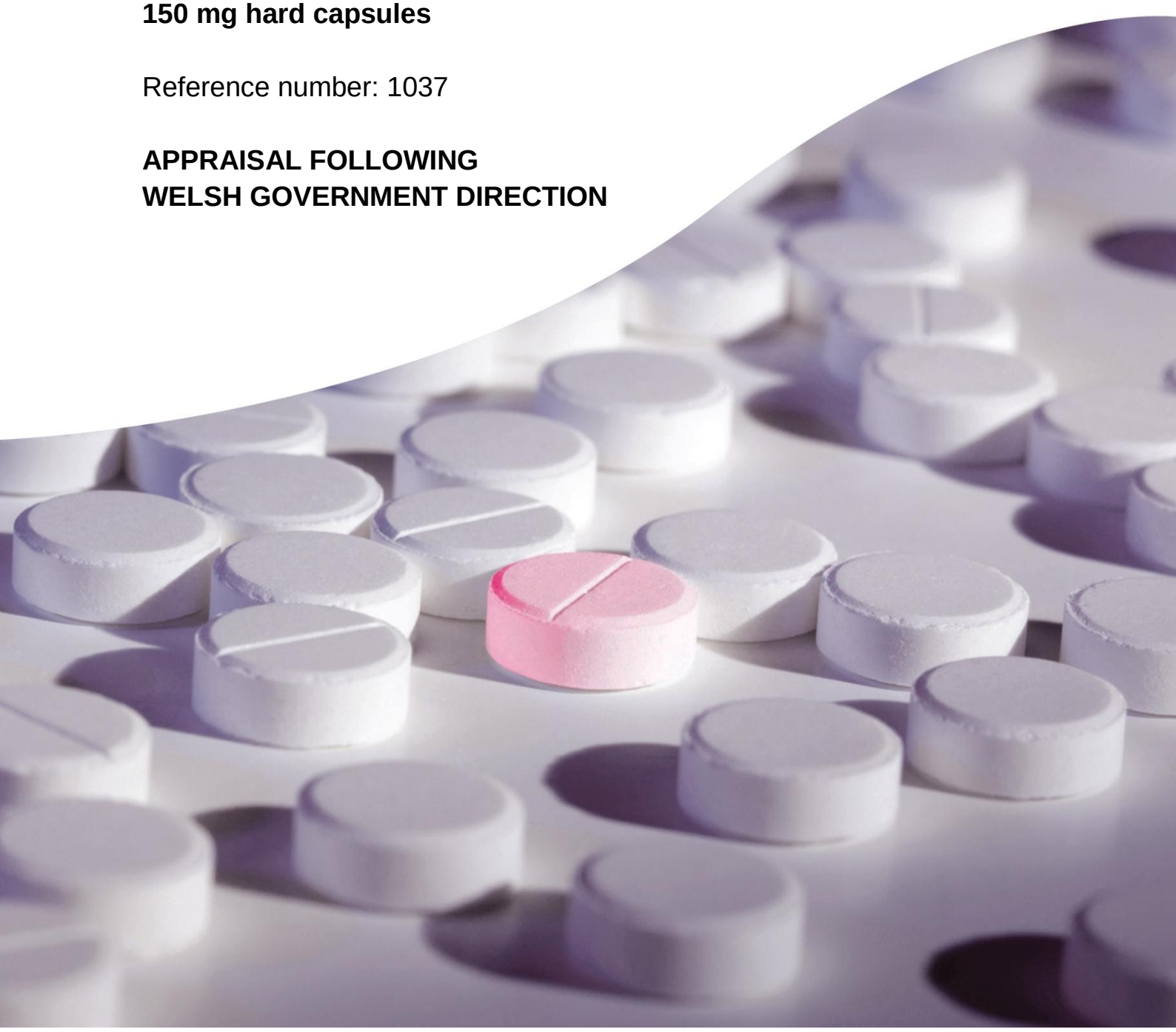
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Vismodegib (Erivedge®)
150 mg hard capsules

Reference number: 1037

APPRAISAL FOLLOWING
WELSH GOVERNMENT DIRECTION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Vismodegib (Erivedge®▼) 150 mg hard capsules

