Ibrutinib (Imbruvica™) Update: Waldenstrom's Macroglobulinemia Indication, First-Line CLL Indication and Hepatic Dosing

National Drug Monograph Addendum

March 2016

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. Updates will be made 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.

This Addendum highlights the latest FDA-approved indication (Waldenstrom's Macroglobulinemia and all lines of Chronic Lymphocytic Leukemia (CLL)) for Ibrutinib as well as the labeling changes subsequent to fulfilling the postmarketing requirement trial that evaluated hepatic impairment on ibrutinib pharmacokinetics.

FDA Approval Information

Description/Mechanism of Action	Ibrutinib is a kinase inhibitor indicated for the treatment of patients with (1) mantle cell lymphoma who have received at least one prior therapy (2) chronic lymphocytic leukemia (3) chronic lymphocytic leukemia with 17p deletion and (4) Waldenstrom's Macroglobulinemia
Indication(s) Under Review	Waldenstrom's Macroglobulinemia (WM) First-line treatment of CLL
Dosage Form(s) Under Review	140 mg capsules
REMS	☐ REMS ☒ No REMs
Pregnancy Rating	Embryo-Fetal Toxic. Can cause fetal harm. Precautions exist for both men and women.

Executive Summary

Efficacy

- FDA approved was based upon an improvement in overall response rate for a rare condition, WM.
- First-line treatment of CLL indication was based upon an improvement in PFS when compared to chlorambucil in an older population (≥ 65 years)

Safety

- Risk of hemorrhage and infections either alone or in conjunction with cytopenias are major safety concerns.
- Prior history of atrial fibrillation may increase potential of cardiac arrhythmias.
- Elderly patients experienced more arrhythmias, hypertension and infections

Other Considerations

Outcome in clinically significant area	WM: ORR 90.5%, Major 73%, 2-yr PFS 69.1%, 2-yr OS 95.2% CLL: PFS NR (Ibrutinib) vs. 18.9 mos (chlorambucil); OS @ 24 mos: 98% (I) vs. 85% (chlorambucil); ORR: 86% (I) vs. 35% (chlorambucil); CR: 4% vs. 2%
Effect Size	WM: ORR 90.5% (95% CI, 80.4-96.4) Major 73% (95% CI, 60.3-83.4) PFS 69.1% (95% CI, 53.2-80.5) OS 95.2% (95% CI, 86-98.4) CLL: PFS HR 0.16 (95% CI, 0.09-0.28); p<0.001; OS HR 0.16 (95% CI, 0.05-0.56); p=0.001;
Potential Harms	WM: Pneumonia 6%; skin infection 2%; thrombocytopenia 13%, neutropenia 19% CLL: Neutropenia 10 vs. 18%; anemia 6 vs. 8%; HTN 4 vs. 0%; pneumonia 4 vs. 2%; diarrhea 4 vs. 0%
Net Clinical Benefit	WM: n/a (expedited review) CLL: minimal (low benefit with low risk of harm)

Potential Impact

Projected place in therapy for WM.

- Ibrutinib is active in previously treated patients with WM with responses noted as early as 4 weeks.
- May be a treatment consideration in those intolerant or no longer responsive to rituximab-based therapy

Projected place in therapy for previously untreated CLL.

- May be a treatment consideration in patients who are not candidates for chemoimmunotherapy (anti-CD20 antibody plus chemotherapy)

Patient convenience.

- Oral therapy taken once daily provides convenience.
- Regular laboratory monitoring is no less frequent, compared to injectable therapies.

Background

New indication

Use in Waldenstrom's Macroglobulinemia approved January, 2015
Updated dosing information in hepatic impairment
Use in first-line treatment of CLL, approved March 2016

Issues to be determined:

- ✓ Evidence of need
- ✓ Does ibrutinib offer advantages to currently available alternatives?
- ✓ What safety issues need to be considered?
- ✓ Can ibrutinib use be managed by the non-formulary process and criteria for use?

