ROCKY MOUNTAIN HEALTH PLANS®
We understand Colorado. We understand you.

UNIFORM PHARMACY PRIOR AUTHORIZATION REQUEST FORM

CONTAINS CONFIDENTIAL PATIENT INFORMATION

Complete this form in its entirety and send to Rocky Mountain Health Plans at 858-357-2538

☐ **Urgent**[1] ☐ **Non-Urgent**

Requested Drug Name: Zelboraf® (vemurafenib)

Patient Information:	**Prescribing Provider Information:**
Patient Name:	Prescriber Name:
Member/Subscriber Number:	Prescriber Fax:
Policy/Group Number:	Prescriber Phone:
Patient Date of Birth (MM/DD/YYYY):	Prescriber Pager:
Patient Address:	Prescriber Address:
Patient Phone:	Prescriber Office Contact:
Patient Email Address:	Prescriber NPI:
	Prescriber DEA:
Prescription Date:	Prescriber Tax ID:
	Specialty/Facility Name (If applicable):
	Prescriber Email Address:

Prior Authorization Request for Drug Benefit: ☐ New Request ☐ Reauthorization

Patient Diagnosis and ICD Diagnostic Code(s):

Drug(s) Requested (with J-Code, if applicable):

Strength/Route/Frequency:

Unit/Volume of Named Drug(s):

Start Date and Length of Therapy:

Location of Treatment: (e.g. provider office, facility, home health, etc.) including name, Type 2 NPI (if applicable), address and tax ID:

Clinical Criteria for Approval, Including other Pertinent Information to Support the Request, other Medications Tried, Their Name(s), Duration, and Patient Response:

Zelboraf® (vemurafenib)

Diagnosis (documentation supportive of diagnosis and mutation status required)

☐ Unresectable or metastatic melanoma with BRAF^{V600E} mutation.
☐ Mutation detected by an FDA-approved test (cobas® 4800 BRAF V600 mutation test).
☐ Other (please state):_____

Clinical Consideration

☐ Baseline monitoring has been completed. This includes electrocardiogram, electrolytes, liver enzymes, and bilirubin ***(for approval, please provide labs)***
☐ Baseline dermatologic evaluation has been completed

Physician Specialty (diagnosis made by):

☐ Oncologist
☐ Other (please state):_____

	☐ For use in clinical trial? (If yes, provide trial name and registration number):		
	Drug Name (Brand Name and Scientific Name)/Strength:		
	Dose:	Route:	Frequency:
	Quantity:	Number of Refills:	
	Product will be delivered to: ☐ Patient's Home ☐Physician Office		Other:
	Prescriber or Authorized Signature:		Date:
	Dispensing Pharmacy Name and Phone Number:		
	☐ **Approved**	☐ **Denied**	
	If denied, provide reason for denial, and include other potential alternative medications, if applicable, that are found in the formulary of the carrier:		

1. A request for prior authorization that if determined in the time allowed for non-urgent requests could seriously jeopardize the life or health of the covered person or the ability of the covered person to regain maximum function, or subject the person to severe pain that cannot be adequately managed without the drug benefit contained in the prior authorization request

Zelboraf® (vemurafenib)