This assessment report is based on evidence identified from a systematic review conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) and information provided by Roche Products Ltd[1,2].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Vismodegib (Erivedge®▼) for the treatment of adult patients with symptomatic metastatic basal cell carcinoma, or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy[3]. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Dosing	The recommended dose is one 150 mg capsule taken once daily. If a dose is missed, patients should not take the missed dose but resume with the next scheduled dose. Benefit of continued treatment should be regularly assessed, with the optimal duration of therapy varying for each individual patient. Refer to the Summary of Product Characteristics (SPC) for further dosing information[3].
Marketing authorisation date	12 July 2013[4]

2.0 DECISION CONTEXT

2.1 Background

Basal cell carcinoma (BCC) is a slow-growing, locally invasive, malignant epidermal skin tumour that predominantly affects Caucasian patients[5,6]. Cure rates are generally high, with the majority of BCCs treated by surgery, photodynamic therapy and approved topical treatments[6]. A small proportion of BCCs can advance to locally advanced BCC (laBCC) or metastatic BCC (mBCC), where current treatments are inappropriate or ineffective: progressive disease results in morbidity from local tissue invasion and destruction, particularly on the face, head and neck[5,6]. In the absence of appropriate licensed therapies, mBCCs have been treated by radiotherapy and cisplatin-based chemotherapy, although the effectiveness of the latter is unclear[6,7].

BCCs are considered the most common skin cancer, forming an estimated 75% of non-melanoma skin cancers (NMSCs)[8]. However, BCC incidence and prevalence is difficult to estimate as cases are recorded under NMSCs, which are not required to be reported to cancer registries[6]. In the UK, an estimated 53,000 new cases are reported each year with incidence continuously rising[9]; Wales and south England had the highest recorded rates between 2004–2010[10]. Prevalence of locally advanced BCC has not been reported, but less than 0.1% of BCC cases are thought to be metastatic[6].

The Hedgehog (Hh) pathway has been identified as an important signalling pathway in human cancers and mutations in the downstream Hh pathway proteins PTCH and SMO have been identified in more than 90% of BCC patients[6]. Basal cell nevus syndrome (BCNS), also known as Gorlin syndrome, is caused by germline mutations in the PTCH gene and one of the main clinical manifestations in BCNS patients are BCCs[6]. Vismodegib is a small molecule inhibitor of the Hh signalling pathway that acts by binding to SMO and preventing the initiation of downstream signalling pathways[6].

Vismodegib is licensed for the treatment of adult patients with symptomatic mBCC, or laBCC inappropriate for surgery or radiotherapy. Some laBCC cases are inoperable, or patients may have medical contraindications to surgery. Radiotherapy may also be contraindicated in some patients, or a prior course of radiotherapy treatment may have been unsuccessful[6].

At the time of marketing authorisation in 2013, the company were not able to provide a submission to AWMSG, and therefore a Statement of Advice was published stating that vismodegib cannot be endorsed for use in NHS Wales. In July 2016, AWMSG were directed by Welsh Government to appraise vismodegib. Subsequently, the company provided a dossier of information on vismodegib, although they were unable to provide a complete submission. AWTTC also conducted a systematic review to identify evidence for this assessment report.

2.2 Comparators

Vismodegib is the first licensed treatment for laBCC inappropriate for surgery or radiotherapy and for symptomatic mBCC. The company state that best supportive care is the most suitable comparator, and that this is likely to consist of palliative rather than curative treatment. See Section 3.5 for further information.

2.3 Guidance and related advice

- European Dermatology Forum. Guidelines for the treatment of basal cell carcinoma (2012)[7].
- British Association of Dermatologists (BAD). Guidelines for the management of basal cell carcinoma (2008)[5].
- National Institute for Health and Care Excellence (NICE). Improving outcomes for people with skin tumours including melanoma (2006, updated 2010)[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Evidence provided by the applicant company highlights two phase II trials (ERIVANCE[12] and STEVIE[13]) and reports results at several different follow-up times, the most recent of which are included in this report[14,15]. A systematic review by AWTTC identified an additional expanded access study (EAS)[16].

3.1 ERIVANCE

ERIVANCE was an open-label, single arm study to evaluate the efficacy and safety of vismodegib in laBCC and mBCC patients[12,17]. Patients were included in the study if they were ≥ 18 years of age with histologically confirmed mBCC or laBCC, had adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2[12]. Patients with laBCC had at least one lesion that was considered inoperable or for which surgery was considered inappropriate; prior radiotherapy to at least one lesion was required unless contraindicated or considered inappropriate[12]. Patients with BCNS were able to enrol if all other inclusion criteria were met[12].

