Ibrutinib (Imbruvica™)

National Drug Monograph

Updated August 2014

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Outcome in clinically significant area	MCL: Objective Response Rate with no survival or disease-related symptom improvement CLL: Progression-Free Survival, Objective Response Rate
Effect Size	MCL: N/A; ORR 68%; CR 21%; PR 47%; SD/PD 32% CLL: HR for PFS 0.22; p<0.0001; ORR 71%; (2 CR; 34 PR)
Potential Harms	MCL: Low risk Grade 3/4 toxicities: neutropenia 16%; thrombocytopenia 11%; anemia 10%; diarrhea 6%; fatigue 5%; peripheral edema 2%; dyspnea 4%; bleeding events 4% CLL: Low risk The most common grade 3/4 non-hematologic adverse events (≥ 5%) were pneumonia, hypertension, atrial fibrillation, sinusitis, skin infection, dehydration and musculoskeletal pain. Grade 3/4 hematologic events included: thrombocytopenia (10%) and neutropenia (27%).
Net Clinical Benefit	MCL: Minimal - Low benefit with low risk of harm CLL: Substantial –High benefit with low risk of harm

Definitions
Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life
Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio
Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)
Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Efficacy

Ibrutinib received accelerated approval for the treatment of relapsed/refractory Mantle Cell Lymphoma and the treatment of Chronic Lymphocytic Leukemia (CLL) after at least one prior therapy.

Mantle Cell Lymphoma (MCL)

- FDA-approval for ibrutinib is based upon an improvement in ORR and limited to patients who have received at least one prior therapy. The study population in the trial leading to approval received treatment with a median of three prior therapies.
- An improvement in overall survival and/or improvement in disease-related symptoms has not been established.
- The ORR to ibrutinib in MCL was 66% (17% CR) with a median time to response of 1.9 months and duration of response lasting 17.5 months.

Chronic Lymphocytic Leukemia (CLL)

- The FDA approved use of ibrutinib in patients with CLL who have received at least one prior therapy and patients with 17p deletion. The study population included patients with a median number of 4 prior treatments.
- ORR included all partial responses, no complete responses.
- The median duration of these responses has not been reached.
- Data from the phase 3 RESONATE trial comparing ibrutinib vs. of atumumab in previously treated CLL or SLL (Small Lymphocytic Leukemia) reports that those receiving ibrutinib experienced longer PFS (primary endpoint) and an improvement in OS and ORR (secondary endpoints).

Safety

- Ibrutinib may lack the significant bone marrow suppressive and neuropathic effects of other alternatives. The most common toxicities are grade 1 and 2 diarrhea, fatigue and nausea.
- Most common severe toxicities include neutropenia and thrombocytopenia.
- Due to primary metabolism via cytochrome P450 route, drug interactions can significantly impact the pharmacodynamics of ibrutinib. Close monitoring and dose-modification may be necessary.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating ibrutinib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Mantle cell lymphoma (MCL) is considered a rare subtype of Non-Hodgkin Lymphoma (NHL), accounting for 3-10% of NHL diagnoses. MCL affects an older male population where the median age of diagnosis is 60-65 years. Following initial treatment, the likelihood of obtaining complete responses (CR) becomes less as well as the duration of those responses (DOR). In general, the DOR is ~ 9 months and the median overall survival of relapsed/refractory MCL is 1-2 years. There is no standard therapy for relapsed MCL. An individualized approach to treatment is taken, with consideration given to patient age, performance status, initial therapy, bone marrow reserve and history of infections.

Chronic Lymphocytic Leukemia (CLL) is a hematopoietic condition characterized by a clonal proliferation of malignant B cells that have accumulated in the bone marrow, lymphoid tissue and peripheral blood. The median age of diagnosis is 72 years, with only 10-15% of cases diagnosed in those less than 50 years old.

For asymptomatic patients with early stage disease, the estimated median survival is greater than 10 years. Those symptomatic with advanced stage disease have a median survival rate of 18 months to 3 years. Treatment is indicated for symptomatic individuals or those who have evidence of progressive disease. Treatment can improve median survival rates to ~ 5 years. It is estimated that 15,720 adults will be diagnosed with CLL in 2014 and ~ 4600 will succumb to the disease.

Pharmacology/Pharmacokinetics[1,2]

Ibrutinib is a Bruton's Tyrosine Kinase (BTK) small molecule inhibitor. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. Overstimulation of the BCR pathway leads to phosphorylation of tyrosine kinases and results in uncontrolled B-cell proliferation, differentiation and survival. Ibrutinib targets this dysregulated pathway.

Absorption
Ibrutinib is orally absorbed with a median T_{max} 1-2 hours. Drug exposure increases with doses up to 840 mg. Administration with food increases ibrutinib exposure 2-fold compared to the fasted state.