CLASSIFICATION

- Antineoplastic Agent

DESCRIPTION

- Vemurafenib has a novel mechanism in that it is a low molecular weight, orally available, inhibitor of oncogenic BRAF serine-threonine kinase, with specific antitumor effects against the mutated $BRAF^{V600E}$ gene. In addition, it also inhibits other kinases in vitro (e.g. CRAF, ARAF, WT-BRAF, SRMS, ACK1, MAP4K5, and FGR).
- Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with **$BRAF^{V600E}$** mutation as detected by an FDA-approved test. It is not recommended in patients with wild-type BRAF melanoma.
- The FDA simultaneously approved Zelboraf and the cobas® 4800 BRAF V600 Mutation Test, a diagnostic test developed by Roche.
- In an international, randomized, phase 3 trial (BRIM-3; n=675) vemurafenib improved overall survival (OS) and progression-free survival (PFS) rates compared with dacarbazine. Patients with unresectable, previously untreated stage IIIC or stage IV melanoma with BRAF V600E mutation were randomized to treatment with either vemurafenib 960 mg orally twice daily (median age 56 years) or dacarbazine 1000 mg/m(2) IV every 3 weeks (median age 52 years). Antiemetics and granulocyte colony-stimulating factor were permitted. The prespecified criteria for the coprimary endpoints, OS and PFS, were achieved at the interim analysis and, subsequently, patients were allowed to cross over to vemurafenib from dacarbazine. At a median follow-up (interim analysis) of 3.8 months and 2.3 months for the patients in the vemurafenib group and dacarbazine group, respectively, the OS, at 6 months, was 84% and 64%; the risk of death was significantly reduced by 63% with results compatible with a reduction of 45% to 74%. The median time to PFS (n=549) was significantly longer for the vemurafenib group compared with the dacarbazine group (5.3 vs 1.6 months), and the response rates (n=439) were significantly greater (48% vs 5%).
- Treatment with vemurafenib yielded an overall response rate (ORR) of 53% in a single-arm, multicenter, phase 2, multinational trial. Patients (n=132) with metastatic melanoma bearing a BRAF V600E mutation and who had received at least 1 prior systemic therapy (49% received 2 or more therapies) were treated with vemurafenib 960 mg orally twice daily until unacceptable toxicity or disease progression. The ORR (primary endpoint) was 53%; complete response occurred in 6%, and partial response in 47% of patients. At a median of 12.9 months, response was maintained in 23 of 70 patients. The median duration of response was 6.7 months, and the median progression-free survival was 6.8 months. The median overall survival was 15.9 months with 24% of patients receiving ipilimumab after disease progression.
- Most common adverse reactions (≥30%) are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma.
- Due to occurrence of Cutaneous Squamous Cell Carcinoma (cuSCC), it is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and every two months while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per standard of care. Monitoring should be considered for 6 months following discontinuation of vemurafenib.
- Due to occurrence of QT prolongation in clinical trials, ECG and electrolytes, including potassium, magnesium, and calcium, should be monitored before treatment and after dose modification. Monitoring of ECGs should occur 15 days after treatment initiation and then monthly during the first 3 months of treatment, followed by every 3 months thereafter or more often as clinically indicated. Initiation of treatment with vemurafenib is not recommended in patients with QTc > 500 ms.
- Baseline monitoring should be completed before starting vemurafenib. This includes electrocardiogram, electrolytes, liver enzymes, and bilirubin.

FORMULARY COVERAGE

Prior authorization: Required
Good Health Formulary: Tier 3
Commercial Formulary: Tier 3
Medicare Part D coverage: Tier 5 (specialty)

COVERAGE CRITERIA

Zelboraf® (vemurafenib) meets the definition of **medical necessity** for the following:

Malignant melanoma, unresectable, stage IIIC or metastatic, $BRAF^{V600E}$ mutation positive (documentation of diagnosis and mutation status required).

- Includes patients who are previously untreated stage IIIc or IV and patients who have received at least one prior systemic therapy.
- Zelboraf is not recommended for use in patients with wild-type BRAF mutation, therefore; **confirmation of $BRAF^{V600E}$ mutation-positive melanoma is required for approval**. The $BRAF^{V600E}$ mutation is detected by the Cobas® 4800 $BRAF^{V600}$ Mutation Test from Roche Molecular Systems.

Zelboraf® (vemurafenib) is considered **experimental** for the following:

- Any condition or diagnosis not FDA approved or Compendia supported.
- This includes but is not limited to:
  - Zelboraf as monotherapy or in combination with erlotinib or erbitux and irinotecan in colorectal cancer
  - Zelboraf in combination with ipilimumab (Yervoy) for the treatment of metastatic melanoma
  - Zelboraf in the treatment of metastatic or unresectable papillary thyroid cancer positive for the $BRAF^{V600}$ mutation
- *Note:* The use of Zelboraf in malignant melanoma that is BRAF V600K mutation positive is not an FDA indication, nor is it Compendia supported. However, the NCCN panel added vemurafenib to the list of available systemic treatments for patients with a documented V600 **E or K** mutation of the BRAF gene. Requests for use of Zelboraf in patients with $BRAF^{V600K}$ mutations will be reviewed on an individual basis.

Required Provider Specialty:

- Approval is limited to Oncology

DOSAGE/ADMINISTRATION

Adult Dosing (safety and efficacy has not been determined for pediatric patients less than 18 years):

For malignant melanoma, unresectable, stage IIIC or metastatic, $BRAF^{V600E}$ mutation positive:

- Normal dosing:
  - 960mg (four 240mg tablets) twice daily taken approximately 12 hours apart
  - Treatment should continue until disease progression or unacceptable toxicity occurs.
- Dose adjustments:
  - Vemurafenib requires treatment interruption, dose reduction, or permanent discontinuation depending on the severity of the toxicity. For development of new primary cutaneous malignancy, dose modifications are not recommended. When adjusting the dose for other toxicities, doses below 480 mg twice daily are not recommended. **See complete prescribing information for toxicity related dose adjustments.**

- QT prolongation: interrupt if the QTc exceeds 500 milliseconds; correct electrolyte abnormalities and control cardiac risk factors for QT prolongation; restart at a lower dose once the QTc decreases below 500 milliseconds; if after correction of associated risk factors, the QTc increase meets values of both greater than 500 milliseconds and greater than 60 milliseconds change from baseline values, then permanently discontinue vemurafenib.
- Preexisting mild or moderate, hepatic or renal impairment: no adjustment needed; use caution in patients with preexisting severe hepatic impairment or severe renal impairment.