A total of 104 patients were enrolled from 31 sites in the United States, Europe and Australia: 71 patients had laBCC and 33 patients had mBCC[17]. Eight laBCC patients were excluded from efficacy analysis as histological BCC was not confirmed; however,

they were still included in the safety analysis[17]. All enrolled patients received oral vismodegib (150 mg daily) until disease progression, intolerable toxicity, or withdrawal from the study[17]. Patients who discontinued treatment were followed up approximately every three months until death, loss to follow-up or study termination[17].

The primary endpoint was objective response rate (ORR), assessed by an independent review facility (IRF). Secondary endpoints included investigator-assessed ORR, independent and investigator-assessed duration of response, and progression-free survival[17].

After 12 months of follow-up, mBCC patients (n = 33) had an independently-assessed ORR of 33.3% (95% confidence interval [CI] 19.2–51.8)[17]. In patients with laBCC (n = 63), the independently assessed response rate was 47.6% (95% CI 35.5–60.6). The median duration of response was 7.6 months for mBCC patients (95% CI 5.5–9.4) and 9.5 months for laBCC patients (95% CI 7.4–21.4)[17].

Results from the most recent data cut-off, representing up to 30 months of follow-up, are outlined in Table 1[14]. Investigator-assessed ORR at 30 months was 48.5% for the mBCC cohort (95% CI 30.8–66.2) and 60.3% for the laBCC cohort (95% CI 47.2–71.7)[14].

Table 1. Primary and secondary endpoints of the ERIVANCE trial at 30 month follow-up[14]

Endpoints	mBCC n = 33	laBCC n = 63	Total n = 96
Primary Endpoint			
Objective response rate, n (%) [95% CI]	16 (48.5) [30.8–66.2]	38 (60.3) [47.2–71.7]	54 (56.3) [45.7–66.4]
Complete response, n (%)	*0 (0.0%)*	*20 (31.7%)*	*20 (20.8%)*
Partial response, n (%)	*16 (48.4%)*	*18 (28.6%)*	*34 (35.4%)*
Secondary Endpoints			
Median duration of response, months [95% CI]	14.8 [5.6–17.0] (n = 16)	26.2 [9.0–37.6] (n = 38)	16.1 [9.5–26.2] (n = 54)
Stable disease, n (%)	14 (42.4%)	15 (23.8%)	29 (30.2%)
Progressive disease, n (%)	2 (6.1%)	6 (9.5%)	8 (8.3%)
Median progression-free survival, months [95% CI]	9.3 [7.4–16.6]	12.9 [10.2–28.0]	12.8 [9.5–18.0]
Median overall survival, months [95% CI]	33.4 [18.1–NE]	NE [NE–NE]	NE [41.2–NE]
mBCC: metastatic basal cell carcinoma; laBCC: locally advanced basal cell carcinoma; CI: confidence interval; NE: not estimable.			

3.2 STEVIE

STEVIE is an ongoing open-label, single-arm study designed to further assess the safety of vismodegib in laBCC and mBCC in a situation similar to routine practice with long-term follow up[13]. Patient inclusion criteria were similar to the ERIVANCE study[2,13,15]. A total of 1,215 evaluable patients (1,119 with laBCC and 96 with mBCC) were enrolled across 36 countries, including the UK[2,13,15].

All enrolled patients received oral vismodegib (150 mg daily) on a continuous basis in 28-day cycles until disease progression, intolerable toxicity, withdrawal from the study, death or other reasons[13,15]. Dose reductions were not allowed, but patients were allowed to interrupt treatment for up to 8 weeks to manage toxic effects or temporary inability to swallow capsules[13,15].

The primary objective of the study was safety (incidence of treatment-emergent adverse events [TEAEs] until disease progression or unacceptable toxic effects)[2,13,15]. Efficacy variables were assessed as secondary endpoints.