Distribution
Apparent volume of distribution at steady state is ~ 10,000 L. In vitro, reversible binding to human plasma proteins was 97.3% with no concentration dependence in the range of 50 to 1000 ng/ml.

Metabolism
The major route of elimination for ibrutinib is metabolism, primarily via CYP3A4 and to a minor extent by CYP2D6. The active metabolite has inhibitory activity 15x lower than ibrutinib.

Elimination
Ibrutinib is primarily eliminated in the form of metabolites in the feces. A single-dose radiolabelled study in healthy subjects noted that ~ 90% was excreted within 168 hours (80% via feces)

FDA Approved Indication(s)

Ibrutinib is a kinase inhibitor that received FDA-approval for the treatment of mantle cell lymphoma (MCL) in patients who have received at least one prior therapy. It is also approved for the treatment of chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy and CLL patients with 17p deletion

The approval in MCL is not based upon improvement in survival or disease-related symptoms, but overall response rate. Data from the confirmatory phase 3 RESONATE trial supports improvement in PFS (primary endpoint) with accompanying improvement in OS and ORR (secondary endpoints) in CLL.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Current areas of investigation per www.clinicaltrials.gov include: relapsed or refractory B-cell malignancies (diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and Waldenstrom Macroglobulinemia), initial therapy in previously untreated elderly patients with CLL or SLL, in combination with rituximab for treatment of previously untreated CLL, in combination with lenalidomide for relapsed/refractory CLL or SLL, monotherapy for treatment of hairy cell leukemia.

Current Therapeutic Alternatives

There is no standard therapy for relapsed/refractory mantle cell lymphoma. Therapeutic alternatives depend on the individual patient, comorbidities, prior therapy, toxicity profile and candidacy for stem cell transplant.

Table 1 summarizes select agents/regimens that have been evaluated in a clinical trial setting, as well as their outcomes.

Table 1. Summary of select agents/regimens evaluated in relapsed/refractory MCL[3-14]

FDA approved for MCL	Drug and/or Regimen studied	Design	ORR
No	Bendamustine-based		
	Bendamustine/**rituximab**	Phase II N=12	ORR 92% (59% CR/Cru) DOR 19 months
	Bendamustine/**rituximab**	Phase II N=16	ORR 75% (50% CR)
	Bendamustine/**mitoxantrone /rituximab**	Phase II N=18	ORR 78% (33% CR)
	Bendamustine/**bortezomib/rituximab**	Phase II N=30	ORR 71%
Yes	Bortezomib-based		
	Bortezomib	Phase II N=40	ORR (50 versus 43%) and PFS (5.6 versus 3.9 months) Relapsed vs. refractory
	Bortezomib	Phase II N=155	ORR 33% (8% CR/CRu) DOR 9.2 months
Yes	Lenalidomide-based		
	Lenalidomide	Phase II Subset analysis N=57	ORR 35% (12% CR/CRu) DOR 16.3 months
	Lenalidomide	Phase II N=15	ORR 53% (20% CR) DOR 13.7 months
No	Fludarabine-based		
	FCM (**fludarabine**, **cyclophosphamide**, **mitoxantrone**) vs. FCM-R (**rituximab**)	Phase III N=128	FCM vs. FCM-R ORR 46 vs. 58%
No	Cladribine-based		
	Cladribine	Phase II N=25	ORR 46% (21% CR) PFS 5 months
Yes	Ibrutinib		
	Ibrutinib	Phase II N=111	ORR 68% 68% no bortezomib vs. 67% prior bortezomib DOR 17.5 months

Key: BOLDED agents are listed on VANF

Patients with relapsed CLL are defined as those who initially responded with a complete or partial remission, but then subsequently develop progressive disease 6 months or more after treatment. Refractory disease is defined as such in those patients who do not achieve a complete or partial remission with initial treatment or develop progressive disease within 6 months of therapy.

Those with relapsed disease can consider repeat use of their initial therapy at time of disease progression, whereas those with refractory disease cannot. Chemotherapy is typically used in refractory cases. There is no standard chemotherapy regimen for refractory disease at this time. Options in relapsed/refractory CLL are provided in Table 2.

