study (based on median follow-up as well as a nominated point) and emphasised the longer response for patients on sonidegib, however the ESC did not consider that it increased the reliability of the analysis as it was based on the same low patient numbers.
- 6.23 The PBAC noted that the pre-PBAC response included data from the 800 mg arm of the BOLT study to further support the efficacy of sonidegib, particularly in mBCC, on the basis of the 800 mg arm be equivalent to the 200 mg in efficacy. The PBAC considered that the addition of the data for the 800 mg arm did not substantially increase the reliability of the comparison with vismodegib in mBCC patients. The PBAC noted the lower ORR in mBCC for both the 200 mg and 800 mg arms of the BOLT study compared to vismodegib, however, considered that there may be a clinical role for sonidegib in the treatment of mBCC.

Comparative harms

6.24 The table below summarises the main adverse events (AEs) from the BOLT, ERIVANCE and STEVIE single arm studies. The median duration of follow-up was shorter for STEVIE compared to that for either BOLT or ERIVANCE.

Table 7: Main AEs from the BOLT, ERIVANCE and STEVIE single arms

Safety outcome	BOLT (N = 79; FAS) Data cut December 2013 Median duration of follow-up: 20 months n (%)	ERIVANCE (N = 104 ^a) Data cut November 2010 Median duration of follow-up up to 21 months ^b n (%)	STEVIE (N = 499; FAS) Data cut November 2013 Median duration of follow-up 12.8 months n (%)
AEs	77 (97.5)	104 (100)	491 (98.4)
Grade 1-2 AEs	47 (59.5)	60 (57.7)	276 (55.3)
Grade 3-4 AEs	30 (38.0)	44 (42.3)	193 (38.7)
Treatment-related AEs	70 (88.6)	98 (94%)	490 (98.2)
Most common treatment-related AE (any grade)			
Muscle spasm	41 (51.9)	68 (65.4)	317 (63.5)
Alopecia	36 (45.6)	63 (60.6)	307 (61.5)
Dysgeusia	31 (39.2)	51 (49.0)	269 (53.9)
Nausea	22 (27.8)	29 (27.9)	80 (16)
Decreased weight	20 (25.3)	46 (44.2)	162 (32.5)
Fatigue	17 (21.5)	36 (34.6)	80 (16)
Decreased appetite	14 (17.7)	23 (22.1)	126 (25.3)
SAEs	13 (16.5)	26 (25)	108 (21.6)
Treatment-related SAEs	2 (2.5)	NR ^c	33 (6.2%)
Deaths	0	7 (6.7)	31 (6.2)
AEs leading to discontinuation	22 (27.8)	12 (11.5)	173 (34.7)

AE = adverse event; FAS = full analysis set; NR = not reported; SAE = serious adverse event

^a ERIVANCE: Analysis set was not defined; STEVIE: At clinical cut-off (Nov 6, 2013), 499 patients (468 with locally advanced basal cell carcinoma and 31 with metastatic basal cell carcinoma) had received study drug and had the potential to be followed up for 12 months or longer.

^b Inferred by study start (February 10, 2009). Median duration of follow-up up to 21 months as described in Table 2.4-1, p55 of the main submission.

^c For the data cut November 2011, the proportion of treatment related SAEs was 3.8% (4/104) as reported in Table 2.6-11, p116 of the main submission.

Source: Tables 2.5-6, 2.5-8 and 2.6-11 of the main submission and the ERIVANCE (Sekulic 2012) and STEVIE (Bassett-Seguín 2015) publications.

6.25 AEs in general were similar among the single arm studies. The majority of patients experienced at least one AE. Grade 3-4 AEs, serious adverse events (SAEs) and common AEs of any grade, numerically favoured sonidegib over vismodegib. The naïve indirect nature of the comparison with differences across study design, populations and prior therapies do not allow a meaningful conclusion to be reached on the comparative safety of sonidegib versus vismodegib.

Interpretation of clinical evidence

6.26 The submission described once daily sonidegib 200 mg as non-inferior in terms of comparative effectiveness and comparative safety over once daily 150 mg vismodegib for the treatment of patients with mBCC or laBCC who are not amenable to curative surgery or radiation therapy.