Other therapeutic options

*Note: ibrutinib is the only drug with FDA-approval for treatment of WM

[@]Potentially stem-cell toxic, should be avoided if ASCT candidate

ASCT autologous stem cell transplant
P2 phase 2
PN peripheral neuropathy
tcp thrombocytopenia
IRR infusion-related reactions

Other therapeutic options for WM*[1-6]

Formulary Alternatives	Other Considerations	IWWM-7 Consensus preferred therapies based upon symptomatology
Dexamethasone/rituximab/ cyclophosphamide (DRC)	Off label R - Restricted to Oncology and Rheumatology; P2 (untreated) ORR 83%, CR 7%; 2-yr OS 81% Median time to response 4 mos Toxicity: nausea, alopecia, neutropenia	• Cytopenias or organomegaly; • Paraprotein-related neuropathy; • Young patients eligible for ASCT • Elderly patients with poor PS
Thalidomide/rituximab	Off label R - Restricted to Oncology and Rheumatology; ORR 70%; PFS 3 yrs	
R-CHOP vs. CHOP	Off label R - Restricted to Oncology and Rheumatology; ORR 90 vs. 67% (untreated); Toxicity: Gr 3, 4 neutropenia 70% Gr 3, 4 infections 10%	• Young patients eligible for ASCT
Rituximab	Off label R - Restricted to Oncology and Rheumatology; ORR 25-45% Toxicity: IgM flare 40-50%, IRR	• Patients with paraprotein-related neuropathy; • Elderly patients with poor PS
Fludarabine[@]/cyclophosphamide/ rituximab (FCR)	Off label R - Restricted to Oncology and Rheumatology; P2 (untreated) ORR 79%, CR 12%) Toxicity: Gr 3, 4 neutropenia 88%	• Symptomatic hyperviscosity, cryoglobulinemia, or cold agglutinemia

Fludarabine®	Off label P3 (untreated) ORR 49% Toxicity: Gr 3, 4 neutropenia 36%; 2nd malignancy 4%	
Chlorambucil®	Off label P3 (untreated) ORR 39% Toxicity: Gr 3, 4 neutropenia 18%; 2nd malignancy 21%	• Elderly patients not eligible for systemic IV therapy; • Elderly patients with poor PS
Bortezomib/rituximab/ dexamethasone (BRD)	R - Restricted to Oncology and Rheumatology; P2 (untreated) ORR 96%, Med time to response 1.1 mos Toxicity: PN 69% (IV bortezomib) P2 (untreated) ORR 85%, CR 3% Median time to response 3 mos 3-yr OS 82%; 3-yr PFS 67% Toxicity: PN 46% (SubQ bortezomib)	• Cytopenias or organomegaly; • Symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia; • Young patients eligible for ASCT
Non-formulary Alternative (if applicable)	**Other Considerations**	
Bendamustine®/rituximab (BR)	Off label R - Restricted to Oncology and Rheumatology; P2 (untreated) ORR 90%, CR 60% Toxicity: gr 3,4 leukopenia 16%; tcp 3%	• Cytopenias or organomegaly; • Symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia; • Young patients eligible for ASCT
Carfilzomib/rituximab/ dex (CaRD)	Off label R - Restricted to Oncology and Rheumatology; P2 ORR 87% (untreated); VGPR/CR 35%; Toxicity: hyperglycemia 77%, ↑ serum lipase 42%; IRR 19%	

Other Therapeutic Options for First-Line CLL

Formulary Alternatives	**Other Considerations**
Chlorambucil/rituximab (C+R) vs. Chlorambucil (C)	C+R vs. C: ORR 67 vs. 30%; CR 8 vs. 0%; PFS 16 vs. 11 mos; OS no difference C+R vs. C: gr 3,4 neutropenia: 25 vs. 15%, infection rate 11 vs. 14%
Chlorambucil (C) vs. Fludarabine (F)	C vs. F: ORR 51 vs. 72%; CR 0 vs. 7%; PFS 18 vs. 19 mos; OS 64 vs. 46 mos OS Age < 70 yrs: HR 0.7, 95% CI 0.5-0.9; OS Age > 70 yrs: HR 1.0, 95% CI 0.6-1.7; C vs. F: gr 3,4 neutropenia 23 vs. 42%; infection rate 32 vs. 26%
Non-formulary Alternative (if applicable)	**Other Considerations**
Chlorambucil/ofatumumab (C+O) vs. C	C+O vs. C: ORR 82 vs. 69%; CR 14 vs. 1%; PFS 22 vs. 13 mos.; 2-yr OS: 89 vs. 87%; 3-yr OS: 85 vs. 83%
Bendamustine (B)	B vs. C: ORR 68 vs. 31%; PFS 21 vs. 8 mos; OS no difference B vs. C: gr 3,4: neutropenia 23 vs. 10%; thrombocytopenia 12 vs. 8%; anemia 3 vs. 0%
Bendamustine/rituximab (B+R)	ORR 88%; CR 23%; EFS 24 mos Gr 3,4: neutropenia 20%; thrombocytopenia 22%; anemia