Table 2. Summary of select agents/regimens evaluated in relapsed/refractory CLL[15-27]

FDA approved for CLL	Drug and/or Regimen studied	Design	Population demo	ORR
Yes	Fludarabine Approved for progressive disease during treatment with at least one standard alkylating-agent			
	Fludarabine monotherapy	Phase II	N=113; untreated vs. prior F	At 3 yrs: ORR 85 vs. 27%
	Fludarabine, cyclophosphamide (FC) vs. FC-Rituximab (FC-R)	Phase III	N=552; prior tx; Except no prior R	At 25 mos: PFS 20 vs. 30 mos
	Fludarabine, cyclophosphamide, mitoxantrone (FCM) vs. FCM-Rituximab (FCM-R)	Phase II	N=52; Rel/Ref; Median 2 prior tx; 63% prior F;	At 2 mos: ORR 58 vs. 65%; MRD negative: 3 vs. 5
Yes	Bendamustine Approval in untreated and relapsed CLL			
	Bendamustine + **rituximab**	Phase II	N=78; Rel/Ref	ORR 59%; CR 9% Gr ¾ tox 50%
	Bendamustine monotherapy	Phase I/II	N=16; Rel/Ref; Median 3 prior tx	PR 7; CR 2 Median DOR 43 mos
Yes	Alemtuzumab – removed from US market in Sept. 2012 to plan for marketing under different name for treatment of MS; accessible through CLL distribution program			
	Alemtuzumab monotherapy	Systematic review		ORR 38%; 6% CR
	Alemtuzumab monotherapy		No LAD vs. LAD < 5cm vs. LAD > 5cm	ORR 87 vs. 40 vs. 9%
	Alemtuzumab + **fludarabine** vs. **Fludarabine** alone	Phase III	N=335; Rel/Ref; 15% prior F	PFS 24 vs. 17 mos Gr ¾ tox 67 vs. 55%
	Alemtuzumab + **rituximab**		N=32; Rel/Ref	ORR 52%; CR 8% Infection rate 52%
	Fludarabine, **cyclophosphamide**, **rituximab**, alemtuzumab (CFAR)	Phase II	N=80; Rel/Ref	ORR 65%; CR 29% Infection rate 46%
Yes	Ibrutinib Approval after ≥ 1 prior therapy			
	Ibrutinib	Phase I/II	N=85; Rel/Ref; Median 4 prior tx	ORR 71%; CR 2%; At 26 mos, PFS 75%; OS 83%
	Ibrutinib (I) vs. ofatumumab (O)	Phase III	N = 391; Rel/Ref; I vs. O Prior tx: 3 vs. 2 ≥ 3 tx: 53 vs. 46% 11q22.3 del: 32 vs. 30% 17p13.1 del: 32 vs. 33%	I vs. O at 9.4 mos PFS: NR vs. 8.1 mos HR 0.22 (95% CI, 0.15-0.32; p<0.001) OS at 12 months OS: 90 vs. 81% HR 0.43 (95% CI, 0.24-0.79; p=0.005) ORR: 43 vs. 4% Odds ratio 17.4 (95% CI, 8.1-37.3; p<0.001)
Yes	Ofatumumab Approval in combination w/ chlorambucil in untreated CLL and treatment in patients refractory to F and A			
	Ofatumumab	Phase I/II	N=33; Rel/Ref; Median 3 prior tx	PR 44%/CR 0
	Ofatumumab	Phase II	N=138; Rel/Ref to F & A or F w/LAD > 5 cm; Median 5 prior tx	PR 58% prior fludarabine; PR 47% prior alemtuzumab; ORR independent of prior rituximab

Key: BOLDED agents are listed on VANF; F fludarabine; A alemtuzumab; LAD lymphadenopathy; tx therapies; PR partial response; CR complete response; ORR objective response rate; Rel relapsed; Ref refractory

Dosage and Administration

Mantle Cell Lymphoma
Ibrutinib is available as 140 mg capsules. A dose is 560 mg (4 x 140 mg caps) taken orally once daily with a glass of water. Capsules should be swallowed whole, not opened, broken or chewed.

Chronic Lymphocytic Leukemia
Ibrutinib dose is 420 mg (3 x 140 mg caps) taken orally daily with a glass of water.

Dose modifications for Adverse Events

- Therapy should be interrupted for any of the following events:
  - Grade 3 or greater non-hematologic event
  - Grade 3 or greater neutropenia with infection or fever
  - Grade 4 hematologic toxicity
- Once the symptoms of the event have resolved to grade 1 or baseline, ibrutinib may be reinitated at the starting dose.
- If toxicity reoccurs, reduce dose by one capsule (140 mg per day).
- A second reduction of dose by one capsule may be considered as needed.
- If toxicity persists despite two dose reductions, ibrutinib therapy should be discontinued.