PRECAUTIONS

- Cutaneous Squamous Cell Carcinoma (cuSCC), including keratoacanthomas, have been reported. Potential risk factors include age greater than 65 years, prior skin cancer, and chronic sun exposure. The incidence of cuSCC in vemurafenib-treated patients in Trial 1 was 24%. CuSCC usually occurred early in the course of treatment with a median time to the first appearance of 7 to 8 weeks. Of the patients who experienced cuSCC, approximately 33% experienced > 1 occurrence with median time between occurrences of 6 weeks. In the clinical trials, cases of cuSCC were managed with excision, and patients were able to continue treatment without dose adjustment.
- Squamous cell carcinoma, noncutaneous, of the head and neck may occur; monitoring recommended.
- Serious hypersensitivity reactions, including anaphylaxis, have been reported during and upon re-initiation of treatment. If this occurs, vemurafenib treatment should be permanently discontinued.
- Severe dermatologic reactions have been reported, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Vemurafenib treatment should be discontinued in patients who experience a severe dermatologic reaction.
- Exposure-dependent QT prolongation was observed in an uncontrolled, open-label Phase 2 QT sub-study in previously treated patients with $BRAF^{V600E}$ mutation-positive metastatic melanoma. Treatment with vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome, or who are taking medicinal products known to prolong the QT interval. Monitoring and possible treatment interruption or discontinuation recommended.
- Liver laboratory abnormalities have occurred with vemurafenib. Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be monitored before initiation of treatment and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption, or treatment discontinuation.
- Mild to severe photosensitivity was reported in patients treated with vemurafenib in clinical trials. All patients should be advised to avoid sun exposure while taking vemurafenib. While taking the drug, patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors to help protect against sunburn. For intolerable grade 2 (tender erythema covering 10 - 30% body surface area) or greater photosensitivity, dose modifications are recommended.
- Serious ophthalmologic reactions (i.e., uveitis, blurred vision, iritis, photophobia, retinal vein occlusion) have been reported. In Trial 1, five cases of uveitis have been reported in patients treated with Zelboraf. Treatment with steroid and mydriatic ophthalmic drops may be required to manage uveitis. Patients should be routinely monitored for signs and symptoms of uveitis. Additionally, there were five patients with blurry vision, five patients with iritis and six patients with photophobia. There was one case of retinal vein occlusion in Trial 2.
- Mild to severe photosensitivity has been reported; dose adjustments recommended for severe reactions.
- New Primary Malignant Melanomas have been reported. There were eight skin lesions in seven patients reported as new primary malignant melanoma in Trial 1. Cases were managed with excision, and patients continued treatment without dose adjustment.
- BRAF wild-type melanoma; increased cell proliferation has occurred with in vitro exposure to BRAF inhibitors; confirm BRAF V600E mutation status prior to initiation of treatment.
- Concomitant use with drugs predominantly metabolized by CYP1A2 that have a narrow therapeutic window is not recommended.
- Concomitant use with strong CYP3A4 inhibitors or strong CYP3A4 inducers should be avoided.
- Malignancy associated with RAS activation may occur; monitoring recommended.

Billing/Coding information

HCPCS Coding:

C9399	Unclassified drugs or biologicals
J8999	Prescription drug, oral, chemotherapeutic, Not otherwise specified

COST

- AWP (January 2012): Zelboraf 240mg oral tablet (240): $12,283
- AWP (February 2013): Zelboraf 240mg oral tablet (240): $13,020

COMMITTEE APPROVAL

- January 2012

GUIDELINE UPDATE INFORMATION

January 2012	Coverage Policy created
May 2014	Coverage Policy updated

REFERENCES

- DRUGDEX®, accessed 01/14/2012, 5/5/2014.
- Product Information: Zelboraf® (vemurafenib), oral tablet. Genentech USA, Inc., South San Francisco, CA, August 2011.
- NCCN Guidelines for Melanoma. Version 3.2012, 12/01/11. http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf (Accessed 01/14/12).
- Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. Jun 30 2011;364(26):2507-16.