	20%; infection 8%
Obinutuzumab/chlorambucil (C-O) vs. C (C)	C-O vs. C: PFS 26.7 vs. 11.1 mos; ORR: 78.2 vs. 33.1%; CR: 20.7 vs. 0%; PR 57.7 vs. 54.1%; OS @ 14 mos: NR vs. NR Gr 3,4: IRR 21 vs. 0%, neutropenia 33 vs. 16%; thrombocytopenia 11 vs. 4%

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to March 2016) using the search terms ibrutinib, Imbruvica,Waldenstrom's Macroglobulinemia and CLL. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Efficacy Measures

IWWM-7 Response Criteria for Waldenstrom Macroglobulinemia[7]

Response Category	Description
Complete Response (CR)	• Absence of serum monoclonal IgM protein my immunofixation • Normal serum IgM level • Complete resolution of extramedullary disease (lymphadenopathy, splenomegaly) if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy
Very Good Partial Response (VGPR)	• Monoclonal IgM protein is detectable • ≥ 90% reduction in serum IgM level from baseline • Complete resolution of extramedullary disease (lymphadenopathy, splenomegaly) if present at baseline • No new signs or symptoms of active disease
Partial response (PR)	• Monoclonal IgM protein is detectable • ≥50 but < 90% reduction in serum IgM level from baseline • Reduction in extramedullary disease (lymphadenopathy, splenomegaly) if present at baseline • No new signs or symptoms of active disease
Minor response (MR)	• Monoclonal IgM protein is detectable • ≥ 25 but < 50% reduction in serum IgM level from baseline • No new signs or symptoms of active disease
Stable disease (SD)	• Monoclonal IgM protein is detectable • < 25% reduction and < 25% increase in serum IgM level from baseline • No progression in extramedullary disease (lymphadenopathy, splenomegaly) • No new signs or symptoms of active disease
Progressive disease	• ≥ 25% increase in serum IgM level from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease*

*An absolute increase of > 5g/L is required when the increase of IgM component is the only applicable criterion.

Efficacy Measures (see Appendix B: Approval Endpoints)

The following outcomes are commonly evaluated in the 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
Waldenstrom's Macroglobulinemia

- The FDA approval of ibrutinib was based on a phase 2 trial in 63 symptomatic patients with WM. These patients had received at least one prior therapy.
- Patients were eligible if they needed treatment per consensus guidelines, had received one or more treatment regimens, had a platelet count of ≥ 50,000/mm^3, hemoglobin ≥ 8g/dL, ANC ≥ 1000/mm^3, SrCr ≤ 2 mg/dL, Total bilirubin ≤ 1.5 mg/dL (≤ 2 mg/dL if attributable to tumor), LFTs ≤ 2.5x ULN, ECOG PS 0-2.
- Patients were excluded if they had CNS lymphoma, clinically significant cardiac disease, were taking warfarin or if they were receiving medication that could prolong the QT interval.
- Ibrutinib 420 mg PO daily was given on twenty-six 4-week cycles until progressive disease or unacceptable toxicity
- Demographics: median age 63 yrs (44-86); male 48%; IPSS score: low 22%; intermediate 43%; high 35%
- Median number of prior therapies 2 (1-9); Prior therapies included: monoclonal antibody 90%; glucocorticoid 67%; proteasome inhibitor 52%; alkylator 51%; nucleoside analog 24%
- Median duration of treatment was 19.1 months (0.5-29.7).
- Primary objective was to determine the overall response rate, which included the rate of minor response, partial response, very good partial response and complete response; in addition to the rate of major response, defined as a complete response or responses with a ≥ 50% reduction in serum IgM levels. Secondary objectives included PFS and drug safety.
- Overall response 90.5%; Major response 73%; est'm 2-yr PFS 69.1%; est'm 2-yr OS 95.2%
- Median time to any response was 4 weeks; partial response was 8 weeks.
    - Results at time of best response: Median serum IgM level declined from 3520 to 880 mg/dL (P<0.001)
    - Median bone marrow involvement decreased from 60 to 25% (p<0.001)
    - Median hemoglobin level increased from 10.5 to 13.8 g/dL (p<0.001)
    - ORR higher among patients with MYD88^{L265P} genotype and without CXCR4 mutations, although improvements were noted among all 3 genotype subgroups.
    - Adenopathy (n=37) was reduced in 68%; remained stable in 24%; increased in 3% (1 pt)
    - Splenomegaly (n=7) was reduced in 57%; stable in 29%; non-evaluable in 14% (1 pt)
    - IgM-related peripheral sensory neuropathy (n=9); 5 with subjective improvement; 4 remained stable
    - Subgroup analysis: high IPSS score prior to therapy, > 3 prior treatment regimens and MYD88^{WT}CXCR4^{WT} genotype were associated with lower rates of PFS