Table 3. Recommended dose modifications for toxicity based on occurrence

Toxicity occurrence	MCL dose modification after recovery; starting dose = 560 mg	CLL dose modification after recovery; starting dose = 420 mg
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

Dose modifications for use with CYP3A Inhibitors

- Ibrutinib is primarily metabolized by the cytochrome P450 route, CYP3A4 and CYP2D6 to a minor extent.
- Because of this, avoid co-administration of ibrutinib with moderate/strong CYP3A4 inhibitors.
- Concomitant, chronic use of strong CYP3A4 inhibitors is not recommended. Examples include ritonavir and nefazodone.
- Short-term use (considered 7 days or less) of strong CYP3A4 inhibitors (eg. Antifungals, antibiotics) should be managed by interrupting ibrutinib therapy until the course of inhibitor therapy is no longer needed.
- Reduce the dose of ibrutinib to 140 mg if a moderate CYP3A4 inhibitor must be used (eg. Fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products and ciprofloxacin)
- Monitor patients closely for signs of ibrutinib toxicity when given with moderate/strong CYP3A4 inhibitors.

Missed doses

If a dose of ibrutinib is not taken at the regularly scheduled time, it can be taken as soon as possible on the same day. Return to the regularly scheduled dosing time on the following day.
Do not take extra capsules to make up for missed doses.

Efficacy

Efficacy Measures (see Appendix 1: Approval Endpoints)

The following outcomes are commonly evaluated in the MCL and CLL trial setting:

- Objective Response Rate (ORR)
  - Complete Response (CR), Complete Response unconfirmed (Cru)
  - Partial Response (PR), Stable Disease (SD), Progressive Disease (PD)
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Duration of Response (DOR)
- Minimal Residual Disease (MRD)

Summary of efficacy findings

Mantle Cell Lymphoma[29]

- Ibrutinib received FDA-approval for the treatment of mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based upon results of an open-label, international, phase 2 trial.
- A total of 111 previously-treated patients were evaluated. All patients had ECOG Performance Status of 0-2.
- The median age of the study population was 68 years (range, 40-84) with 77% male gender. Patients received a median of 3 prior therapies (range, 1-5) that included intensive HyperCVAD (30%), Stem Cell Transplant 11%, lenalidomide 24% and a rituximab-based regimen 89%.
- Patients were stratified according to prior bortezomib therapy or no prior bortezomib therapy.
- Ibrutinib 560 mg PO once daily was given until progressive disease or toxicity.
- At a median follow-up 15.3 mos (range, 1.9-22.3), patients remained on ibrutinib for a median of 9 cycles (range, 1-24).
- The overall ORR was 68% with a breakdown of 68% no prior bortezomib vs. 67% prior bortezomib.
- Duration of Response for the entire group was 17.5 months [15.8 months in the no prior bortezomib group; the DOR was not yet reached in the prior bortezomib arm].
- The Independent Review Committee noted an ORR of 69%; CR 21% and DOR 19.6 months.

Chronic Lymphocytic Leukemia (CLL)[25, 28, 30]

- Ibrutinib was granted accelerated approval in CLL for patients who have received at least one prior therapy and those with 17p deletion.
- A phase 1b-2 multicenter trial of 85 patients with relapsed or refractory CLL were evaluated; these patients received a median of 4 prior therapies (range, 1-12). A total of 65% had advanced stage disease, 33% with 17p13.1 deletions, 36% with 11q22.3 deletions.
- Patients were separated into 3 cohorts: cohorts 1 and 2 included patients that received at least 2 prior therapies that included a purine analog; cohort 3 was composed of patients with high risk disease that did not respond to a chemoimmunotherapy regimen or progressed within 24 months after completion of the regimen.
- 27 patients in cohort 1 and 24 patients in cohort 3 received Ibrutinib 420 mg PO once daily; 34 patients in cohort 2 received ibrutinib 840 mg PO once daily until progressive disease or unacceptable toxicity.
- At median follow-up of 20.9 months, 64% of patients were still receiving treatment; 36% had discontinued therapy due to disease progression (13%), patient/PI decision (15% - 5 proceeded to HSCT), adverse events (8%)
- Overall response rate was 71% (CR 2; PR 34) in the 420 mg cohort and 71% (PR 24) in the 840 mg cohort. The 26-month estimate of PFS was 75% and OS was 83%

