CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
1Q18 January – February

BRAND NAME
Zelboraf®

GENERIC NAME
Vemurafenib

MANUFACTURER
Genentech

DATE OF APPROVAL
November 6, 2017

PRODUCT LAUNCH DATE
Currently commercially available

REVIEW TYPE
☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
New/Revised Indication
Treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation

Current Indication
Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test

OFF LABEL USES
- Hairy cell leukemia

- Non-small cell lung cancer
- Thyroid carcinoma
- Brain metastases

CLINICAL EFFICACY

Background

Erdheim-Chester Disease (ECD) is a hematopoietic neoplasm that represents clonal proliferation of myeloid progenitor cells. It is a rare non-Langerhans histiocytic disorder most commonly characterized by multifocal osteosclerotic lesions of the long bones, with or without histiocytic infiltration of extraskeletal tissues.

The most common clinical presentations of ECD are bone pain (26%), neurologic features (23%), diabetes insipidus (22%), and constitutional symptoms (20%). ECD was first described by Erdheim and Chester in 1930. Only several hundred cases have been reported in the medical literature since that time.

BRAF V600E is found in approximately half of ECD cases.

	Hyman DM, et al. Vemurafenib in multiple nonmelanoma cancers with *BRAF* V600 mutations[1,2]
Study Design	• Open-label, multicenter, single-arm, multiple cohort study • Subjects ≥ 16 years of age • Diagnosis of BRAF V600-positive ECD • Median duration of follow-up was 26.6 months
N	22
Drug Regimen	Zelboraf 960 mg orally twice daily (For eight patients, the dose was reduced to 720 mg orally twice daily. For the remaining 14 patients, the dose was ultimately reduced to 480 mg.)
Primary Outcome	Overall response rate (ORR) maintained on two occasions at least four weeks apart. ORR is defined as the number of patients with complete or partial response.
Secondary Outcome*	Clinical benefit rate (defined as the overall proportion of patients with a complete or partial response or stable disease) *Reported for a smaller cohort of 14 patients with either ECD or Langerhans'-cell histiocytosis who were evaluable at the time of the initial analysis
Results	• ORR: 12/22 (54.5%; 95% CI: 32.2, 75.6) • Clinical benefit rate: 14/14 (100%)
# Withdrew due to Lack of Efficacy	Not reported

# Withdrew due to Adverse Effects	A total of 7 (32%) patients withdrew from the study due to adverse effects.

CONTRAINDICATIONS
Not applicable

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
Avoid concomitant use with:

- Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, saquinavir,
- ritonavir, indinavir, nelfinavir, voriconazole)
- Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin)
- CYP1A2 substrates with narrow therapeutic indices
- P-gp substrates with narrow therapeutic indices (e.g., digoxin)

Use concurrently with caution: ipilimumab

ADVERSE REACTIONS
The most commonly reported adverse reactions (> 50%) in patients with BRAF V600 mutation-positive ECD treated with Zelboraf were arthralgia, rash maculo-papular, alopecia, fatigue, electrocardiogram QT interval prolonged, and skin papilloma.

The most common (≥ 10%) Grade ≥ 3 adverse reactions were squamous cell carcinoma of the skin, hypertension, rash maculopapular, and arthralgia.

The incidence of adverse reactions resulting in permanent discontinuation of study medication was 32%.

DOSAGE AND ADMINISTRATION
The recommended dose of Zelboraf is 960 mg orally twice daily.

PRODUCT AVAILABILITY
Tablets: 240 mg

THERAPEUTIC ALTERNATIVES[3]

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Pegasys® (pegylated interferon alfa-2a)	135-200 mcg subcutaneously once weekly	Off-label usage; current standard of care

Intron-A® (interferon alfa-2a)	3-9 mIU subcutaneously three times per week	Off-label usage; current standard of care

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be maintained for the following reason:
  ☒ Opportunity exists to obtain clinically significant medical or laboratory information necessary to determine appropriate use of the medication.
  i) Zelboraf is approved for use only in patients with ECD with a BRAF V600 mutation.
  ii) Recommended utilization management tool(s): (check all that apply)
  (1) ☒ Prior authorization
  (2) ☐ Quantity limits
  (3) ☐ Provider newsletter
  (4) ☐ Hard block (plan exclusion)
  (5) ☐ Messaging
  (6) ☐ Electronic step therapy
  (7) ☐ Clinical program
  iii) Zelboraf currently requires a PA; recommend to maintain PA status.

Product Comparison

Based on specialist feedback:

- It would not be clinically appropriate to require a trial of an interferon alfa product before Zelboraf for BRAF V600 mutation positive Erdheim-Chester disease.
- It would be clinically appropriate to require a trial of Zelboraf before an interferon alfa product for BRAF V600 mutation positive Erdheim-Chester disease.

REFERENCES

[1] Hyman DM, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 2015;373:726-36.
[2] Zelboraf Prescribing information. South San Francisco, CA: Genentech USA, Inc.; November 2017.
[3] Diamond EL, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood 2014;124(4):483-92.