CLINICAL UPDATE

Brand Name	Imbruvica®
Generic Name	ibrutinib
Drug Manufacturer	Pharmacyclics LLC

Clinical Update

TYPE OF CLINICAL UPDATE

New Indication; Dosage Form

FDA APPROVAL DATE

August 24, 2022

LAUNCH DATE

August 28, 2022

REVIEW DESIGNATION

Priority; Orphan

TYPE OF REVIEW

Type 5 - New Formulation or New Manufacturer

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Imbruvica® is a kinase inhibitor 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 a confirmatory trial(s).
- Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).
- Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion.
- Adult patients with Waldenström's macroglobulinemia (WM).
- Adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based 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 a confirmatory trial(s).
- Adult and pediatric patients aged 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

MECHANISMS OF ACTION

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of

the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion in vitro.

DOSAGE FORM(S) AND STRENGTH(S)

- Capsules: 70 mg and 140 mg
- Tablets: 140 mg, 280 mg, 420 mg, and 560 mg
- Oral suspension: 70 mg/mL

DOSE & ADMINISTRATION

- MCL and MZL: 560 mg taken orally once daily.
- CLL/SLL and WM: 420 mg taken orally once daily.
- cGVHD:
  - Patients 12 years and older: 420 mg taken orally once daily.
  - Patients 1 to less than 12 years of age: 240 mg/m2 taken orally once daily (up to a dose of 420 mg)

EFFICACY

Study 1129

The safety and efficacy of Imbruvica® in cGVHD were evaluated in Study 1129 (NCT02195869), an open-label, multi-center, single-arm trial of 42 patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. Imbruvica® was administered orally at 420 mg once daily. The responses were assessed by investigators using the 2005 National Institute of Health (NIH) Consensus Panel Response Criteria with two modifications to align with the updated 2014 NIH Consensus Panel Response Criteria.

The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were White. The most common underlying malignancies leading to transplantation were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since cGVHD diagnosis was 14 months, the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments), and 60% of patients had a Karnofsky performance score of ≤ 80. The majority of patients (88 %) had at least 2 organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily corticosteroid dose (prednisone or prednisone equivalent) at baseline was 0.3 mg/kg/day, and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections were managed per institutional guidelines with 79% of patients receiving combinations of sulfonamides and trimethoprim and 64% receiving triazole derivatives.

Efficacy results are shown in Table 1

Table 1: Best Overall Response Rate (ORR) and Sustained Response Rate Based on Investigator Assessment[a] in Patients with cGVHD in Study 1129

	Total (N=42)
ORR	28 (67%)
95% CI	(51%, 80%)
Complete Response (CR)	9 (21%)
Partial Response (PR)	19 (45%)
Sustained response rate[b]	20 (48%)

CI = confidence interval.

[a] Investigator assessment based on the 2005 NIH Response Criteria with two modifications (added "not evaluable" for organs with non-cGVHD abnormalities, and organ score change from 0 to 1 was not considered disease progression.)

[b] Sustained response rate is defined as the proportion of patients who achieved a CR or PR that was sustained for at least 20 weeks.

The median time to response coinciding with the first scheduled response assessment was 12.3 weeks (range, 4.1 to 42.1 weeks). Responses were seen across all organs involved for cGVHD (skin, mouth, gastrointestinal tract, and liver). ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score in 24% (10/42) of patients on at least 2 consecutive visits.

iMAGINE

The safety and efficacy of Imbruvica® were evaluated in iMAGINE (NCT03790332), an open-label, multi-center, single-arm trial of Imbruvica® for the treatment of pediatric and young adult patients age 1 year to less than 22 years with moderate or severe cGVHD as defined by NIH Consensus Criteria. The study included 47 patients who required additional therapy after failure of one or more prior lines of systemic therapy. All patients had platelets ≥ 30 x 10^9 /L; absolute neutrophil count ≥ 1.0 x 10^9 /L; AST or ALT ≤ 3 x ULN; total bilirubin of ≤ 1.5 x ULN; and estimated creatinine clearance ≥ 30 mL/min. Patients were excluded if single organ genitourinary involvement was the only manifestation of cGVHD.

Patients aged 12 years and older were treated with Imbruvica® 420 mg orally once daily, and patients age 1 year to less than 12 years were treated with Imbruvica® 240 mg/m2 orally once daily. Concomitant treatment with supportive care therapies for cGVHD was permitted. Initiation of new systemic cGVHD therapy while on study was not permitted.

The median age was 13 years (range, 1 to 19 years). Of the 47 patients, 70% of patients were male, and 36% were White, 9% were Black or African American, 55% were other or unreported. The median time since cGVHD diagnosis was 16.1 months, the median number of prior cGVHD treatments was 2 (range, 1 to 12). The majority of patients (87%) had at least 2 organs involved at baseline, with lung involvement at baseline in 49% of patients; 26% of patients had a Karnofsky/Lansky performance score of <80. The median daily corticosteroid dose (prednisone or prednisone equivalent) at baseline was 0.47 mg/kg/day, and 61% (19 of 31) patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections was managed per institutional guidelines, with 72% of patients receiving combinations of sulfonamides and trimethoprim and 70% receiving systemic antifungal agents.

The efficacy of Imbruvica® was established based on overall response rate (ORR) through Week 25, where overall response included complete response or partial response according to the 2014 National Institutes of Health (NIH) Consensus Development Project Response Criteria. The efficacy results are shown in Table 2:

Table 2: Efficacy Results in Patients with Previously Treated cGVHD[a] in iMAGINE

	Total (N=47)
ORR by Week 25	28 (60%)
95% CI (%)	(44, 74)
Complete Response (CR)	2 (4%)
Partial Response (PR)	26 (55%)
Median Duration of Response, months (95% CI)[b]	5.3 (2.8, 8.8)

CI = confidence interval; ORR = overall response rate.

[a] Assessment based on 2014 NIH Consensus Development Project Response Criteria.
[b] Based on all responders in the study, calculated from first response to progression, death, or new systemic therapies for cGVHD.
The median time to first response was 0.9 month (range, 0.9 to 6.1 months). The median time from first response to death or new systemic therapies for cGVHD was 14.8 months (95% CI: 4.6, not evaluable). ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score through Week 25 in 50% (13/26) of patients aged 12 years and older.