- Accelerated approval from the FDA was supported by 48 patients who received ibrutinib 420 mg daily. The ORR in this select group was 58% at a median 15 month follow-up.
- Disease progressed in 11 patients (13%); 7 progressed by biologic transformation, also known as Richter's syndrome/transformation. Ten of these 11 patients had high risk features.
- Among 28 patients with high risk feature, 17p13.1 deletion, the 26-month estimate of PFS was 57% and OS 70%.
- A total of 20% (420 mg cohort) and 15% (840 mg cohort) experienced partial responses with persistent lymphocytosis. Lymphocytosis was noted by day 7 in 78% of patients. It peaked at a median of 4 weeks, then slowly declined. The lymphocyte count normalized or was reduced by 50% in 79% of patients. In patients with unmutated genes, lymphocyte counts normalized quicker than those with mutations (median 6.4 vs. 14.8 months). Lymphocytosis occurred with concomitant reduction in lymph node, spleen size and improvement in cytopenias.
- Improvements were noted in patients with the following baseline cytopenias: thrombocytopenia 78% improvement; anemia 82% improvement, neutropenia 77% improvement.
- RESONATE (Study of Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia) trial was stopped at the point of preplanned interim analysis. A total of 391 patients at 67 sites were enrolled throughout the U.S., Australia and Europe. Enrolled patients had a diagnosis of CLL or SLL, had received at least one prior therapy and were considered to be inappropriate for purine analog therapy (due to short PFS after chemoimmunotherapy or because of concomitant illness, age $\geq$ 70 years, or possessed a chromosome 17p13.1 deletion. Patients were required to have ECOG PS < 2, adequate bone marrow, hepatic and liver function. Those requiring warfarin or strong CYP3A4/5 inhibitors were excluded. Participants were randomized to ibrutinib 420 mg PO daily or ofatumumab for up to 24 weeks (initial dose 300 mg at week 1, then 2000 mg weekly x 7 weeks, then every 4 weeks x 16 weeks. Stratification was done according to purine analog chemoimmunotherapy resistance and presence/absence of chromosome 17p13.1 deletion. The primary endpoint was PFS (assessed by IRC) with secondary endpoints of OS and ORR.
    - At the median follow-up of 9.4 months, the median duration of PFS was not reached versus median duration of PFS of 8.1 months with ofatumumab. The hazard ratio for progression or death was 0.22 (95% CI, 0.15-0.32; p<0.001) for ibrutinib – a 78% reduction in the risk of progression/death compared to those receiving ofatumumab. The subgroup analysis noted that the effect on PFS was observed regardless of baseline or molecular characteristics.
    - Patients with chromosome 17p13.1 deletion also appreciated the improvement in PFS. A total of 127 patients with chromosome 17p13.1 deletion were included in RESONATE (63 received ibrutinib; 64 received ofatumumab). The median PFS had not been reached for the ibrutinib subset of patients, while it was estimated to be 5.8 months in the ofatumumab arm [HR 0.25 (95% CI 0.14-0.45)]. The ORR was 47.6 vs. 4.7% in the ibrutinib vs. ofatumumab arms, respectively. All responses were partial; no patients achieved a complete response.
    - At 6 months, 83% vs. 49% of ibrutinib vs. ofatumumab patients were alive with no progressive disease. The secondary endpoint of OS was prolonged in the ibrutinib arm (HR 0.43; 95% CI 0.24-0.79; P=0.005), reducing the risk of death by 57%. Although 57 patients originally randomized to ofatumumab crossed over to receive ibrutinib, the survival effect was based on analyses censored at the time of crossover. The overall response rate was higher for the ibrutinib vs. ofatumumab arm, respectively (42.5 vs. 4.1%; p< 0.001). Neither arm reported any complete responses, only partial ones.

Adverse Events (Safety Data) in MCL

The adverse effect profile is reflective of the study population of 111 previously-treated patients with MCL who received ibrutinib 560 mg orally daily with median treatment duration of 8.3 months.

Deaths and Other Serious Adverse Events

The most common grade 3/4 non-hematologic adverse events (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue and skin infections.

Grade 3/4 hematologic events included: thrombocytopenia (17%), neutropenia (29%) and anemia (9%). Patients who developed lymphocytosis greater than 400,000/µL have developed intracranial hemorrhage, lethargy, gait instability and headache. Some of these cases were in the setting of disease progression.

Fatal and serious cases of renal failure have been reported. Serum creatinine increases of 1.5-3x ULN have occurred in 9% of patients.

Common Adverse Events

The most common adverse events (≥ 20%) reported were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite.

Other Adverse Events

A total of 40% of patients had elevated uric acid levels (13% with uric acid > 10 mg/dL). Hyperuricemia overall, was reported in 15% of patients.

Tolerability

A total of 10 patients (9%) discontinued treatment with ibrutinib due to adverse events. The most common event leading to drug discontinuation was subdural hematoma (1.8%). Events leading to dose-reduction were reported in 14% of patients.

Table 4. Adverse Event Profile of Ibrutinib in Relapsed/Refractory MCL

Organ system	Event	All grades (%)	Grade 3 or 4 (%)
Gastrointestinal	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	dyspepsia	11	0
Infection/infestation	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	sinusitis	13	1
General	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	asthenia	14	3
Skin	Bruising	30	0
	Rash	25	3
	petechiae	11	0
Musculoskeletal	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory/thoracic	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism/ nutrition	Decreased appetite	21	2
	Dehydration	12	4
Nervous system	Dizziness	14	0
	Headache	13	0

Adverse Events (Safety Data) in CLL

The adverse effect profile is reflective of the study population of 48 previously-treated patients with CLL who received ibrutinib 420 mg orally daily with median treatment duration of 15.6 months. Safety data from RESONATE (n=391) is included.

