CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
1Q18 January – February

BRAND NAME
Calquence®

GENERIC NAME
Acalabrutinib

MANUFACTURER
AstraZeneca Pharmaceuticals LP

DATE OF APPROVAL
October 31, 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)
Calquence is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

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

OFF LABEL USES
Not applicable

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CLINICAL EFFICACY

Background

Mantle cell lymphoma (MCL) is a type of B-cell, non-Hodgkin's lymphoma (NHL). It accounts for 6% of all NHL's. Although it is a slow-growing cancer, it is usually widespread by the time of diagnosis. Thus MCL can become life threatening quickly and aggressive treatment is typically required[1].

	Wang M, Rule S, Z PL, et al. Efficacy and safety of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma in the phase 2 ACE-LY-004 study[2, 3, 4]
Study Design	Open label, single-arm, phase 2 study Inclusion criteria: • Men and women age ≥ 18 years • Pathologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1 • ECOG performance status of ≤ 2 • Agreement to use contraception during the study and for 30 days after the last dose of study drugs if sexually active and able to bear or beget children Exclusion criteria: • Prior BTK or B-cell lymphoma-2 inhibitor exposure • Life-threatening illness, medical condition or organ system dysfunction with risk of compromising study outcomes and subject's safety • Significant cardiovascular disease (e.g., uncontrolled/symptomatic arrhythmias, congestive heart failure, myocardial infarction within 6 months of screening, or NYHA class III/IV heart disease, or corrected QTc > 480 msec • Malabsorption syndrome, or other diseases significantly affecting gastrointestinal function • Breast feeding or pregnant
N	124
Drug Regimen	Acalabrutinib PO 100 mg BID
Primary Outcome(s)	Overall response rate (ORR) by investigator assessment (using 2014 Lugano Classification response criteria)
Secondary Outcome(s)	ORR by Independent Review Committee (IRC) assessment; duration of response, progression-free survival (PFS), overall survival (OS)
Results	

<table>
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<tr><th>Outcome n (%) [95% CI]</th><th>Investigator Assessed (n=124)</th><th>IRC Assessed (n=124)</th></tr>
<tr><td>Overall Response Rate</td><td>100 (81) [73, 87]</td><td>99 (80) [72, 87]</td></tr>
<tr><td>Complete Response</td><td>49 (40) [31, 49]</td><td>49 (40) [31, 49]</td></tr>
<tr><td>Partial Response</td><td>51 (41) [32, 50]</td><td>50 (40) [32, 50]</td></tr>
<tr><td>Duration of Response (median months)</td><td>Not reached [1+ to 20+]</td><td>Not reached [0+ to 20+]</td></tr>
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Median PFS and OS were not reached.
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<tr><td># Withdrew due to Lack of Efficacy</td><td>Treatment discontinuation due to progressive disease occurred in 31% of patients.</td></tr>
<tr><td># Withdrew due to Adverse Effects</td><td>Adverse effects resulting in treatment discontinuation included aortic stenosis, B-cell lymphoma (DLBCL), blood blister and petechiae, dyspnea and leukostasis syndrome, noncardiac chest pain, pulmonary fibrosis, and thrombocytopenia. This accounted for 6% of withdrawals.</td></tr>
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CONTRAINDICATIONS
Not applicable

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
- CYP3A Inhibitors: Avoid co-administration with strong CYP3A inhibitors. If a strong CYP3A inhibitor will be used short-term, interrupt Calquence. For moderate CYP3A inhibitors, reduce Calquence dose to 100 mg once daily.
- CYP3A Inducers: Avoid co-administration with strong CYP3A inducers. If concurrent use cannot be avoided, increase the dose of Calquence to 200 mg twice daily.
- Gastric Acid Reducing Agents: Avoid co-administration with proton pump inhibitors (PPIs). If treatment with a gastric acid reducing agent is required, consider use of an H2-receptor antagonist or an antacid. Take Calquence 2 hours prior to an H2RA. Separate dosing of Calquence and antacids by at least 2 hours.

ADVERSE REACTIONS
The most common adverse reactions (≥ 20%) of any grade were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. Adverse reactions Grade 3 or higher include neutropenia (23%), infections (18%), anemia (11%), thrombocytopenia (8%), bleeding events (2%), and atrial fibrillation and atrial flutter (1%). The most common Grade 3 or higher non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea.