At the clinical cut off point (November 2013) an initial pre-planned interim analysis was performed on 499 patients (468 with laBCC and 31 with mBCC) who had received vismodegib and had the potential to be followed up for 12 months or longer[13]. Treatment was discontinued in 400 (80%) of these patients; 180 (36%) had adverse events, 70 (14%) had progressive disease, and 51 (10%) requested to stop treatment. Median duration of vismodegib exposure was 36·4 weeks (interquartile range 17·7–62·0)[13]. Safety data are discussed further in Section 3.4.

Secondary objectives included efficacy as assessed by investigators. A total of 302 of 453 evaluable patients with laBCC (66·7%, 95% CI 62·1–71·0) had an overall response (153 complete responses and 149 partial responses); 11 (37·9%; 95% CI 20·7–57·7) of 29 evaluable patients with mBCC had an overall response (two complete responses, nine partial responses)[13]. Secondary outcomes for the primary analysis (n = 1,215) are outlined in Table 2.

Table 2. Efficacy endpoints for the STEVIE trial at the primary analysis[2,15]

Efficacy endpoints	mBCC n = 89	laBCC n = 1,103	Total n = 1,192
Objective response rate, n (%) [95% CI]	31 (36.9%) [26.63–48.13]	738 (68.5%) [65.66–71.29]	769 (66.2%) [63.43–68.96]
Complete response, n (%)	*4 (4.8%)*	*360 (33.4%)*	*364 (31.4%)*
Partial response, n (%)	*27 (32.1%)*	*378 (35.1%)*	*405 (34.9%)*
Stable disease, n (%)	39 (46.4%)	270 (25.1%)	309 (26.6%)
Progressive disease, n (%)	9 (10.7%)	21 (1.9%)	30 (2.6%)
Missing or NE, n (%)	5 (6.0%)	48 (4.5%)	53 (4.6%)
Median progression-free survival, months [95% CI]	13.1 [12.0–17.7]	23.2 [21.4–26.0]	22.1 [20.3–24.7]
Median overall survival, months [95% CI]	NE [NE–NE]	NE [NE–NE]	NE [NE–NE]
Median time to respond, months [95% CI]	NE [5.49–NE]	3.7 [2.9–3.7]	3.7 [3.5–3.7]
Median duration of response, months [95% CI]	13.9 [9.2–NE]	23.0 [20.4–26.7]	22.7 [20.3–24.8]

mBCC: metastatic basal cell carcinoma; laBCC: locally advanced basal cell carcinoma; CI: confidence interval; NE: not estimable.

This study used the Skindex-16 questionnaire to assess the impact of vismodegib treatment on patient quality of life from baseline to the first days of Cycle 2 and Cycle 7 (6 months of treatment)[2,18]. Clinically meaningful improvements were observed in all emotional score subgroups (worry, appearance, frustration, embarrassment, annoyance and depression). Symptom scores (itching, burning or stinging, hurting and

irritation) were maintained throughout, with clinically meaningful improvements observed in female patients and patients ≥ 65 years of age at Cycle 7. Borderline clinically meaningful improvements for symptom scores was seen in patients with lesions not located on the head or neck. A higher proportion of clinically meaningful improvements in emotion, functional and symptom domains were observed in patients with complete or partial tumour response[2,18].

3.3 Expanded access study (EAS)

EAS was an open-label, single-arm, multi-centre study to assess the safety and efficacy of vismodegib[16]. The study provided early access to vismodegib prior to FDA approval, and was terminated when approval was granted. Patient inclusion criteria were similar to ERIVANCE. A total of 120 patients were enrolled at 11 US sites: 62 patients had laBCC and 58 patients had mBCC[16].

Patients received 150 mg oral vismodegib daily in 28-day treatment cycles until disease progression, unacceptable toxic effects, patient/physician request to discontinue treatment, or study termination by sponsor[16]. Dose reductions were not allowed, but patients were allowed to interrupt treatment for up to 8 weeks to manage toxicity[16].

The primary reason for treatment discontinuation was sponsor study termination following FDA approval[16]. For this reason, the median duration of treatment was relatively short at 5.5 months. Following study termination, 79/120 patients were transitioned to commercial vismodegib[16].

Assessed efficacy parameters are outlined in Table 4. Of the 120 patients enrolled, 95 were efficacy-evaluable (56 laBCC patients and 39 mBCC patients)[16].