Deaths and Other Serious Adverse Events

The most common grade 3/4 non-hematologic adverse events (≥ 5%) were pneumonia, hypertension, atrial fibrillation, sinusitis, skin infection, dehydration and musculoskeletal pain.

Grade 3/4 hematologic events included: thrombocytopenia (10%) and neutropenia (27%).

Common Adverse Events

The most common adverse events (≥ 20%) reported were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, pyrexia, constipation, rash, abdominal pain, arthralgia, nausea, stomatitis, sinusitis and dizziness.

Other Adverse Events

A total of 38% of patients had elevated uric acid levels (4% with uric acid > 10 mg/dL). Data from RESONATE indicates that atrial fibrillation was noted in 3 vs. 0% of ibrutinib vs. ofatumumab patients, respectively. One patient discontinued ibrutinib therapy for this reason. Blurred vision was also more common among ibrutinib patients (10 vs. 3%) as well as rash (8 vs. 4%) and pyrexia (24 vs. 15%). These events were grade 1 or 2. Cataracts were more common among ibrutinib patients (3 vs. 1%). RESONATE data reports reduced creatinine clearance (any grade) in 16 vs. 17% of ibrutinib vs. ofatumumab patients, respectively

Tolerability

A total of 5 patients (10%) discontinued treatment with ibrutinib due to adverse events. This included 3 patients with infections and 2 patients with subdural hematomas. Events leading to dose-reduction were reported in 13% of patients. Discontinuation from treatment within RESONATE was reported in 4% of patients in each study group. Events leading to dose-reductions (diarrhea) occurred in 4% of ibrutinib patients.

Table 5. Adverse Event Profile of Ibrutinib in Relapsed/Refractory CLL

Organ system	Event	All grades (%)	Grade 3 or 4 (%)
Gastrointestinal	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
	dyspepsia	13	0
Infection/infestation	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infections	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
General	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
Skin	Bruising	54	2
	Rash	27	0
	petechiae	17	0
Musculoskeletal	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
Respiratory/thoracic	Cough	19	0
	Oropharyngeal pain	15	0

	Dyspnea	10	0
Metabolism/ nutrition	Decreased appetite	17	2
Nervous system	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
Vascular disorders	Hypertension	17	8

Contraindications

None

Warnings and Precautions

Hemorrhage

- Grade 3 or higher bleeding events (including subdural hematoma, GI bleeding, hematuria) were noted in 5% of patients with MCL and 6% of patients with CLL Bleeding events of any grade was reported in 48% of patients (MCL) and 63% of patients (CLL).
- Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.
- Consider the risks vs. benefits of ibrutinib therapy in patients that require antiplatelet or anticoagulant therapies. Also, consider risks vs. benefits of withholding ibrutinib for at least 3 to 7 days pre- and post-surgery, depending on the type of surgery and risk of bleeding.
- RESONATE: bleeding-related events (any grade) were more common with ibrutinib vs. ofatumumab (4 vs. 2%, respectively); major bleed events grade 3 or higher were noted in 1 vs. 2% of ibrutinib vs. ofatumumab patients, respectively.

Infections

- Fatal and non-fatal infections have been reported with ibrutinib
- At least 25% of patients with MCL and 26% of patients with CLL experienced infections grade 3 or greater.
- Monitor patients for fever/infections with prompt workup on detection.
- RESONATE: infections (any grade) were more common with ibrutinib (70 vs. 54%), but grade 3 or higher infections were similar between groups (24 vs. 22%).

Cytopenias

- Grade 3/4 events affected 41% of MCL patients and 35% of CLL patients; Events included neutropenia (29%), thrombocytopenia (17%) and anemia (9%) in MCL and neutropenia (27%) and thrombocytopenia (10%) in CLL.
- Complete blood counts should be monitored monthly.

Atrial Fibrillation

- Atrial fibrillation and atrial flutter have been reported in 6-9% of patients treated with ibrutinib
- Those with cardiac risk factors, acute infections and prior history of atrial fibrillation appear to be at greatest risk
- Patients who develop cardiac dysrhythmia or new onset dyspnea should be followed up with an ECG
- Consider risks vs. benefits of ibrutinib in any patient with paroxysmal or persistent atrial fibrillation
- Patients should be monitored periodically for signs and symptoms (e.g. lightheadedness, palpitations)

Second Primary Malignancies

Second primary malignancies, including skin cancers (4%) and other carcinomas (1%), have been reported in 5% of MCL patients receiving ibrutinib; 10% of CLL patients reported other malignancies which includes 8% with skin cancers and 2% with other carcinomas.