- 6.27 The PBAC noted that the comparison between the treatments was based on disease control/overall response rates.
- 6.28 Sonidegib belongs to the same drug class as vismodegib and has the same mechanism of action via the inhibition of the hedgehog signalling pathway. However, the evidence provided was of low quality and was based on naïve indirect comparisons across non-transitive single-arm studies. Transitivity concerns included different patient characteristics, analysis time points and methods used to assess response outcomes. Compounding these concerns was the small number of mBCC patients enrolled into the BOLT study. The PBAC noted the limitations associated with the evidence, particularly in the context of the recent positive recommendation of vismodegib and the extent of current clinical need for mBCC or laBCC patients.
- 6.29 The PBAC noted the limitations with the available evidence, however considered that given the patient population, it was sufficient to support the clinical claims of non-inferior efficacy and non-inferior safety to vismodegib.

Economic analysis

- 6.30 The submission presented a cost-minimisation analysis based on the claim that sonidegib was non-inferior to vismodegib in terms of both effectiveness and safety. The cost-minimisation analysis presented in the submission was based on the published price for vismodegib.
- 6.31 The equi-effective doses were estimated as sonidegib 200 mg once daily and vismodegib 150 mg once daily. The dose relativity was sourced from the four clinical studies involved in the naïve indirect comparison and is consistent with the recommended doses in the respective Product Information documents.
- 6.32 The cost-minimisation analysis was performed on the basis of a daily cost of sonidegib versus vismodegib, rather than a cost per treatment course. The mean treatment duration of sonidegib therapy in BOLT was [REDACTED] at the latest data cut-off (median duration of follow-up: [REDACTED]), with the vast majority of patients ([REDACTED]%) having discontinued treatment. Of the three vismodegib studies, ERIVANCE was the study with a relatively complete follow-up (only 7.7% patients were still on treatment at the latest data cut-off). This study, however, only reported data on the median duration of treatment with vismodegib, which was not considered to be an appropriate proxy for the mean value in terms of treatment duration. Thus, a cost-minimisation analysis on a per treatment course basis could not be performed.
- 6.33 Sonidegib does not require additional resources beyond those used to treat patients with vismodegib. Therefore a cost-minimisation approach based solely on the cost of sonidegib and vismodegib was appropriate.
- 6.34 The results of the cost-minimisation analysis are presented in the table below. Dispensed prices for sonidegib and vismodegib were re-calculated during the evaluation using the July 2017 updated mark-ups and dispensing fee.

Table 8: Results of economic evaluation

	Sonidegib 200 mg	Vismodegib 150 mg
Cost-minimisation analysis, based on the ex-manufacturer price		
AEMP	\$7,821.43	\$7,300.00
Maximum quantity (units)	30	28
Ex-manufacturer price per day ^a	\$260.71	\$260.71
Difference in treatment cost per day (sonidegib – vismodegib)		\$0.00
Cost-minimisation analysis, based on the dispensed price^b		
DPMQ	\$7,970.95	\$7,449.52
Maximum quantity (units)	30	28
Dispensed price per day ^a	\$265.70	\$266.05
Difference in treatment cost per day (sonidegib – vismodegib)		-\$0.36

AEMP = approved ex-manufacturer price; DPMQ = dispensed price maximum quantity

^a The dose regimen for both sonidegib and vismodegib is one capsule per day.

^b Dispensed prices calculated using the mark-ups and dispensing fee as updated in July 2017.

Source: Table 3.4-2, p133 of the submission.

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

- 6.35 The estimated average cost per patient per course for sonidegib was \$ [REDACTED], based on the dispensed price proposed by the submission, an average treatment duration of [REDACTED] months and a 90.1% compliance rate. The average treatment duration and the compliance rate were derived from the BOLT study. The cost per treatment course increases to \$ [REDACTED] using the 1 July 2017 mark-ups and dispensing fee.
- 6.36 The vismodegib cost per course was estimated to be \$102,126, using the published price for vismodegib and assuming the same treatment duration and compliance rate as for sonidegib. This increases to \$102,149 using the 1 July 2017 mark-ups and dispensing fee.

