CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Alunbrig™

GENERIC NAME
Brigatinib

MANUFACTURER
ARIAD Pharmaceuticals, Inc.

DATE OF APPROVAL
April 28, 2017

PRODUCT LAUNCH DATE
Mid-May 2017

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 Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
Alunbrig is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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OFF-LABEL USES
ALK+ NSCLC with progression on ceritinib

CLINICAL EFFICACY
The efficacy of Alunbrig was demonstrated in ALTA, a two-arm, open-label, multicenter, phase 2 trial in adult patients with locally advanced or metastatic ALK-positive NSCLC with progression on crizotinib. Key eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, life expectancy ≥ 3 months, and adequate organ and hematologic function. Exclusion criteria included treatment with any prior ALK-targeted tyrosine kinase inhibitors other than crizotinib, use of crizotinib within 3 days of the first dose of Alunbrig, and history of interstitial lung disease or drug-related pneumonitis.

At baseline, patients were a median age of 54 years (range: 18-82 years) with 67% being white, 31% being Asian, and 57% being female. Ninety-three percent had ECOG PS 0-1, 98% had stage IV disease, 69% had brain metastases, and 64% had an objective response to prior crizotinib.

A total of 222 patients were randomized to receive either 90 mg once daily (n=112) or 90 mg once daily for 7 days, followed by 180 mg once daily thereafter (n=110). The primary efficacy endpoint was the overall response rate (ORR) as assessed by the investigators. Secondary endpoints included independent review committee (IRC)-assessed ORR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

The investigator-assessed ORR was 45% (97.5% CI: 34-56) for the 90 mg dose and 55% (97.5% CI: 44-65) for the 90→180 mg dose. The majority of patients achieved partial response with 2 and 5 patients in each dose group, respectively, achieving a complete response. The median DOR was 12 months for the 90 mg dose (95% CI: 7.4-NR [not reached]) and 13.8 months for the 90→180 mg dose (95% CI: 9.2-NR). Similar outcomes were observed when assessed by the IRC. The median duration of follow-up was 10.2 months for the 90 mg dose group and 11 months for the 90→180 mg dose group.

Further IRC analysis in a subgroup of patients with measurable brain metastases revealed an intracranial ORR of 42% (95% CI: 23-63) for the 90 mg dose (n=26) and 67% (95% CI: 41-87) for the 90→180 mg dose (n=18). The majority of patients achieved partial response. Of the patients who responded, 78% who received the 90 mg dose and 68% who received 90→180 mg dose maintained a response for at least 4 months The median DOR was not estimable for the 90 mg dose and was 5.6 months for the 90→180 mg dose (95% CI: 1.9-9.2 months).

The median PFS for the 90 mg dose was 8.8 months by investigator assessment and 9.2 months by IRC assessment. For the 90→180 mg dose, the median PFS was 15.6 months by both investigator assessment and IRC assessment.

Although the median OS had not yet been reached in either dose group, the probability of OS at one year was 71% for the 90 mg dose and 82% for the 90→180 mg dose.

Three percent of patients receiving the 90 mg dose and 10% of patients receiving the 90→180 mg dose discontinued therapy due to adverse effects. Thirty percent of patients receiving the 90 mg dose and 23% of patients receiving the 90→180 mg dose discontinued therapy due to disease progression.

CONTRAINDICATIONS
Not applicable

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
- CYP3A inhibitors: Avoid concomitant use of Alunbrig with strong CYP3A inhibitors due to potentially increased brigatinib plasma concentrations, resulting in increased adverse reactions. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose of Alunbrig.
- CYP3A inducers: Avoid concomitant use of Alunbrig with strong CYP3A inducers due to potentially decreased brigatinib plasma concentrations, resulting in decreased efficacy.
- CYP3A substrates: Hormonal contraceptives and other CYP3A substrates may be ineffective due to decreased exposure.

ADVERSE REACTIONS
The most common adverse reactions (≥ 25%) with Alunbrig were nausea, diarrhea, fatigue, cough, and headache.

In addition, Alunbrig has warnings for interstitial lung disease/pneumonitis, hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation, hyperglycemia, and embryo-fetal toxicity.

DOSAGE AND ADMINISTRATION
The recommended dosage of Alunbrig is 90 mg orally once daily taken with or without food for the first 7 days. The dose should then be increased to 180 mg orally once daily if tolerated.

PRODUCT AVAILABILITY
Tablets: 30 mg, 90 mg

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THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Crizotinib (Xalkori)	ALK+ NSCLC 250 mg PO BID	• 1st line
Ceritinib (Zykadia)	ALK+ NSCLC 750 mg PO QD	• 1st line
Alectinib (Alecensa)	ALK+ NSCLC 600 mg PO BID	• 2nd line in patients failing or intolerant to Xalkori

Boldface indicates generic availability

Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be considered for the following reason(s):

  i) To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes:
  - Alunbrig is indicated specifically for ALK-positive NSCLC and not for any other genomic aberrations.
  - Alunbrig is a second-line therapy indicated in patients who have progressed on or are intolerant to Xalkori (crizotinib).

  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

Product Comparison

- It is clinically appropriate to require a trial of Xalkori (crizotinib) prior to Alunbrig.
- 58 vs. Zykadia (ceritinib) – Equal therapeutic outcomes anticipated

  i) It is clinically appropriate to provide equal access to Alunbrig and Zykadia, or to require a trial of one before the other in patients who have progressed on or are intolerant to Xalkori.

  ii) It is clinically appropriate to require a trial of Zykadia prior to Alunbrig in patients who are naïve to targeted ALK therapy based on Zykadia's NCCN category 1 recommendation and FDA indication.

- 57 vs. Alecensa (alectinib) – Equal therapeutic outcomes anticipated

  i) It is clinically appropriate to provide equal access to Alunbrig and Alecensa, or to require a trial of one before the other.

REFERENCES

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