Embryo-Fetal Toxicity

- Based on animal findings, ibrutinib can lead to fetal harm if taken by a pregnant woman.
- Women of child-bearing potential should be advised to avoid becoming pregnant while taking ibrutinib therapy.
- If the drug is used during pregnancy or if pregnancy occurs while taking ibrutinib, the patient should be alerted of the potential hazard to the fetus.

Special Populations

Pregnancy Category D

Based on animal findings, ibrutinib can lead to fetal harm if taken by a pregnant woman. Women of child-bearing potential should be advised to avoid becoming pregnant while taking ibrutinib therapy. If the drug is used during pregnancy or if pregnancy occurs while taking ibrutinib, the patient should be alerted of the potential hazard to the fetus.

Advise women to avoid becoming pregnant while taking ibrutinib due to the risk of fetal harm.

Nursing Mothers

It is not known if ibrutinib is excreted in human milk. Due to the potential for serious adverse events in nursing infants, a decision should be made whether to continue ibrutinib therapy and discontinue nursing or discontinue the drug, considering the importance of the drug to the mother.

Pediatric Use

Safety and efficacy has not been established in the pediatric population.

Geriatric Use

Among a total of 111 MCL patients receiving ibrutinib for the treatment of MCL, 63% were aged 65 years or older. Overall, no differences were noted with regard to effectiveness compared to these and younger study patients. Of note, cardiac (afib, HTN), infectious (pneumonia, cellulitis) and gastrointestinal events (diarrhea, dehydration) were more common among the elderly population.

Among a total of 48 CLL patients, 52% were aged 65 years or older. No overall differences in effectiveness were noted between older and younger patients. Grade 3 or higher adverse events occurred more often among elderly patients (80% of patients 65 yrs or older vs. 61% of younger patients).

Renal Impairment

Renal excretion accounts for < 1% of ibrutinib elimination. Patients with creatinine clearance > 25 ml/min do not have altered ibrutinib exposure. There is no data with regards to patients with creatinine clearance < 25 ml/min or on dialysis.

Hepatic Impairment

Ibrutinib is metabolized in the liver, so patients with hepatic impairment may likely experience significant exposure to the drug. There is insufficient data to support a particular dosing regimen in patients with baseline hepatic insufficiency as patients with AST/ALT > 3x ULN were excluded from the clinical trials.

Sentinel Events

No data.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:
LA/SA for generic name *ibrutinib*: ibritumomab, imatinib, sunitinib, ibutilide, ipilimumab
LA/SA for trade name *Imbruvica:* Invega, Invokana

Drug Interactions

Drug-Drug Interactions

Ibrutinib is primarily metabolized by the cytochrome P450 route, CYP3A4 and CYP2D6 to a minor extent.

CYP3A4 Inhibitors
Among healthy volunteer, concomitant administration of ketoconazole and ibrutinib resulted in increase in ibrutinib C_{max} 29-fold and AUC 24-fold.

Avoid co-administration of ibrutinib with moderate/strong CYP3A4 inhibitors.
Concomitant, chronic use of strong CYP3A4 inhibitors is not recommended. Examples include ritonavir, and nefazodone.

Short-term use (considered 7 days or less) of strong CYP3A4 inhibitors (eg. Antifungals, antibiotics) should be managed by interrupting ibrutinib therapy until the course of inhibitor therapy is no longer needed.

Reduce the dose of ibrutinib if a moderate CYP3A4 inhibitor must be used (eg. Fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products and ciprofloxacin)

Monitor patients closely for signs of ibrutinib toxicity when given with moderate/strong CYP3A4 inhibitors.

Avoid grapefruit and Seville oranges during ibrutinib therapy.

CYP3A4 Inducers
Concomitant administration of ibrutinib with strong CYP3A4 inducers reduces ibrutinib concentrations by 10-fold. Therefore, avoid concomitant use of CYP3A4 inducers such as carbamazepine, rifampin, phenytoin and St. John's Wort. Consider alternative agents with less CYP3A4 inducing activity.

Acquisition Costs

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

There are no published pharmacoeconomic analyses to date.

