Vismodegib (Erivedge)

National Drug Monograph

November 2013

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

**Executive Summary**

Vismodegib is an oral inhibitor of the Hedgehog pathway approved by the US Food and Drug Administration in January 2012. It is the first systemic treatment for patients with locally advanced or metastatic basal cell carcinoma (BCC) that is not amenable to surgery or radiation.

**Efficacy:**

FDA approval was based on a Phase II study that enrolled 104 patients with either metastatic basal cell carcinoma (BCC) or locally advanced BCC. Patients received vismodegib 150mg once daily until disease progression or unacceptable toxicity.

A partial response was seen in 30% of the metastatic BCC patients. In the locally advanced patients, 20.6 % achieved a complete response and 22.2% achieved a partial response (Overall response rate was 43%).

Duration of therapy in the trial was approximately 10 months.

**Safety:**

Most common adverse events seen include muscle spasms (71.17%), alopecia (63.8%), fatigue (39.9%), dysgeusia (55.1%) and subsequent weight loss (44.9%) and decreased appetite (25.4%).

There were seven fatal events in the treatment group which included hypovolemic shock, MI, meningeal disease, and ischemic stroke. Relationship between vismodegib and the adverse events were unknown.

More information about vismodegib in different populations is needed, such as patients with renal or hepatic impairment and geriatric patients. As BCC is prevalent in geriatric population, more data on toxicity and pharmacokinetics is needed.

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| **Outcome in clinically significant area** | ORR and meaningful duration of response where there is no standard of care |
| **Effect Size** | N/A |
| **Potential Harms** | Risk of Grade 3 or 4 toxicity was experienced by <20% of the study population |
| **Net Clinical Benefit** | Minimal: Low chance of benefit and low risk of harm |

Introduction

Basal cell and squamous cell skin cancers are collectively known as non- melanoma skin cancers (NMSC). They are the most common cancer in the United States. The incidence of this common malignancy is rising rapidly. It is estimated that more than 2.1 million new patients were treated for nonmelanoma skin cancer in 2006 in the US1. Basal cell carcinomas (BCC) are about four to five times more common than squamous cell carcinomas (SCC). Although rarely metastatic, BCC and SCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone.

BCC and SCC are most commonly treated with surgery or radiation. In an evidence-based review of the literature, the best results were obtained with surgery. However, consideration of function, cosmetic outcome and patient preference may lead to the choice of radiation therapy as primary treatment in order to achieve optimal overall results. Superficial therapies, such as topical treatment with 5-flurouracil or imiquimod, photodynamic therapy and cryotherapy, are options reserved for localized disease. Therapy of BCC depends upon the location and extent of the tumor and generally consists of wide surgical excision alone for local recurrence or in combination with chemotherapy and radiation therapy for distant metastasis. The main aim of the surgery is complete excision of the tumor with clear margins. The recurrence rate following surgical excision varies between 5% for complete excision and 30% for excisions with positive margins. Mohs’ micrographic surgery is the treatment of choice for histopathologically aggressive BCC subtypes owing to low recurrence rate. Several chemotherapeutic agents including 5-FU, cisplatin, vincristine, etoposide, bleomycin, cyclophosphamide, methotrexate, and doxorubicin have been used alone or in combination as detailed in case reports. But no standard of therapy currently exists for metastatic disease.

Metastatic disease affects males two times more often than females. Factors that play a role in predicting metastases include the age at presentation, the site and size of lesion, depth of invasion, duration and recurrence of disease, incomplete surgical resection, multiple lesions, and infiltrative histological pattern. The incidence of metastasis is 2% for tumors larger than 3cm in diameter; it increases to 25% for tumors larger than 5cm in diameter and 50% for tumors larger than 10cm in diameter.

The prognosis for overall survival in metastatic BCC is poor, estimated at 8 months in the presence of distant metastasis and 3.5 years for patients with disease confined to lymph nodes

Most common site of metastases include regional lymph nodes (60%), lungs (42%), bones (20%), skin (10%), or to other organs in 2% cases via hematogenous spread or direct extension.