Estimated PBS usage & financial implications

- 6.37 This submission was not considered by DUSC. The submission used a mixed epidemiological/market share approach to estimate the financial impacts related to the proposed listing of sonidegib in the first 6 years of listing. This approach was appropriate, as vismodegib was listed on the PBS in March 2017 and there were insufficient Medicare Australia utilisation data to facilitate a market share approach.
- 6.38 The estimated financial implications of listing sonidegib are summarised in the table below. The submission's estimate of the number of patients per year likely to be treated was based on the BCC prevalence in 2002 estimated by the Cancer Council Australia, prevalence and incidence data concerning laBCC not amenable to curative surgery or radiation therapy (NATSOR) and mBCC from other countries (the UK and the US), as well as the sponsor's assumptions regarding the uptake of vismodegib in the absence of sonidegib and the market share of sonidegib following its listing. There was a paucity of epidemiological data on the prevalence and incidence of laBCC NATSOR and mBCC in Australia. Thus, the number of patients who would be treated with sonidegib, if listed on the PBS, cannot be reliably estimated. However, this uncertainty was not expected to have a big impact on the net financial implications to the health budget, given the cost-minimisation approach for pricing sonidegib to be the same as vismodegib.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed ^a	■	■	■	■	■	■
Estimated financial implications of sonidegib						
Cost to PBS/RPBS	■	■	■	■	■	■
Co-payments	■	■	■	■	■	■
Cost to PBS/RPBS less co-payments	■	■	■	■	■	■
Estimated financial implications of vismodegib						
Cost to PBS/RPBS	■	■	■	■	■	■
Co-payments	■	■	■	■	■	■
Cost to PBS/RPBS less co-payments	■	■	■	■	■	■
Net financial implications						
Net cost to PBS/RPBS	■	■	■	■	■	■
Net cost to MBS	■	■	■	■	■	■
Net cost to PBS/RPBS/MBS	■	■	■	■	■	■

^a The average number of prescriptions per patient by treatment year was assumed to be 10.97 in Year 1 and 1.83 in Year 2.
 Source: Table 4.2-2 to Table 4.2-6, pp143-145; Table 4.3-2 to Table 4.3-4, pp147-148; Tables 4.4-1, p14; and Tables 4.4-1, p149 of the submission

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

- 6.39 The PBAC considered the estimated number of treated patients to be overestimated. However it noted that sonidegib would be included in the vismodegib Risk Sharing Arrangement and this would reduce the financial risk associated with use in more patients.

Quality use of medicines

- 6.40 Sonidegib is a hedgehog pathway inhibitor and is embryotoxic and/or teratogenic. The approved TGA Product Information (PI) provides further details. This is a similar issue for vismodegib.
- 6.41 Sonidegib should be taken whole on an empty stomach, at the same time each day, either at least 1 hour before, or two hours after a meal (TGA Approved PI). Vismodegib should also be taken whole but unlike sonidegib, may be taken with or without food (vismodegib TGA approved PI). This may cause some confusion with clinicians when prescribing and will need to be communicated to patients at the time of prescribing.

Financial management – risk sharing arrangements

- 6.42 The PBAC advised that sonidegib should be included in the existing RSA agreement for vismodegib as the two medicines treat the same patient population.

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

7 PBAC Outcome

- 7.1 The PBAC recommended sonidegib as an Authority Required (in writing) listing for the treatment of metastatic or locally advanced BCC inappropriate for surgery and curative radiotherapy. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of sonidegib would be acceptable if it were cost-minimised against vismodegib and if the following measures were implemented to contain risks associated with the cost of the drug to the PBS: joining the current Risk Sharing Arrangement for vismodegib in the same indication.
- 7.2 The PBAC noted the relatively small population of patients with metastatic or locally advanced BCC who are inappropriate for surgery and curative radiotherapy and considered that there was a clinical role for an additional therapy.
- 7.3 The PBAC advised that vismodegib was the appropriate comparator. The PBAC noted that sonidegib and vismodegib belong to the same therapeutic class and that they have a similar mode of action.
- 7.4 The PBAC noted that the submission was based on a naïve indirect comparison of nonrandomised studies (one study for sonidegib and three studies for vismodegib), and that the comparison was not robust due to low patient numbers in the sonidegib BOLT study and transitivity issues across the studies.
- 7.5 The PBAC considered that, given the patient population, the available clinical evidence was sufficient to support the clinical claims of non-inferior efficacy and non-inferior safety to vismodegib, and therefore a cost-minimisation approach against vismodegib was appropriate.
- 7.6 The PBAC advised that the equi-effective doses are 150 mg vismodegib and 200 mg sonidegib.
- 7.7 The PBAC noted that it was not possible, given the available evidence, to consider the comparative treatment duration of vismodegib and sonidegib in the cost-minimisation analysis. The PBAC considered it reasonable to assume the treatment duration of either treatment would be similar.
- 7.8 The PBAC advised that the restriction should align with that of vismodegib and that switching between two treatments should only be allowed for adverse reactions of a severity necessitating permanent treatment withdrawal. The PBAC advised that this switching rule would need to flow on to the restriction for vismodegib. The PBAC considered that patients should not be treated with sonidegib and vismodegib sequentially, and vice versa, when disease progression has occurred on one of the agents. This limitation to treatment with one of sonidegib or vismodegib will also need to flow on to the restriction for vismodegib.
- 7.9 The PBAC advised that sonidegib would need to join the current Risk Sharing Agreement for vismodegib.
- 7.10 The PBAC advised that sonidegib is not suitable for prescribing by nurse practitioners.