Table 3. Efficacy results of the EAS study[16]

Efficacy responses	mBCC n = 39	laBCC n = 56	Total n = 95
Objective response rate, n (%) [95% CI]	12 (30.8%) [17.0–47.6]	26 (46.4%) [33.0–60.3]	38 (40.0%) [nc]
Complete response, n (%)	*2 (5.1%)*	*6 (10.7%)*	*8 (8.4%)*
Partial response, n (%)	*10 (25.6%)*	*20 (35.7%)*	*30 (31.6%)*
Stable disease, n (%)	20 (51.3%)	27 (48.2%)	47 (49.5%)
Progressive disease, n (%)	3 (7.7%)	0 (0.0%)	3 (3.2%)
Missing or NE, n (%)	4 (10.3%)	3 (5.4%)	7 (7.4%)
Median time to respond, months (range)	2.6 (1.4-12.6)	2.6 (1.0-11.0)	nc
mBCC: metastatic basal cell carcinoma; laBCC: locally advanced basal cell carcinoma; CI: confidence interval; nc: not calculated; NE: not estimable.			

3.4 Safety

Safety data are primarily taken from STEVIE, as this is the largest study of vismodegib (1,215 patients) and safety was the primary study endpoint[2,15]. TEAEs were reported in 1,192 patients (98%). At data cut-off, 147 patients (12%) were receiving ongoing treatment, whereas 1,068 patients (88%) had discontinued treatment[2,15]. The main reasons for discontinuation were TEAEs (349 patients [28.7%]), disease progression (189 patients [15.6%]), patient request (113 patients [9.3%]), physician decision (76 patients [6.3%]), death (37 patients [3.0%]), loss to follow-up (21 patients [1.7%]), or other reasons (283 patients [23.3%])[2,15]. Other reasons included discontinuation due to complete remission, which occurred in 96 patients (7.9%)[15].

The majority of TEAEs were graded mild to moderate (54%), and patients with a longer treatment exposure (≥ 12 months) experienced a higher incidence of TEAEs[2,15]. The most common TEAEs were muscle spasm (66.4%), alopecia (61.5%), dysgeusia (54.6%), weight decrease (40.6%) and decreased appetite (24.9%). Serious TEAEs occurred in 249 patients (24%) and included pneumonia (1.5%), cutaneous squamous cell carcinoma (1.0%) and general physical health deterioration (1.0%). A total of 110 patients (9.1%) died whilst on study or during follow up, 71 (5.8%) of which were as a result of AEs. Grade 5 (fatal) TEAEs occurred in 46 patients (3.8%), 7 of which were considered by the investigator as related to vismodegib. However, all 7 cases showed presence of comorbidities/risk factors, thereby confounding the assessment of causality[2,15].

Similar safety results were observed in the ERIVANCE[14] and EAS studies[16].

3.5 AWTTC critique

- Vismodegib is the first licensed treatment for laBCC inappropriate for surgery or radiotherapy and for symptomatic mBCC. The company view best supportive care (using palliative rather curative treatment) to be the most appropriate comparator. Guidelines on BCC management[7] and clinical experts consulted by AWTTC indicate that there is no standard therapy for either of these patient groups, and current treatment options are severely limited: possible treatment options include palliative care, best supportive care or unlicensed platinum-based chemotherapy. A second Hh signalling inhibitor, sonidegib (Odomzo®), is licensed for treatment of adult patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiation therapy. However, in the absence of a submission from the holder of the marketing authorisation, sonidegib cannot be endorsed for use within NHS Wales[19]. Sonidegib has not been appraised, and is not scheduled for appraisal, by any other UK health technology appraisal bodies.
- No evidence was identified that compares the clinical effectiveness of vismodegib to placebo, best supportive care or any active comparator. This makes it difficult to assess the comparative clinical benefit of vismodegib. The design of the ERIVANCE study attempted to address this by interpreting ORRs against a predefined threshold[2]. In ERIVANCE, ORRs in vismodegib-treated patients exceeded predefined thresholds for clinical benefit (20% and 10% for laBCC and mBCC, respectively). The lower limit of the CI was also above these pre-defined margins, and therefore the ORR in vismodegib-treated patients met the prespecified margin for a clinically significant treatment effect in laBCC and mBCC[2,12].
- The ERIVANCE study used IRF-assessed ORR as the primary endpoint for the primary analysis, along with additional IRF-assessed parameters for secondary endpoints. The use of independent assessment may reduce the risk of bias in the reporting of tumour response. However, IRF-assessed endpoints were not included beyond the 12 month follow-up and therefore on-site investigator-assessed endpoints were used at the 18 and 30 month updates. Both STEVIE and EAS used investigator-assessed endpoints.
- The STEVIE study provided safety data from a large cohort of patients. However, patients with mBCC made up a relatively small proportion of the evaluable population (96 patients, 7.9%); in ERIVANCE and EAS, 34.4% and 41.1% of patients respectively had mBCC.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context and results