Metastasis to liver, other viscera, or subcutaneous tissues may occur following involvement of lymph nodes, lungs, or bones. Primary tumors may also invade deep into the extradermal structures such as cartilage, skeletal muscles, or bones.

Recent FDA approval of the new agent vismodegib, a first-in-class Hedgehog pathway inhibitor, provided another option for patients who have exhausted surgical and radiation options for treating advanced BCC.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, cost and other pharmaceutical issues that would be relevant to evaluating vismodegib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rationale use in the VA.

Pharmacology/Pharmacokinetics

Molecular and genetic studies have shown that the majority of BCC contain genetic alterations in the hedgehog signaling pathway, resulting in abnormal pathway activation and uncontrolled proliferation of basal cells. These alterations can cause loss of function of patched homologue 1 (PTCH1), which normally acts to inhibit the signaling activity of smoothened homologue (SMO), a seven-transmembrane protein. Vismodegib binds to and inhibits Smoothened (SMO). Vismodegib acts as a competitive [antagonist](http://en.wikipedia.org/wiki/Receptor_antagonist) of SMO. SMO inhibition causes the transcription factors [GLI1](http://en.wikipedia.org/wiki/GLI1) and [GLI2](http://en.wikipedia.org/wiki/GLI2) to remain inactive, which prevent the expression of tumor mediating genes within the hedgehog pathway 2.

**Absorption and Distribution**: Vismodegib is a highly permeable compound with low water solubility. The single dose absolute bioavailability of vismodegib is 31.8%. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg or 540 mg vismodegib. Vismodegib capsule may be taken without regard to meals because the systemic exposure of vismodegib at steady state is not affected by food. The volume of distribution of vismodegib ranges from 16.4 to 26.6 L and plasma protein binding in patients is greater than 99%3.

**Metabolism:** Greater than 98% of the total circulating drug-related components are the parent drug. Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and pyridine ring cleavage by CYP2C9 and CYP3A4/5. However, drug exposure is not expected to be altered because patients were treated concomitantly with CYP3A4 inhibitors and inducers in trials with little change in exposure. Results of in vitro studies suggest that vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2C19, and the BRCP (breast cancer resistance protein) transporter. Rosiglitazone, a CYP2C8 substrate, was given with vismodegib at steady state with no clinically significant change in rosiglitazone exposure, suggesting that there is no clinically significant inhibition of CYP2C8 by vismodegib. Vismodegib was also found in vitro to be a substrate of the efflux p-glycoprotein transporter. The manufacturer cautions that systemic exposure and the subsequent adverse effects may be increased when given concomitantly with drugs that inhibit p-glycoprotein, such as clarithromycin, erythromycin, or azithromycin3.

**Elimination**: Vismodegib is eliminated primarily by the hepatic route with 82% recovered in feces and 4.4% recovered in urine. The estimated t½ of the drug is 12 days after a single dose and 4 days after continuous once-daily administration. A trial has been designed to study vismodegib in patients with renal or hepatic impairment, but these populations have not been included in the trials produced thus far. Population pharmacokinetic analyses demonstrated that weight (range, 41–140 kg), age (range, 26–89 years), creatinine clearance (range, 30–80 mL/min), and sex do not have a clinically meaningful influence on the systemic exposure of vismodegib3.

# FDA Approved Indication(s)

Vismodegib is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

# Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s [Guidance on “Off-label” Prescribing](http://vaww.national.cmop.va.gov/PBM/Directives%20Policies%20and%20Information%20Letters/Guidance%20on%20Off%20Label%20Prescribing.pdf) (available on the VA PBM Intranet site only).

An abstract published in the April 2013 issue of Journal of Clinical Oncology described the neoadjuvant use of vismodegib to decrease cosmetic defects. In a small case series, patients were given vismodegib 150mg daily for 3 months prior to surgical removal. Resection of basal cell carcinoma tumors resulted in smaller cosmetic defects when patients received neoadjuvant vismodegib. The area of the defect was reduced by about 50% in patients. After a median 5.5 months of follow-up, no recurrences were seen in any of five patients given the drug prior to surgery for lesions in surgically challenging locations, such as the eyelid. The interim analysis included five patients with seven lesions treated for a median of 3.4 months. Mean estimated surgical defect decreased from 3 cm2 to 1.6 cm2 after preoperative treatment, a 46% reduction from baseline (P = .008).