Subgroup Analysis of Overall Responses

Subgroup	Number of patients	ORR (95% CI)
All patients	63	90.5 (80.4-96.4)
Age < 65 yrs	32	93.8 (79.2-99.2)
Age ≥ 65 yrs	31	87.1 (70.2-96.4)
ECOG at baseline = 0	47	91.5 (79.6-97.6)
ECOG at baseline ≥ 1	16	87.5 (61.7-98.4)
WM IPSS		
Low	15	93.3 (68.1-99.8)
Intermediate	27	92.6 (75.7-99.1)
High	21	85.7 (63.7-97.0)
B_2-microglobulin		
≤ 3 mg/L	18	94.4 (72.7-99.9)
> 3 mg/L	43	88.4 (74.9-96.1)
Hemoglobin level		
≤ 11 g/dl	38	92.1 (78.6-98.3)
> 11 g/dL	25	88.0 (68.8-97.5)
IgM		
< 4000 mg/dL	37	89.2 (74.6-97.0)
≥ 4000 mg/dL	26	92.3 (74.9-99.1)
Number of prior regimens		
1-3	40	90.0 (76.3-97.2)
> 3	23	91.3 (72.0-98.9)
Mutation		
MYD88^{WT}CXCR4^{WT}	7	71.4 (29-96.3)
MYD88^{L265P}CXCR4^{WT}	34	100 (89.7-100)
MYD88^{L265P}CXCR4^{WHIM}	21	85.7 (63.7-97.0)

Chronic Lymphocytic Leukemia (previously untreated patients)

- The approval of ibrutinib for the broad indication of CLL that includes indication as a first-line therapy is based upon evidence from a trial comparing ibrutinib vs. chlorambucil in the first-line setting. A phase 3 trial conducted in 269 previously untreated patients with CLL with evidence of active disease and aged ≥ 65 years were included.
- Eligibility included ECOG PS 0-2, ANC ≥ 1000/µL, platelet count ≥ 50,000/µL, AST and ALT < 2.5x ULN, total bilirubin ¸ 1.5x ULN, CrCl ≥ 30 ml/min.
- Patients were randomized 1:1 to either Ibrutinib 420 mg PO daily or chlorambucil 0.5 mg/kg on days 1 & 15 of each 28-day cycle up to a maximum of 12 cycles until progressive disease or unacceptable toxicity. The chlorambucil dose could be increased to a max of 0.8 mg/kg until disease progression, toxicity or lack of response.
- Demographics: median age 73 yrs (70% > 70 yrs); male 65 vs. 61%; Rai stage III or IV 44 vs. 47%; 11q22.3 deletion 21 vs. 19%; bulky disease ≥ 5 cm 40 vs. 30%; cytopenias 53 vs. 55%
- Median duration of treatment was 18.4 months.
- Primary endpoint was PFS, secondary endpoints included ORR, OS and sustained hematologic improvement.
- At time of follow-up, PFS in ibrutinib vs. chlorambucil arms was NR vs. 18.9 months, respectively [HR 0.16 (95% CI 0.09-0.28); p<0.0001]
- OS rate at 24 months was 98 (I) vs. 85% (C) [HR 0.16 (95% CI 0.05-0.56); p=0.001]
- ORR 86% (I) vs. 35% (C) and CR 4% (I) vs. 2% (C)
- Those with sustained hematologic improvement (≥ 56 days) were significantly greater in the ibrutinib arm.