The evidence provided by the company did not include a pharmacoeconomic evaluation. Therefore, there are no cost-effectiveness results to report.

4.1.2 AWTTC critique

It is standard practice to report on cost-effectiveness. However, no pharmacoeconomic advice has been provided to critique.

4.2 Review of published evidence on cost-effectiveness

A systematic review conducted by AWTTC identified a conference abstract[20] and poster[21] reporting on the cost-effectiveness of vismodegib 150 mg versus standard of care therapy in the treatment of laBCC or symptomatic mBCC in Hungary. However, these did not report on QALY gains and thus are not informative for the purpose of this appraisal.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company has provided budget impact analyses that consider vismodegib in isolation (i.e. no displacement of any comparator is considered). To calculate the expected incidence in Wales the company has combined Office for National Statistics (ONS) population estimates[22] with US incidence and prevalence data for BCC and laBCC[9], and an assumption that 40% of laBCC are eligible for treatment. The company report a lack of prevalence data for advanced BCC, but suggest incidence is a suitable proxy. Company calculations indicate that there are likely to be 65 patients with advanced BCC in Wales in 2016. The company assume that 40% of these patients will be ineligible for surgery or radiotherapy, resulting in an eligible population for vismodegib of 28 patients. The cost of treatment with vismodegib has been calculated according to whether a patient has laBCC or mBCC. Median durations from the STEVIE study[13] have been used to guide this approach. The mean durations for laBCC and mBCC are 36.3 weeks and 52 weeks respectively. The analyses suggest that the net cost in year one is likely to reach a maximum of approximately £969,000, and £1,071,000 by year five. However, the company further anticipate that this is likely an overestimate. It is suggested that the actual number of patients likely to receive treatment per year is greater than one but less than 28.

5.1.2 Results

Table 4. Company-reported costs associated with use of vismodegib[1]

	Year 1 2017	Year 2 2018	Year 3 2019	Year 4 2020	Year 5 2021
Number of eligible patients - laBCC	25	26	27	27	28
Number of eligible patients - mBCC	3	3	3	3	3
Total number of eligible patients	28	29	30	31*	31
Uptake (%)	100%	100%	100%	100%	100%
Medication costs for all eligible patients - laBCC	£829,018	£850,586	£872,281	£894,038	£915,903
Medication costs for all eligible patients - mBCC	£140,175	£143,786	£147,417	£151,057	£154,714
Total medication cost (£)	£969,194	£994,372	£1,019,698	£1,045,094	£1,070,617
Cumulative total medication cost (£)	**£969,194**	**£1,963,565**	**£2,983,263**	**£4,028,357**	**£5,098,974**

laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma
*N.B. numbers have been rounded

5.1.3 AWTTC critique

The company has provided a transparent account of the methods used to estimate the potential budget impact in Wales, should this medicine be approved. However, the budget impact model is characterised by a number of uncertainties and limitations:

- The model is limited to the inclusion of vismodegib 150 mg only; no comparators have been included. Although treatment options in this group of patients are severely limited, palliative care, best supportive care or unlicensed chemotherapy are all potential comparators. Because the potential for vismodegib to displace any other treatments is not considered, the model does not capture any potential cost savings from this.
- The model is limited to medicine acquisition costs. Wider resource use associated with the administration of vismodegib is not captured. Given the adverse event profile of this treatment, it would have been insightful if the company had also reported on the costs of monitoring and treatment of adverse events.
- Incidence figures from the US have been used, and AWTTC attempts to verify the size of the populations of interest suggest that the actual numbers may be lower than reported; this possibility was acknowledged by the company. The budget impact reported may therefore be an over-estimate. This likely negates the limitations of the company approach to costing treatment using per-tablet and not per-pack calculations for the laBCC population.