Review of ongoing trials or trials actively recruiting subjects identifies 40 studies that are examining the potential use of vismodegib in a variety of settings which include: metastatic colon cancer, ovarian cancer, advanced head and neck cancer, medulloblastomas, pancreatic cancer, glioblastoma multiforme, extensive stage small cell lung cancer, and stomach cancer. Comments on safety and efficacy in these populations cannot be made at this time4.

# Current VA National Formulary Alternatives

There are no VA Formulary alternatives for locally advanced or metastatic basal cell carcinoma. All formulary agents topical therapies are for superficial localized disease.

Superficial therapies include topical treatment with 5-fluorouracil or imiquimod can be used for lesions with a low risk of recurrence as these agents have shown to have lower cure rates than surgery or radiation. Please see VA criteria for use for imiquimod.

There have only been case reports of systemic chemotherapy used in this population, such as platinum based regimens, but there are currently no standard therapies for advanced disease that cannot be treated with surgery or radiation.

# Dosage and Administration

The FDA-approved dosing of vismodegib is 150 mg orally daily until disease progression or unacceptable toxicity is experienced. Vismodegib may be taken with or without food. Swallow capsules whole. Do not open or crush capsules.If a dose of vismodegib is missed, do not make up that dose; resume dosing with the next scheduled dose3.

# Efficacy

## Efficacy Measures 6

**Primary Outcome:**

The assessment of benefit in the following studies is based on the endpoint of overall response rate (ORR), based on response evaluation criteria in solid tumors (RECIST) in patients with metastatic BCC (mBCC) and a composite criteria of bi-dimensional measurements of externally assessable tumor, bi-dimensional measurements of tumor ulceration, and standardized digital photography of target lesion(s) in patients with locally advanced BCC (laBCC).

The response criteria differed for each cohort. For the mBCC cohort RECIST was used, which specifies that a target lesion must shrink by at least 30% and maintain the reduction for ≥ 28 days. In the laBCC cohort, tumor response evaluation utilized a composite endpoint of visual assessment and measurement of externally assessable tumor and ulceration, radiographic assessment of target lesions (if appropriate), and tumor biopsy.

A patient with laBCC was considered to respond if at least one of the following criteria was met and the patient did not experience progression:

(1) ≥ 30% reduction in lesion size [sum of the longest diameter (SLD)] from baseline in target lesions by radiographic assessment;

(2) ≥ 30% reduction in SLD from baseline in externally visible dimension of target lesions;

(3) Complete resolution of ulceration in all target lesions.

Progression in the laBCC cohort was defined as meeting any of the following criteria:

(1) ≥ 20% increase in the sum of the longest dimensions (SLD) from nadir in target lesions (either by radiography or by externally visible dimension)

(2) new ulceration of target lesions persisting without evidence of healing for at least 2 weeks; (3) new lesions by radiographic assessment or physical examination

(4) progression of non-target lesions by RECIST.

**Secondary Endpoint**

The secondary endpoints included median duration of response, median progression-free survival and duration of treatment.

Table #1 Definition of Response

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| Complete response (CR) | Disappearance of all target lesions |
| Partial response (PR) | At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter |
| Progressive disease (PD) | At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions |
| Stable disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started |

## Summary of efficacy findings

Phase II:

Sekulic et al conducted a Phase II multicenter, international, two cohort, non- randomized study of patients with metastatic BCC and locally advanced BCC with inoperable disease or for whom surgery was inappropriate. This included patients with multiple recurrences and low likelihood of surgical cure or substantial anticipated disfigurement. The median age was 62 years old, 73% were male and 100% were white. The contraindications to surgery or radiation were as follows and patients could fall into more than one category: Inoperable tumor (38%), Surgery inappropriate (62%), radiation previously administered (21%), radiation therapy inappropriate or contraindicated (79%)2.