Indirect Comparisons of Regimens in Previously Untreated CLL*

Parameter	Obinutuzumab + C vs. C[7]	Rituximab + C vs. C[7]	Ofatumumab + C vs. C[8]	Ibrutinib Vs. C
Chlorambucil dose	0.5 mg/kg PO days 1 & 15, every 28 days	0.5 mg/kg PO days 1 & 15, every 28 days	10 mg/m2 PO days 1-7, every 28 days	0.5 mg/kg PO days 1 & 15, every 28 days
Population	N = 781 Previously untreated; CIRS > 6 and/or CrCl < 70 ml/min Median CIRS 8 (range, 0-22) Median CrCl 62 ml/min 82% ≥ 3 comorbidities	N = 781 Previously untreated; CIRS > 6 and/or CrCl < 70 ml/min Median CIRS 8 (range, 0-22) Median CrCl 62 ml/min 82% ≥ 3 comorbidities	N=447 Previously untreated; Inappropriate for fludarabine (adv age or comorbidities) 72% ≥ 2 comorbidities 48% CrCl ≤ 70 ml/min	N=269 Previously untreated; Inappropriate for fludarabine, cyclophosphamide or rituximab; 31% CIRS > 6 44% CrCl < 60 ml/min
Age	73 yrs (range, 39-90)	73 yrs (range, 39-90)	69 yrs (range, 35-92) 69% ≥ 65 years	73 yrs (range, 65-90) 70% ≥ 70 years
ECOG PS	Not stated	Not stated	0-2	0-2
Primary endpoint	PFS 26.7 vs. 11.1 mos; HR 0.18 (0.13-0.24); p<0.001	PFS 16.3 vs. 11.1 mos; HR 0.44 (0.34-0.57); P<0.001	PFS 22.4 vs. 13.1 mos; HR 0.57 (0.45-0.72); p<0.001	At 18.4 months: PFS NR vs. 18.9 mos; HR 0.16 (0.09-0.28); p<0.001
Secondary endpoints	Death rate 9 vs. 20%; HR 0.41; 0.23-0.74; p=0.002 ORR 78.2% vs. 33.1%; P<0.001 CR 28.2 vs. 0 DOR 22.4 vs. 9.7 mos	Death rate 15 vs. 20%; HR 0.66; 0.39-1.11; p=0.11 ORR 66.3% vs. 33.1%; P<0.001 CR 8.8 vs. 0 DOR 19.6 vs. 9.7 mos	ORR 82.4% vs. 68.6%; p=0.001 CR 12 vs. 1% DOR 22.1 vs. 13.2 mos	OS @ 24 mos: 98% (I) vs. 85% (c); HR 0.16 (95% CI, 0.05-0.56); p=0.001 ORR 86% (I) vs. 35% (c) CR 4% (I) vs. 2% (c)
Grade 3,4 toxicity	IRR 21% Neutropenia 33% Thrombocytopenia 11%	IRR 4% Neutropenia 28%	Neutropenia 16% Thrombocytopenia 4%	Neutropenia 10 vs. 18%; Anemia 6 vs. 8%; HTN 4 vs. 0%; Pneumonia 4 vs. 2%; Diarrhea 4 vs. 0%

* Anti-CD20 antibody/chlorambucil combinations have not been directly compared in the previously untreated population. The combinations have been directly compared to a control arm of chlorambucil alone. This chart is an indirect comparison of treatments, study population and results.

Safety
(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• None
Warnings/Precautions	• Hemorrhage. Grade 3 or higher bleeding events have occurred in up to 6% of patients. Bleeding events of any grade occurred in 50% of patients. Risk of bleed may occur in patients receiving antiplatelet or anticoagulant therapies. Consider risk-benefit of withholding ibrutinib for at least 3-7 days pre and post-surgery depending upon the type of surgery and risk of bleeding. • Infections. Grade 3 or greater infections occurred in 14-26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in treated patients. Monitor for fever and infections. Evaluate promptly. • Cytopenias. Grade 3, 4 cytopenias include neutropenia (19-29%), thrombocytopenia (5-17%) and anemia (0-9%). Monitor CBCs monthly. • Atrial Fibrillation. Atrial fibrillation (afib) and atrial flutter (6-9%) has occurred, especially in those with cardiac risk factors, acute infections and prior history of atrial fibrillation. Periodically monitor patients clinically for afib. If arrhythmic symptoms or new onset dyspnea develops, perform an ECG. If afib persists, consider risk-benefit of ibrutinib and dose modification. • Hypertension (range, 6-17%). The median time to onset of HTN is 4.5 months (range, 0.03-18.4 months). Patients should be monitored for new onset HTN and pre-existing HTN that is not adequately controlled during therapy. Anti-hypertensive medications should be adjusted as needed. • Second primary malignancies (range, 5-16%). Most frequent second primary malignancy to develop in patients treated with ibrutinib was non-melanoma skin cancer (4-13%). • Tumor Lysis Syndrome (TLS). TLS has been reported. Monitor patients closely and use appropriate precautions in those at high risk for TLS. • Embryo-Fetal Toxicity. Ibrutinib can cause fetal harm when given to a pregnant woman. Advise women to avoid becoming pregnant while taking ibrutinib and for one month after end of therapy. If used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Safety Considerations