5.2 Comparative unit costs

Vismodegib is the only available licensed treatment for adult patients with symptomatic metastatic basal cell carcinoma or locally advanced basal cell carcinoma inappropriate for radiation therapy. Acquisition costs for vismodegib are given in Table 5.

Table 5. Medicine acquisition costs

Regimens	Example doses	Approximate costs (per month)
Erivedge® (vismodegib) 150 mg capsule – once daily	28 × 150 mg capsules orally*	£6,285
See relevant Summary of Product Characteristics for full licensed indication and dosing details. Costs are based on MIMS list prices as of October 2016. Costs of administration are not included. * recommended dose is 150 mg once daily until disease progression or unacceptable toxicity.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, vismodegib (Erivedge®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

STEVIE is ongoing and has an estimated completion date of October 2017[23].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 4 August 2016
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The applicant company suggests that the prevalence of the population for the full licensed indication of vismodegib meets the AWMSG criteria for an ultra-orphan medicine, despite there being no EMA orphan status designation. Currently, vismodegib is only licensed for the patient groups considered in this submission. The company estimate of 28 eligible patients in 2017, rising to 31 patients in 2021, is based on ONS population estimates for Wales[22], combined with US incidence and prevalence data for BCC and laBCC[9], and an assumption that 40% of laBCCs are eligible for treatment.

AWTTC consider vismodegib to be eligible to be appraised as an ultra-orphan medicine as the full population of the licensed indication does not exceed the threshold of ≤ 1 in 50,000 in the UK (or ≤ 60 patients in Wales).

NMG/AWMSG will consider additional criteria (see Table 6) if they consider vismodegib to be an ultra-orphan medicine. These criteria are usually considered when the cost per QALY for an ultra-orphan drug is above the normal thresholds applied. In this instance, the company has not provided a cost utility analysis, and therefore no cost per QALY estimates are available.

Table 6. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	Advanced BCC is a rare form of non-melanoma skin cancer comprised of laBCC and mBCC. Due to their size, invasiveness, or location, advanced BCC lesions can cause significant disfigurement or deformity, disability, and/or premature mortality.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Prior to the regulatory approval of vismodegib, patients with advanced BCC had no approved or standard therapeutic options when surgery or radiotherapy was inappropriate.
Whether the medicine can reverse or cure, rather than stabilise the condition	Complete response in the clinical trials was defined as disappearance of all target lesions. Partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter, in the mBCC cohort. In the locally advanced BCC cohort of patients in the STEVIE study[15], complete response was obtained in 33.4% of the 1,077 patients with measurable disease at baseline. A complete response was obtained in 4.8% of the 84 patients with mBCC. Partial responses were seen in 35.1% and 32.1% of laBCC and mBCC patients respectively. Therefore, vismodegib treatment can result in shrinkage of lesion/tumour size and/or resolution of ulceration in lesions.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	The company are not aware of any definitive therapy in development.
The innovative nature of the medicine	Vismodegib is a novel, first-in-class, oral antineoplastic agent, hedgehog pathway inhibitor.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	The Skindex-16 questionnaire was used to assess the impact of skin disease on patients' quality of life in the STEVIE study[18]; skin symptoms, the impact on patients' emotions, and impact of skin disease on physical and social functioning were assessed. Clinically meaningful improvements in emotional scores (worry, appearance, frustration, embarrassment, annoyance and depression) were seen in all subgroups at almost all time points. Itching, burning or stinging, hurting and irritation (symptom domains) demonstrated clinically meaningful improvements in cycle 7 in female patients, and in those patients over the age of 65 years. Symptoms were also improved by cycle 7 in patients whose lesions were not located on their head/neck. When the Skindex-16 results were analysed with respect to response, clinically meaningful improvements in emotion, functional and symptom domains were seen in those patients who achieved a complete or partial response. [Commercial in confidence text removed]
Added value to the patient's family (e.g. impact on a carer or family life)	There is no published evidence relating to treatment with vismodegib and its impact on carers. However, the company report that anecdotal evidence suggests that the reason for BCC being neglected and developing into a tumour that is too advanced to be treated by surgery or radiotherapy is sometimes due to patients caring for other family members and not 'having time' to seek treatment.

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