Thirty three patients with metastatic BCC and 63 patients with locally advanced BCC were treated with vismodegib 150mg once daily. The primary endpoint was an objective response rate (ORR) defined as those achieving a partial and complete response. Thirty percent of the patients with metastatic BCC responded (95% CI, 16 - 48; p=0.001) and 43% of the patients with locally advanced BCC responded (95% CI, 31-56; P<0.001) per independent review. Thirteen patients (21%) with locally advanced BCC achieved a complete response (CR), defined as absence of residual BCC on assessment of biopsy specimen. Biopsy specimens in 54% of patients from this cohort showed no residual basal-cell carcinoma in target lesions, and the majority of this cohort had visible reductions in tumor size. The median duration of response was 7.6 months in both groups and the median progression free survival was 9.5 months. Data on overall survival were not mature. Seven deaths due to adverse events were noted.

Phase I:

Von Hoff et al conducted a Phase I clinical trial assessing the safety and pharmacokinetics of vismodegib and responses of metastatic or locally advanced basal cell carcinoma. Thirty-three patients with metastatic or locally advanced basal cell carcinoma were selected. Median age was 53 years old, 76% were male, 85% had undergone previous surgery, 58% radiotherapy and 45% systemic therapy, 18 patients with metastatic disease and 15 with locally advanced disease. The overall response rate among patients with metastatic disease was 50% (95% CI, 29-71). Of the 15 patients with locally advanced disease, overall response rate was 60% (95% CI, 33-83). Median time of participation was 9.8 months, and median duration of response was 8.8 months. Overall, of the 33 patients with locally advanced or metastatic tumors, 18 had a response. Of the remaining 15 patients, 11 had stable disease for up to 10.8 months and 4 had progressive disease. There was no dose limiting toxicities noted5.

Case Series:

Amin et al published a case series of three patients with locally advanced basal cell carcinoma, one with metastases. Two patients showed a complete clinical response and radiological resolution of disease; whereas one patient has significant reduction in tumor burden. Side effects seen were taste changes, mild to moderate hair loss, and muscle cramps. Duration of therapy was not directly stated, however appeared that patients were on therapy for a least 1 year7.

Basal Cell Nevus:

Vismodegib has been studied in patients with Gorlin syndrome, a subtype of BCC called basal cell nevus syndrome. Forty-one patients were randomized in a 2:1 ratio to receive vismodegib 150mg daily or placebo for 18 months. Significant difference in reduction of existing surgically eligible BCC was noted between the treatment and placebo group 5.

# Adverse Events (Safety Data) 6

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| **Adverse Event** | **All Grades (%)** | **Grade 3 (%)** | **Grade 4 (%)** |
| GI* Nausea
* Diarrhea
* Constipation
* Vomiting
 | 42 (30.4%)40 (29.0%)29 (21.0%)19 (13.8%) | 1 (0.7%)1 (0.7%)-- | ---- |
| Fatigue | 55 (39.9%) | 7 (5.1%) | 1 (0.7%) |
| Weight loss | 62 (44.9%) | 10 (7.2%) | - |
| Muscle SpasmArthralgias | 99 (71.7%)22 (15.9%) | 5 (3.6%)1 (0.7%) | - |
| DysgeusiaAgeusia | 76 (55.1%)15 (10.9%) | -- | -- |
| Alopecia | 88 (63.8%) | - | - |

**Common Adverse Events:** muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia.

**Sentinel Events (Deaths and Other Serious Adverse Events)8**

Data from the Phase II trial indicated that 7 of 96 patients experienced grade 5 adverse events:

1) A 59-year-old female experienced ischemic strokes on day 448 and day 452. Vismodegib was discontinued on day 452. A third ischemic stroke occurred on day 475. The patient died on day 514.

2) A 51-year-old male died after an acute myocardial infarction on day 535 of vismodegib therapy.

3) A 72-year-old male with metastatic BCC, autonomic neuropathy, hypotension, and paroxysmal atrial fibrillation died at home on day 350; the cause of death was unknown.

4) A 55-year-old female with a history of renal deficiency was hospitalized on day 88 for diuretic intoxication, and on days 272 and 309 for hypokalemia, each related to diuretic use without prescription. On day 335, the patient died of an unknown cause. The investigator assessed diuretics to be a suspected cause of death.

