CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
1Q17 January – February

BRAND NAME
Imbruvica®

GENERIC NAME
ibrutinib

MANUFACTURER
Pharmacyclics LLC

DATE OF APPROVAL
November 13, 2013

PRODUCT LAUNCH DATE
November 13, 2013

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)

☐ New Drug Approval
☒ New Indication Approval: Marginal zone lymphoma (MZL)

FDA APPROVED INDICATION(S)
Imbruvica is a kinase inhibitor indicated for the treatment of patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy
    - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma(SLL)

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- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma(SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
    - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

OFF-LABEL USES
Imbruvica is currently being evaluated in clinical trials for many uses, including follicular lymphoma, multiple myeloma, refractory/recurrent primary central nervous system lymphoma, refractory/recurrent secondary central nervous system lymphoma, non-small cell lung cancer, and advanced carcinoid and pancreatic neuroendocrine tumors.

CLINICAL EFFICACY
Mantle Cell Lymphoma (MCL):
The safety and efficacy of Imbruvica in 111 patients with mantle cell lymphoma (MCL) who received at least one prior therapy was evaluated in a single arm, phase II, open-label, multi-center trial. Imbruvica 560 mg once daily until disease progression or unacceptable toxicity was given. The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were Caucasian. At baseline, 89% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 42 months and median number of prior treatments was three (range, 1 to 5 treatments), including 11% with prior stem cell transplant.[1]

The primary end point was the rate of overall response, defined as either a partial response or a complete response according to the Revised International Working Group Criteria for non-Hodgkin's lymphoma. The secondary end points included response duration, progression-free survival or death from any cause, overall survival, and safety. Investigators assessed safety based on the frequency and severity of adverse events and graded adverse events according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

One hundred fifteen patients with relapsed or refractory mantle-cell lymphoma were enrolled and split into two groups: patients with prior Velcade treatment (50 patients) or no prior Velcade treatment.
The primary endpoint in this study was investigator-assessed overall response rate (ORR). The response data included only those patients who received Imbruvica and had at least one post-baseline efficacy assessment.

The ORR was 67.6% (95% CI, 58.9–76.3) and the median duration of response months was 17.5 (95% CI 15.8–NR).

	No Prior Treatment with Velcade	Prior Treatment with Velcade	All Patients
	(N = 63)	(N = 48)	(N = 111)
Response — no. (%)			
— Overall	43 (68)	32 (67)	75 (68)
— Complete	12 (19)	11 (23)	23 (21)
— Partial	31 (49)	21 (44)	52 (47)
— None	20 (32)	15 (31)	35 (32)
Median Response duration (months) 95% CI	15.8 (5.6–NR)	NR (NR–NR)	17.5 (15.8–NR)
Median Progression-free survival (months) 95% CI	7.4 (5.3–19.2)	16.6 (8.3–NR)	13.9 (7.0–NR)
Median Overall survival (months) 95% CI	NR (10.0–NR)	NR (11.9–NR)	NR (13.2–NR)

NR = not reached.

After an estimated median follow-up time of 15.3 months (range, 1.9 to 22.3), 46 patients were still receiving treatment, and 65 had discontinued therapy. Reasons for treatment discontinuation included progression of disease in 50 patients, patient or investigator decision for seven patients and adverse events in eight patients.

Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL):

Study 1:

The safety and efficacy of Imbruvica in patients with CLL who have received at least one prior therapy were evaluated in an open-label, multi-center trial of 48 previously treated patients. The median age was 67 years (range, 37 to 82 years) and the median number of prior treatments was 4 (range, 1 to 12 treatments). Imbruvica was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The overall response rate (ORR) and duration of response (DOR) were assessed using a modified version of the International Workshop on CLL Criteria by an Independent Review Committee. The ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved a complete response. The DOR ranged from 5.6 to 24.2+ months. The median DOR was not reached.

Study 2:

A randomized, multicenter, open-label Phase 3 study of Imbruvica versus Arzerra was conducted in patients with previously treated CLL or SLL. Patients (n=391) were randomized 1:1 to receive either Imbruvica 420 mg daily or Arzerra for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks. This study included 127 patients with del 17p CLL. The median age was 67 years (range, 30 to 84 years) and the median number of prior treatments was 4 (range, 1 to 12 treatments). The overall

response rate (ORR) and median progression free survival was assessed using a modified version of the International Workshop on CLL Criteria by an Independent Review Committee. The ORR for patients with chromosome 17p deletion for the Imbruvica group was 47.6% (95% CI: 43.2%, 72.4%), all partial responses compared to vs 4.7% in the Arzerra group. The median progression free survival was not reached in the Imbruvica group vs. 5.8 months in the Arzerra group.

Study 3:
A randomized, multi-center, open-label study of Imbruvica versus chlorambucil was conducted in patients with treatment naïve CLL (n=249) or small lymphocytic lymphoma (SLL) (n=20) who were 65 years of age or older. Patients were randomized 1:1 to receive either Imbruvica 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles. The overall response rate (complete response or partial response) was seen in 82.4% or patients receiving Imbruvica versus 35.3% of patients receiving chlorambucil. Imbruvica showed a statistically superior progression free survival compared to chlorambucil (median not reached with Imbruvica versus 19 months with chlorambucil). Imbruvica significantly prolonged overall survival; the estimated survival rate at 24 months was 98% with Imbruvica versus 85% with chlorambucil, with a relative risk of death that was 84% lower in the Imbruvica group than in the chlorambucil group (hazard ratio, 0.16; P=0.001).