- 7.11 The PBAC recommended that the Early Supply Rule should apply as the requested maximum quantity is sufficient supply for 30 days of treatment.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

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	
SONIDEGIB Capsule 200 mg, 30	1	3	Odomzo®	Sun Pharma Ltd.

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 treatment
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:	The condition must be inappropriate for surgery, AND The condition must be inappropriate for curative radiotherapy, AND Patient must not have received previous PBS-subsidised treatment with another hedgehog (Hh) inhibitor for this condition; OR Patient must have developed intolerance to another hedgehog (Hh) inhibitor of a severity necessitating permanent treatment withdrawal, AND Patient must not receive more than 16 weeks of treatment under this restriction.

<p>Prescriber Instructions</p>	<p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> a) A completed authority prescription form; and b) A completed Basal Cell Carcinoma Initial PBS Authority Application Form - Supporting Information Form; and c) A histological confirmation of BCC and whether the condition is metastatic or locally advanced ; and d) A letter from a surgically qualified clinician demonstrating inappropriateness for surgery for patients with locally advanced BCC; and e) A letter from a radiation oncologist demonstrating inappropriateness for curative radiotherapy for patients with locally advanced BCC; and f) A signed patient acknowledgement. <p>The assessment of the patient's response to this PBS-subsidised course of therapy must be made within the 4 weeks prior to completion of the course of treatment. It is recommended that an application is submitted to the Department of Human Services no less than 2 weeks prior to the date the next dose is due in order to ensure continuity of treatment for those patients who meet the continuation criteria.</p> <p>Inappropriate for surgery is defined as:</p> <ul style="list-style-type: none"> i/ Curative resection is unlikely, such as where BCC has recurred in the same location after two or more surgical procedures; or ii/ Anticipated substantial morbidity 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); or iii/ Medical contraindication to surgery <p>Inappropriate for curative radiotherapy is defined as:</p> <ul style="list-style-type: none"> i / Hypersensitivity to radiation due to genetic syndrome such as Gorlin Syndrome; or ii/ Limitations due to location of tumour; or iii/ Limitations due to cumulative prior radiotherapy dose; or iv/ Progressive disease despite prior irradiation of locally advanced BCC.
<p>Administrative Advice</p>	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p> <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 Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p>
<p>Cautions</p>	<p>Sonidegib is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 20 months and 6 months period after cessation of treatment for female and male patients respectively, as according to the TGA approved Product Information.</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 treatment
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 received PBS-subsidised treatment with this drug for this condition,</p> <p>AND</p> <p>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.</p> <p>AND</p> <p>The condition must remain inappropriate for surgery,</p> <p>AND</p> <p>The condition must remain inappropriate for curative radiotherapy,</p> <p>AND</p> <p>Patient must not receive more than 16 weeks of treatment per continuing treatment under this restriction.</p>
Prescriber Instructions:	<p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> A completed authority prescription form; and A completed Basal Cell Carcinoma Continuing PBS Authority Application Form - Supporting Information Form; and A confirmation statement from the treating doctor that the disease has not progressed; and In patients with locally advanced BCC, a letter from a surgically qualified clinician demonstrating that the condition remains inappropriate for surgery; or a letter from a radiation oncologist demonstrating that the condition remains inappropriate for curative radiotherapy <p>The assessment of the patient's response to this PBS-subsidised course of therapy must be made within the 4 weeks prior to completion of the course of treatment. It is recommended that an application is submitted to the Department of Human Services no less than 2 weeks prior to the date the next dose is due in order to ensure continuity of treatment for those patients who meet the continuation criteria.</p> <p>Inappropriate for surgery is defined as:</p> <ol style="list-style-type: none"> Curative resection is unlikely, such as where BCC has recurred in the same location after two or more surgical procedures; or Anticipated substantial morbidity 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); or Medical contraindication to surgery <p>Inappropriate for curative radiotherapy is defined as:</p> <ol style="list-style-type: none"> Hypersensitivity to radiation due to genetic syndrome such as Gorlin Syndrome; or