5) A 56-year-old male with multiple co-morbidities was hospitalized for viral meningitis on day 73. He was again hospitalized for “meningeal disease” on day 113, at which time MRI scans revealed widespread leptomeningeal disease, cord edema, and an extensive brainstem tumor”. Vismodegib was discontinued on day 123. The patient died on day 124 due to “meningeal disease”; the physician reported that death was most likely due to progression of BCC and possibly concurrent illness.

6)An 89-year-old female mitral insufficiency, chronic atrial fibrillation, coronary heart disease, type 2 diabetes mellitus, and hypertension was hospitalized on day 67 for cardiac failure and pneumonia. Vismodegib was discontinued on day 67. On day 93, she was hospitalized for left ventricular systolic dysfunction and renal failure, and died on day 109 due to an unknown cause.

7) An 85-year-old male with laBCC and concurrent Alzheimer’s disease, arteritis, diabetes mellitus, hyperlipidemia, and ischemic cardiomyopathy, experienced hypovolemic shock on day 188, which resulted in the patient’s death the next day. The investigator assessed concurrent illness as another possible cause of death.

**Tolerability2**

Approximately half of the patients in the study discontinued the vismodegib, with the highest percentage owing to subject decision or adverse event.

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| **Reasons for Vismodegib Discontinuation** | **mBCC (N=33)****no. (%)** | **IaBCC(N=71)****no. (%)** |
| Total vismodegib treatment discontinuations | 14 (42.4) | 39 (54.9) |
| Adverse event | 1 (3.0)  | 11 (15.5) |
| Death  | 1 (3.0) | 2 (2.8) |
| Lost to follow-up | 2 (6.1) | 1 (1.4) |
| Physician decision to discontinue therapy | 2 (6.1) | 1 (1.4) |
| Subject decision to discontinue therapy | 2 (6.1) | 18 (25.4) |
| Disease progression | 6 (18.2) | 5 (7.0) |
| Other | 0 (0.0) | 1 (1.4) |

# Contraindications

None listed by the manufacturer other than in women who are pregnant. See Boxed Warning below.

# Warnings and Precautions

**Boxed Warning**: Vismodegib capsules can cause fetal harm when administered to a pregnant woman. Vismodegib is teratogenic, embryotoxic, and fetotoxic in rats at maternal exposures lower than the human exposures at the recommended dose of 150 mg/day. In rats, malformations included craniofacial anomalies, open perineum, and absent or fused digits. Pregnancy status must be verified prior to the initiation of vismodegib. Advise male and female patients of the risks of embryo-fetal death and severe birth defects and the need for contraception during and after treatment. If vismodegib is used during pregnancy or if the patient becomes pregnant while taking (or for a male patient, if his female partner is exposed to) vismodegib, the patient should be apprised of the potential hazard to the fetus3.

**Blood Donations**: Advise patients not to donate blood or blood products while receiving vismodegib and for at least 7 months after the last dose of vismodegib3.

# Special Populations

**Pregnancy Category:** D

**Nursing Mothers:**

It is unknown if vismodegib is excreted in breast milk, therefore infant risk cannot be ruled out.

**Renal Impairment**

Vismodegib has not been studied in patients with renal impairment. Population pharmacokinetics found that a creatinine clearance of 30 to 80 mL/min did not have a clinically meaningful influence on the systemic exposure of vismodegib.

**Hepatic Impairment**

Vismodegib has not been studied in patients with hepatic impairment. In the phase 2 clinical trial patients were excluded if they had an AST and ALT > 3 times the upper limit of normal and a total bilirubin > 1.5 times the upper limit of normal (or > 3 times the upper limit of normal for patients with Gilbert disease).

**Pediatrics**

The safety and efficacy of vismodegib in pediatric populations have not been well established. In animal studies closure of the epiphyseal growth plate and abnormalities in the development of incisor teeth (degeneration of odontoblasts, formation of fluid-filled cysts in dental pulp, ossification of the root canal, and hemorrhage resulting in breakage or tooth loss). Because inhibition of the Hh pathway may have application in the treatment of medulloblastoma, pharmacokinetics, efficacy, and toxicities are being assessed in an ongoing Phase II study of its use in pediatric patients aged 3 to 21 years who have medulloblastoma.9

**Geriatrics**

To date, there have been an insufficient number of patients > 65 years of age in studies of vismodegib to determine whether there are any differences in the pharmacokinetics or safety and efficacy in the geriatric population. Because the majority of BCCs occur in the older population, this group will need to be assessed in the postmarketing phase.