Conclusions

Outcome in clinically significant area	MCL: Objective Response Rate with no survival or disease-related symptom improvement CLL: Progression-Free Survival, Objective Response Rate
Effect Size	MCL: N/A; ORR 68%; CR 21%; PR 47%; SD/PD 32% CLL: HR for PFS 0.22; p<0.0001; ORR 71%; (2 CR; 34 PR)
Potential Harms	MCL: Low risk Grade 3/4 toxicities: neutropenia 16%; thrombocytopenia 11%; anemia 10%; diarrhea 6%; fatigue 5%; peripheral edema 2%; dyspnea 4%; bleeding events 4% CLL: Low risk The most common grade 3/4 non-hematologic adverse events (≥ 5%) were pneumonia, hypertension, atrial fibrillation, sinusitis, skin infection, dehydration and musculoskeletal pain. Grade 3/4 hematologic events included: thrombocytopenia (10%) and neutropenia (27%).
Net Clinical Benefit	MCL: Minimal - Low benefit with low risk of harm CLL: Substantial –High benefit with low risk of harm

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life
Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio
Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)
Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Mantle Cell Lymphoma

Ibrutinib received accelerated approval for the treatment of relapsed/refractory Mantle Cell Lymphoma. MCL is a rare condition that affects an older male population. In relapsed or refractory cases, there is no standard of care. Treatment is individualized and takes many patient factors into consideration, such as patient age, comorbidities, prior treatment, performance status, bone marrow reserve and side effect profile.

Current therapies in this setting report ORR in the range of 33-92%, with Complete Responses ranging from 8-60% and variable response durations of 5-20 months. The majority of trials evaluating MCL therapies in the relapsed/refractory setting are Phase II, single-arm design with small numbers of participants, reflective of the rare nature of this condition.

Aside from the response rates, differences exist between treatments with regard to FDA-approval, mechanism of action, mode of administration, and toxicity profile. Both bortezomib and lenalidomide have FDA-approval for the treatment of MCL. Bortezomib is approved in patients with MCL who have received at least one prior therapy. Lenalidomide is approved in patients with disease that has relapsed or progressed on two prior therapies, one of which included bortezomib.

Similar to lenalidomide, ibrutinib is an oral formulation. FDA-approval for ibrutinib is based upon an improvement in ORR and limited to patients who have received at least one prior therapy. An improvement in overall survival and/or improvement in disease-related symptoms has not yet been established. The ORR for ibrutinib does not vary based on prior bortezomib therapy. Patients with prior bortezomib exposure and those without showed similar ORR (68 vs. 67%; no prior bortezomib vs. prior bortezomib, respectively).

Chronic Lymphocytic Leukemia

Ibrutinib received FDA-approval for the treatment of CLL in patients who have received at least one prior therapy and CLL with 17p deletion.

Treatment options for relapsed/refractory disease include fludarabine-, bendamustine- or alemtuzumab-based regimens with or without rituximab, ofatumumab monotherapy and ibrutinib. The choice of therapy depends on whether disease has relapsed or is considered refractory, current symptomatology, the time elapse since prior therapies as well as response, patient comorbidities and their ability to tolerate a particular side effect profile.

Overall Response Rate is a commonly used endpoint in CLL trials and reflects both Complete and Partial Responses. The ORR for current therapies range from 25-75% in relapsed/refractory disease. Most of the responses are partial responses (PR) with the minority being complete (CR). CR rates in this setting range from 2-30%. As the majority of responses with ibrutinib were partial, there is some concern that persistence of disease may lead to the development of resistant clones over time. In addition, concern has been expressed with regards to the patients with Richter's Transformation, which is an aggressive lymphoma that can be fatal.

Ibrutinib is an oral formulation that may provide the ease of convenience for patients. Due to primary metabolism via cytochrome P450 route, drug interactions can significantly impact the pharmacodynamics of ibrutinib. Patients receiving antiplatelet or anticoagulant therapies may be at increased risk as bleeding events of any grade were reported in 50-60% of patients. The concern for development of infections and marrow suppression is present with ibrutinib. Although renal excretion is minimal, there have been serious cases of renal toxicity. Close monitoring and dose-modification based on toxicities may be necessary.

As 65% of participants in the Byrd, et al. trial had advanced stage disease and ~ 30% carried mutations associated with poorer prognosis, ibrutinib may be an option for heavily pretreated patients or those not considered appropriate candidates for other options in relapsed/refractory disease.

Results of the recently published RESONATE trial indicate an improvement in PFS (primary endpoint) with the median duration not reached at the follow-up point of 9.4 months. This compares to a median PFS of 8.1 months with ofatumumab. Secondary endpoints of OS and ORR were also statistically significant in the ibrutinib arm. The RESONATE study population was heavily pretreated with a median of 3 prior therapies and good functional status as evidenced by ECOG PS 0 (40%) or 1 (60%). The effect of ibrutinib on PFS was consistent regardless of chromosomal deletions, which affected ~ 60% of the study population.

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Appendix 1: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	•Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases •Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	•Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

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