	<p>ii/ Limitations due to location of tumour; or iii/ Limitations due to cumulative prior radiotherapy dose; or iv/ 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 Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p>
Cautions	<p>Sonidegib is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 20 months and 6 months period after cessation of treatment for female and male patients respectively, as according to the TGA approved Product Information.</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:	Initial treatment or continuing treatment – balance of supply
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" 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 received insufficient therapy with this drug under the Initial treatment restriction to complete maximum of 16 weeks of treatment;</p> <p>OR</p> <p>Patient must have received insufficient therapy with this drug under the Continuing treatment restriction to complete maximum of 16 weeks of treatment,</p> <p>AND</p> <p>The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions.</p>
Administrative Advice	Authority approval for sufficient therapy to complete a maximum of 16 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Cautions	Sonidegib is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 20 months and 6 months period after cessation of treatment for female and male patients respectively, as according to the TGA approved Product Information.

8.2 Amend existing listing for vismodegib as follows (additions are noted in italics):

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 treatment			
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>The condition must be inappropriate for surgery,</p> <p>AND</p> <p>The condition must be inappropriate for curative radiotherapy,</p> <p>AND</p> <p><i>Patient must not have received previous PBS-subsidised treatment with another hedgehog (Hh) inhibitor for this condition; OR</i></p> <p><i>Patient must have developed intolerance to another hedgehog (Hh) inhibitor of a severity necessitating permanent treatment withdrawal,</i></p> <p>AND</p> <p>Patient must not receive more than 16 weeks of treatment under this restriction.</p>			

<p>Prescriber Instructions</p>	<p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> a) A completed authority prescription form; and b) A completed Basal Cell Carcinoma Initial PBS Authority Application Form - Supporting Information Form; and c) A histological confirmation of BCC and whether the condition is metastatic or locally advanced ; and d) A letter from a surgically qualified clinician demonstrating inappropriateness for surgery for patients with locally advanced BCC; and e) A letter from a radiation oncologist demonstrating inappropriateness for curative radiotherapy for patients with locally advanced BCC; and f) A signed patient acknowledgement. <p>The assessment of the patient's response to this PBS-subsidised course of therapy must be made within the 4 weeks prior to completion of the course of treatment. It is recommended that an application is submitted to the Department of Human Services no less than 2 weeks prior to the date the next dose is due in order to ensure continuity of treatment for those patients who meet the continuation criteria.</p> <p>Inappropriate for surgery is defined as:</p> <ul style="list-style-type: none"> i/ Curative resection is unlikely, such as where BCC has recurred in the same location after two or more surgical procedures; or ii/ Anticipated substantial morbidity 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); or iii/ Medical contraindication to surgery <p>Inappropriate for curative radiotherapy is defined as:</p> <ul style="list-style-type: none"> i / Hypersensitivity to radiation due to genetic syndrome such as Gorlin Syndrome; or ii/ Limitations due to location of tumour; or iii/ Limitations due to cumulative prior radiotherapy dose; or iv/ Progressive disease despite prior irradiation of locally advanced BCC.
<p>Administrative Advice</p>	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p> <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:</p> <p>Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p>
<p>Cautions</p>	<p>Vismodegib is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 9 months and 2 months period after cessation of treatment for female and male patients respectively, as according to the TGA approved Product Information.</p>

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

SUN Pharma welcomes the PBAC's decision to recommend listing of sonidegib on the PBS for Australian patients with advanced BCC.