**Females of Reproductive Potential and Males**

Vismodegib can cause harm to the embryo or fetus if administered during pregnancy. Patients should be counseled about pregnancy planning and prevention and advised to contact their provider if they suspect they (or, if male, their partner) may be pregnant.

Female patients

Determine pregnancy status within 7 days of initiating therapy in females of reproductive potential. Initiate a highly effective form of contraception (failure rate <1%) prior to the first dose. Continue contraception during therapy and for 7 months after the last dose of vismodegib. Advise patients who become pregnant during therapy and during the 7 months after the last dose to report the pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage pregnant females to participate in the vismodegib pregnancy pharmacovigilance program by calling the same number.

Amenorrhea has been observed in clinical trials in females of reproductive potential, and reversibility is unknown.

Male Patients

Male patients should use condoms with spermicide, even after vasectomy, during sexual intercourse with female partners of childbearing potential while being treated with vismodegib and for 2 months after the last dose to avoid exposure of an embryo or fetus to vismodegib.

# Postmarketing Safety Experience

There has been case reports published regarding vismodegib and development of keratoacanthomas (KA). The first case involves rapid onset of KA on the arm after 2 weeks of vismodegib treatment for locally advanced BCC on lower eyelid and the second case involves a new KA development on the brow after 7 weeks of vismodegib treatment for locally advanced BCC on the medial canthus 10.

# Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs.  Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Sound-alike/look-alike issues:

Vismodegib may be confused with vandetanib, vemurafenib, Vepesid

Erivedge may be confused with Erbitux, eribulin, efavirenz

## Drug-Drug Interactions3

Vismodegib is a substrate of P-glycoprotein (P-gp). When vismodegib is coadministered with drugs that inhibit P-gp (e.g. clarithromycin, erythromycin, azithromycin), systemic exposure of vismodegib and incidence of adverse events of vismodegib may be increased.

Drugs that alter the pH of the upper GI tract (e.g. proton pump inhibitors, H2-receptor antagonists, and antacids) may alter the solubility of vismodegib and reduce its bioavailability. However, no formal clinical study has been conducted to evaluate the effect of gastric pH altering agents on the systemic exposure of vismodegib. When administered concurrently systemic exposure of vismodegib may be decreased and the effect on efficacy of vismodegib is unknown.

Vismodegib is highly protein bound. When co-administered with drugs that are also protein bound, there is potential for displacement. When administered concurrently there is potential for displacement. Monitor closely for agents with a narrow therapeutic index that are highly protein bound, such as warfarin which may result is warfarin displacement and elevations in INR.

No dose modifications due to potential drug-drug interactions have been recommended.

## Drug-Lab Interactions

None noted.

# Acquisition Costs

Refer to VA pricing sources for updated information.

# Pharmacoeconomic Analysis

The estimated cost of non-melanoma skin cancer in patients with Medicare coverage is approximately $426 million per year, which ranks as the fifth most costly cancer in this population. The overall cost in the United States is approximately $650 million annually. Most costs are associated with services received during the physician’s office visit, with the dermatologist managing up to 82% of the visits in some studies through office-based surgical procedures. However, economic analyses have only looked at the treatment of early-stage nonmelanoma skin cancers in which surgical excision is used, sometimes in combination with radiation or topical therapy. No analysis is currently available for treatment in those patients with advanced cancer that is unresectable. It is difficult to systematically assess the economics of advanced BCC due to the lack of histology-specific International Classification of Diseases, Ninth Revision, codes for BCC until October 2011. The introduction of vismodegib is a new area in which to look at economic impact because there is nothing to compare it with beyond symptomatic management11.