DOSAGE AND ADMINISTRATION
The recommended dose is 100 mg orally approximately every 12 hours until disease progression or unacceptable toxicity. Capsules should be swallowed whole with water and may be taken with

or without food. Capsules are not recommended to be broken, opened, or chewed. Toxicities should be managed using treatment interruption, dose reduction, or discontinuation.

PRODUCT AVAILABILITY
Capsules: 100 mg

THERAPEUTIC ALTERNATIVES[5]

DRUG NAME	USAGE REGIMEN (route of admin/ frequency of use)	COMMENTS
First-Line Treatment Regimens		
CALGB (rituximab + methotrexate + cyclophosphosphamide, doxorubicin, vincristine, prednisone; etoposide, cytarabine, rituximab; carmustine, etoposide, cyclophosphamide/autologous stem cell rescue; rituximab)	Varies	Varies
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate/ cytarabine) + rituximab	Varies	Varies
NORDIC (rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone/rituximab + cytarabine)	Varies	Varies
RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)	Varies	Varies
RDHAP (rituximab, dexamethasone, cisplatin, cytarabine)	Varies	Varies
RCHOP/RICE (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, ifosfamide, carboplatin, etoposide)	Varies	Varies
Bendeka® (bendamustine) + Rituxan® (rituximab)	Varies	Varies
VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Rituxan® (rituximab)	Varies	Varies
Revlimid® (lenalidomide) + Rituxan® (rituximab)	Varies	Varies
Second-Line Treatment Regimens		
Bendeka® (bendamustine) ± Rituxan® (rituximab)	Varies	Varies
Velcade® (bortezomib) ± Rituxan® (rituximab)	Varies	Varies
cladribine ± Rituxan® (rituximab)	Varies	Varies
Imbruvica® (ibrutinib)	Varies	Varies
Revlimid® (lenalidomide) ± Rituxan® (rituximab)	Varies	Varies

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DRUG NAME	USAGE REGIMEN (route of admin/ frequency of use)	COMMENTS
Venclexta® (venetoclax)	Varies	Varies

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 considered for the following reason(s):
  - ☒ To prevent inappropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes.
    - i) Calquence is indicated for use as second line for the treatment of mantle cell lymphoma in patients who have received at least one prior therapy
    - ii) Calquence is being studied in clinical trials for various other indications, such as Waldenstrom Macroglobulinemia, chronic lymphocytic leukemia, and multiple myeloma.
    - iii) 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

- CPAC score: 57 vs. Imbruvica – Equal therapeutic outcomes anticipated
  - Equal therapeutic outcomes are anticipated for Calquence and Imbruvica for the treatment of MCL; therefore, it would be clinically appropriate to provide equal access to both or to require a trial of one before the other for the treatment of MCL.
  - It would be clinically appropriate to provide equal access to Calquence and NCCN-recommended treatment regimens for MCL, such as a rituximab-containing regimen.

REFERENCES

[1] Mantle cell lymphoma. National Center for Advancing Translational Sciences. April 2016; https://rarediseases.info.nih.gov/diseases/6969/mantle-cell-lymphoma. Accessed November 6, 2017.
[2] Calquence Prescribing Information. Wilmington, DE; AstraZeneca Pharmaceuticals LP: October 2017. Available at www.calquence.com. Accessed November 6, 2017.
[3] Wang M, Rule S, Z PL, et al. Efficacy and safety of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma in the phase 2 ACE-LY-004 study. Abstract retrieved from American Society of Hematology 59th Annual Meeting & Exposition. Available at https://ash.confex.com/ash/2017/webprogram/Paper100664.html. Accessed November 6, 2017.
[4] An open-label, phase 2 study of ACP-196 (acalabrutinib) in subjects with mantle cell lymphoma. (2017). Retrieved from https://clinicaltrials.gov/ct2/show/study/NCT02213926?view=record (Identification No. NCT02213926).

Accessed November 6, 2017.
[5] National Comprehensive Cancer Network. B-cell Lymphomas Version 6.2017. Available at https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed November 27, 2017.