Study 4:
A randomized, multicenter, double-blinded Phase 3 study of Imbruvica in combination with bendamustine and rituximab (BR) versus placebo + BR was conducted in patients with previously treated CLL or SLL. Patients (n = 578) were randomized 1:1 to receive either Imbruvica 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m2 in the first cycle, Day 1, and 500 mg/m2 Cycles 2 through 6, Day 1.The primary endpoint was progression free survival (PFS) evaluated by an independent review committee (IRC). The results showed that less number of events occurred in Imbruvica + BR arm (19.4%) versus placebo + BR arm (63.3%), resulting in a hazard ratio of 0.20 (CI: 0.15,0.28).

<u>Waldenström's Macroglobulinemia:</u>
The safety and efficacy of Imbruvica in WM were evaluated in an open-label, multi-center, single-arm trial of 63 previously treated patients. The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL).

Imbruvica was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an IRC using criteria adopted from the International Workshop of Waldenström's Macroglobulinemia.

The primary endpoint measured was overall response rate with response defined as partial response or better per IRC. The results showed 61.9% response rate (CI: 48.8, 73.0) with 0% complete response, 11.1% very good partial response, and 50.8% partial response. The median time to response was 1.2 months (range, 0.7-13.4 months).

Marginal Zone Lymphoma (MZL):[2,3]
The safety and efficacy of Imbruvica in MZL (N=63) were evaluated in an open-label, multi-center, single-arm trial of patients who received at least one prior therapy. The primary end point was the rate of overall response assessed by investigators and an IRC using criteria adopted from the International Working Group criteria for malignant lymphoma.

The efficacy analysis included 63 patients with 3 sub-types of MZL: mucosa-associated lymphoid tissue (MALT; N=32), nodal (N=17), and splenic (N=14). The median age was 66 years (range, 30 to 92 years), 59% were female, and 84% were Caucasian. Ninety two percent of patients had a baseline ECOG performance status of 0 or 1 and 8% had ECOG performance status 2. The median time since diagnosis was 3.8 years, and the median number of prior treatments was 2 (range, 1 to 9 treatments). Overall, 38 patients (60%) discontinued treatment (PD: 30%; AEs: 19%, patient decision: 5%; physician decision: 6%). The most common adverse event leading to treatment discontinuation was diarrhea in 2 pts (3%).

Imbruvica was administered orally at 560 mg once daily until disease progression or unacceptable toxicity.

The median time to response was 4.5 months (range, 2.3 to 16.4 months). Overall response rates were 46.9%, 41.2%, and 50.0% for the 3 MZL sub-types (MALT, nodal, splenic), respectively.

Overall Response Rate (ORR) and Duration of Response (DOR) Based on IRC Assessment in Patients with MZL:

	Total (N = 63)
Response Rate (CR + PR) (%)	46.0%
95% CI (%)	33.4, 59.1
Complete Response (CR) (%)	3.2
Partial Response (PR) (%)	42.9
Median Duration of Response (months) (range)	NR (16.7, NR)

CI = confidence interval; NR = not reached
Median follow-up time on study = 19.4 months

CONTRAINDICATIONS

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Not applicable

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
- CYP3A Inhibitors: Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce IMBRUVICA dose
- CYP3A Inducers: Avoid co-administration with strong CYP3A inducers

ADVERSE REACTIONS
The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia.

DOSAGE AND ADMINISTRATION
- MCL and MZL: 560 mg taken orally once daily (four 140 mg capsules once daily)
- CLL/SLL and WM: 420 mg taken orally once daily (three 140 mg capsules once daily)

PRODUCT AVAILABILITY
Capsules: 140 mg

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
rituximab (Rituxan)	MZL: varies	Can be used alone or as part of RCHOP depending on MZL subtype, histology, and stage of disease.

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): (1) To prevent inappropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes. (2) Imbruvica is being evaluated in clinical trials for many other uses, including follicular lymphoma, multiple myeloma, refractory/recurrent primary central nervous system

lymphoma, refractory/recurrent secondary central nervous system lymphoma, non-small cell lung cancer, and advanced carcinoid and pancreatic neuroendocrine tumors.

- 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
- It would be clinically appropriate to require a trial of rituximab-containing regimen prior to approval of Imbruvica for MZL.

REFERENCES:

[1] Wang ML, Rule S, Martin P, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2013;369:507-16.
[2] Imbruvica Prescribing Information. Sunnyvale, CA: Pharmacyclics LLC; January 2017. Available at www.imbruvica.com. Accessed January 20, 2017.
[3] Noy A, de Vos S, Thieblemont C, et al. Single-agent ibrutinib demonstrates efficacy and safety in patients with relapsed/refractory marginal zone lymphoma: a multicenter, openlabel, phase 2 study [oral presentation]. 58th Annual Meeting & Exposition of the American Society of Hematology; December 3-6, 2016; San Diego, CA. Abstract 1213.