- Evaluate chronic patient medications (prescription and OTC) for those that may add to the bleed risk. Of note, fish-oil supplements were thought to contribute to grade 2 epistaxis events during the WM trial. Events resolved when the supplements were discontinued.
- Consider tumor lysis risk prior to therapy initiation so that appropriate precautions to prevent TLS can be taken.
- Elderly patients with WM experienced more afib, htn, pneumonia and urinary tract infections than younger patients.
- Heavily pretreated WM patients were more likely to experience severe neutropenia (7/9; 78%) and thrombocytopenia (7/8; 88%).
- Higher levels of peripheral lymphocytosis were noted in WM patients who had major responses.

Adverse Reactions (based upon open label trial in 63 previously treated patients with WM)

Common adverse reactions	WM: $\geq$ 20% neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms and fatigue CLL: $\geq$ 20% diarrhea, fatigue, cough, nausea
Death/Serious adverse reactions	WM Grade 3 or 4 events: thrombocytopenia 13%, neutropenia 19%, anemia 8%, pneumonia 6%, skin infection 2% CLL grade 3 or 4 events: neutropenia 10%, anemia 6%, HTN 4%, pneumonia

	4%, hemorrhage 4%
Discontinuations due to adverse reactions	WM: 6% discontinued treatment due to adverse events; Adverse events lead to dose reduction in 11% CLL: 9% discontinued treatment due to adverse events; Reasons include atrial fibrillation (2 patients) and hemorrhage (3 patients); 2 deaths due to unknown causes

Drug Interactions

Drug-Drug Interactions
CYP3A4 Inhibitors

- 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).

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.

Drug-food Interactions

- Avoid grapefruit and Seville oranges during ibrutinib therapy.

Other Considerations

Use in Waldenstrom's Macroglobulinemia

- WM is considered to be a rare condition, with an incidence rate of about 3 cases per million people per year in the United States. Roughly 1,000 to 1,500 people are diagnosed with WM each year in the U.S.
- WM is almost twice as common in men as it is in women, and it is more common among whites than African Americans.
- There are few cases of WM in younger people, but the average age at the time of diagnosis of WM is in the mid-60s.
- Median survival of patients with WM is approximately 5 years. A search of ICD-9 code (273.3) in FY15 indicates that there are 1124 unique patients with WM.
- $MYD88^{L265P}$ is a common mutation (> 90%) among patients with WM. Lower responses to ibrutinib were noted among $MYD88^{WT}$.
- Evidence leading to FDA-approval evaluated ibrutinib after prior therapies. Regardless of number of prior therapies, responses to ibrutinib were noted.
- Some experts consider ibrutinib as an alternative first-line therapy for those who are not appropriate candidates for rituximab chemoimmunotherapy.
- Hepatitis C has been associated with WM, especially those with cryoglobulinemia. Liver function tests and hepatitis C serology should be obtained.
- If considering rituximab therapy, screening for hepatitis B virus should be performed as there is a high chance of hepatitis B reactivation with anti-CD20 therapy. Patients HBsAg-positive/anti-HBc-positive patients that are about to receive immunosuppressive therapy should also receive antiviral therapy during and for 6-12 months after completing therapy.

Use in Previously Untreated CLL

- The FDA granted broad approval for use of ibrutinib in CLL. This latest change in CLL indication now includes data that supports use in the first-line setting, as well as relapsed/refractory disease.
- RESONATE-2 was a phase 3 trial that compared ibrutinib vs. chlorambucil in previously untreated elderly patients (defined as age $\geq$ 65 years) with active CLL. The comparator arm of chlorambucil alone could be a

questionable comparison, as chlorambucil, which was once the standard-of-care, has since been replaced with chemoimmunotherapy, which has been proven to be better than chlorambucil alone.[15] NCCN Guidelines version 2.2016 give ibrutinib a category 1 rating in the first-line CLL setting for (1) frail patients with significant comorbidities and (2) patients ≥ 70 years and younger patients with significant comorbidities. Chemoimmunotherapy is recommended for those age < 70 years without significant comorbidities.