# Conclusions

Efficacy of vismodegib 150mg once daily in patients with locally advanced or metastatic basal cell carcinoma with inoperable disease was established in a Phase II multicenter study. Thirty percent of the patients with metastatic BCC responded (95% CI, 16 - 48; p=0.001) and 43% of the patients with locally advanced BCC responded (95% CI, 31-56; P<0.001). Thirteen patients (21%) with locally advanced BCC achieved a complete response (CR), defined as absence of residual BCC on assessment of biopsy specimen. The median duration of response was 7.6 months in both groups and the median progression free survival was 9.5 months 2.

A Phase I study conducted in 2009 assessed the safety and pharmacokinetics of vismodegib and responses of metastatic or locally advanced basal cell carcinoma. The overall response rate among patients with metastatic disease was 50% (95% CI, 29-71). Of the 15 patients with locally advanced disease, overall response rate was 60% (95% CI, 33-83). Median time of participation was 9.8 months, and median duration of response was 8.8 months. Overall, of the 33 patients with locally advanced or metastatic tumors, 18 had a response. Of the remaining 15 patients, 11 had stable disease for up to 10.8 months and 4 had progressive disease5.

Vismodegib is also undergoing clinical trials for metastatic colorectal cancer, small-cell lung cancer, advanced stomach cancer, advanced head and neck cancer, pancreatic cancer, medulloblastoma and chondrosarcoma4.

The most common adverse reactions in subjects receiving vismodegib (≥ 10%) were muscle

spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite,

constipation, cough, arthralgias, vomiting, headache, ageusia, insomnia, and upper respiratory

tract infection. The most common serious adverse reactions (≥ 1%) in subjects receiving

vismodegib were death (2.2%), pneumonia (2.2 %), cardiac failure (1.4%), gastrointestinal

hemorrhage (1.4%), pulmonary embolism (1.4%), deep vein thrombosis (1.4%), and hemorrhage

(1.4%)3,6.

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| **Outcome in clinically significant area** | ORR and meaningful duration of response where there is no standard of care |
| **Effect Size** | N/A |
| **Potential Harms** | Risk of Grade 3 or 4 toxicity was experienced by <20% of the study population |
| **Net Clinical Benefit** | Minimal: Low chance of benefit and low risk of harm |

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**Appendix 1: Approval Endpoints**

**Table 1. A Comparison of Important Cancer Approval Endpoints**

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| **Endpoint**  | **Regulatory Evidence**  | **Study Design**  | **Advantages**  | **Disadvantages**  |
| Overall Survival  | Clinical benefit for regular approval  | • Randomized studies essential • Blinding not essential  | • Universally accepted direct measure of benefit • Easily measured • Precisely measured  | • May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths  |
| Symptom Endpoints (patient-reported outcomes)  | Clinical benefit for regular approval  | • Randomized blinded studies  | • Patient perspective of direct clinical benefit  | • Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments  |
| Disease-Free Survival  | Surrogate for accelerated approval or regular approval\*  | • Randomized studies essential • Blinding preferred • Blinded review recommended  | • Smaller sample size and shorter follow-up necessary compared with survival studies  | • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies  |
| Objective Response Rate | Surrogate for accelerated approval or regular approval\* | • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended | • Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history | • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit |
| Complete Response | Surrogate for accelerated approval or regular approval\* | • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended | • Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies | • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit |
| Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored) | Surrogate for accelerated approval or regular approval\* | • Randomized studies essential • Blinding preferred • Blinded review recommended | • Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment | • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms |

\*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

**Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.**  **U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.**

# Appendix 2: Clinical Trials

A literature search was performed on PubMed/Medline using the search term vismodegib through April 18, 2013. The search was limited to clinical trials in humans that were published in the English language. Reference lists of review articles were searched for additional relevant clinical trials. At the time of the initial review, there were two trials available for review, one Phase I trial and one Phase 2 trial.

Table 2. Vismodegib Clinical Trials

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| Citation | Von Hoff D, LoRusso, PM, Rudin, CM. Inhibition of the Hedgehog pathway in Advanced Basal-Cell Carcinoma New England Journal of Medicine 2009;361:1164-72  |
| Study Goals | Phase I clinical trial assessing the safety and pharmacokinetics of vismodegib and responses of metastatic or locally advanced basal cell carcinoma. |
| Methods | Thirty-three patients with metastatic or locally advanced basal cell carcinoma were selected. Median age was 53 years old, 76% were male, 85% had undergone previous surgery, 58% radiotherapy and 45% systemic therapy, 18 patients with metastatic disease and 15 with locally advanced disease.Study Design : Open label, multicenter two-stage Phase I trial to evaluate the safety and tolerability  |
| Criteria | Inclusion criteria18 yo with histologically confirmed locally advanced or metastatic basal cell carcinoma documented on pathological analysis that were considered ( by the investigator) refractory to standard therapy. ECOG ≤ 2Documentation of a negative pregnancy test> 3 weeks since last therapy or major surgical procedureExclusion criteriaMajor organ dysfunction Long QT or on any medications known to prolong the QTActive infections requiring IV antibioticsPregnancyInability to swallow pillsOther conditions that in the opinion of the study investigator would contraindicate investigational drug use |
| Results | Data analysisThe overall response rate among patients with metastatic disease was 50% (95% CI, 29-71). Of the 15 patients with locally advanced disease, overall response rate was 60% (95% CI, 33-83). Median time of participation was 9.8 months, and median duration of response was 8.8 months. Overall, of the 33 patients with locally advanced or metastatic tumors, 18 had a response. Of the remaining 15 patients, 11 had stable disease for up to 10.8 months and 4 had progressive disease. |
| Conclusions | Authors conclusions: Confirm the participation of the hedgehog pathway in basal cell carcinoma and suggest that inhibition of the hedgehog pathway can be treating inoperable tumors |
| Critique | Strengths: Decent external validity, good results to prompt further researchLimitations: Phase 1 study, no comparator group, small sample size |

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| Citation | Efficacy and Safety of Vismodegib in Advanced Basal- Cell Carcinoma NEJM 2012; 366:2171-9 |
| Study Goals | Primary endpoint was the objective response rate; primary hypotheses were that the response rate would be greater than 20% for patients with locally advanced basal cell carcinoma and greater than 10% for those with metastatic basal cell carcinoma.The secondary endpoint was duration of response.  |
| Methods | Study Design: Phase II multicenter, international, two cohort, non- randomized study of patients with metastatic BCC and locally advanced BCC with inoperable disease or for whom surgery was inappropriate. All patients were treated with vismodegib 150mg once daily until disease progression or unacceptable toxicity. The primary endpoint was an objective response rate (ORR) defined as those achieving a partial and complete response based on the RECIST criteria. Data Analysis:Exact binomial one-sided tests were performed to assess whether the response rate was > 10% among patients with metastatic disease and > 20% in patients with locally advanced disease |
| Criteria | Inclusion criteria18 yo old, ECOG ≤2Patients with metastatic disease needed measurable disease according to the RECIST criteria assessed with CT or MRIPatients with locally advanced disease had at least 1 lesion that was 10 mm or more in the longest diameter and considered inoperable or where surgery was inappropriate in the opinion of a Mohs specialistPatients with Gorlin syndrome (basal cell nevus) could enroll if all other criteria were metExclusion criteriaMajor organ dysfunction, pregnancy, lactation, participation in an investigational study in the previous 4 weeks, life expectancy less than 12 weeks, uncontrolled medical illnesses, other conditions that would contraindicate the use of an investigational drug, and inability to swallow capsules.  |
| Results | Thirty-three patients with metastatic BCC and 63 patients with locally advanced BCC were treated with vismodegib 150mg once daily. The primary endpoint was an objective response rate (ORR) defined as those achieving a partial and complete response. Thirty percent of the patients with metastatic BCC responded (95% CI, 16 - 48; p=0.001) and 43% of the patients with locally advanced BCC responded (95% CI, 31-56; P<0.001). Thirteen patients (21%) achieved a complete response (CR), defined as absence of residual BCC on assessment of biopsy specimen. The median duration of response was 7.6 months in both groups and the median progression free survival was 9.5 months. And seven deaths due to adverse events were noted. |
| Conclusions | Authors conclusions: data suggests that vismodegib is a new treatment option for patients with advanced basal cell carcinoma |
| Critique | Good external validityNo comparator group, small study population, no overall survival, high incidence of side effects, high incidence of patient discontinuation |