- Questions remain for the CLL patient in the first-line setting, such as ibrutinib resistance patterns, sequential therapies post-ibrutinib, impact of non-adherence, duration of therapy, long-term safety data especially with regard to cardiovascular health and second primary malignancies and impact on quality of life.

Outcome in clinically significant area	WM: ORR 90.5%, Major 73%, 2-yr PFS 69.1%, 2-yr OS 95.2% CLL: PFS NR (Ibrutinib) vs. 18.9 mos (chlorambucil); OS @ 24 mos: 98% (I) vs. 85% (chlorambucil); ORR: 86% (I) vs. 35% (chlorambucil); CR: 4% vs. 2%
Effect Size	WM: ORR 90.5% (95% CI, 80.4-96.4) Major 73% (95% CI, 60.3-83.4) PFS 69.1% (95% CI, 53.2-80.5) OS 95.2% (95% CI, 86-98.4) CLL: PFS HR 0.16 (95% CI, 0.09-0.28); p<0.001; OS HR 0.16 (95% CI, 0.05-0.56); p=0.001;
Potential Harms	WM: Pneumonia 6%; skin infection 2%; thrombocytopenia 13%, neutropenia 19% CLL: Neutropenia 10 vs. 18%; anemia 6 vs. 8%; HTN 4 vs. 0%; pneumonia 4 vs. 2%; diarrhea 4 vs. 0%
Net Clinical Benefit	WM: n/a (expedited review) CLL: minimal (low 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)

Dosing and Administration

Waldenstrom's Macroglobulinemia and 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.

Recommended dose modifications for toxicity based on occurrence

Toxicity occurrence	WM and CLL dose modification after recovery; starting dose = 420 mg
First	Restart at 420 mg daily
Second	Restart at 280 mg daily
Third	Restart at 140 mg daily
Fourth	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.

Dose modification for Use in Hepatic Impairment

The recommended dose for patients with mild liver impairment (Child-Pugh class A) is 140 mg daily (one capsule). Avoid use of ibrutinib in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C).

Special Populations (Adults)

	Comments
Elderly	• Of 552 patients within the clinical trial population, 69% were 65 years or older and 24% were ≥ 75 years of age. No overall differences in effectiveness were noted between younger and older populations. Pneumonia (≥ grade 3) occurred more frequently among elderly patients.
Pregnancy	• 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.
Females and Males of Reproductive Potential	• Verify the pregnancy status of females of reproductive potential prior to starting ibrutinib • Advise females to avoid pregnancy during and for one month after ending ibrutinib therapy. • Advise males to avoid fathering a child during therapy and for 1 month following the last dose of ibrutinib.
Lactation	• 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.
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	• In a hepatic impairment study, data indicated increased ibrutinib exposure. Following a single dose, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to those with normal liver function. Monitor patients for signs of drug toxicity and follow dose

	modification guidance. It is not recommended to administer ibrutinib to those with moderate or severe hepatic impairment. The dose should be reduced in those with mild hepatic impairment.
Pharmacogenetics/genomics	• No data identified
Plasmapheresis	• Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with ibrutinib. Dose modifications are not required in these situations.

References

1. Dimopoulos MA, Anagnostopoulos A, Kyrsonis MC, et al. Primary treatment of Waldenstrom Macroglobulinemia with dexamethasone, rituximab and cyclophosphamide. J Clin Oncol 2007; 25: 3344.

2. Treon SP, Loakimidis L, Soumerai JD, et al. Primary therapy of Waldenstrom Macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. J Clin Oncol 2009; 27: 3830.

3. Dimopoulos MA, Garcia-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom Macroglobulinemia with weekly bortezomib, low-dose dexamethasone and rituximab: long-term results of a phase 2 study of the European Myeloma Network. Blood 2013; 122: 3276.

4. Rummel MJ, Al-Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-hodgkin's lymphoma. J Clin Oncol 2005; 23: 3383.

5. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab and dexamethasone treatment offers a neuropathy-sparing approach for treating Waldenstrom's Macroglobulinemia. Blood 2014; 124: 503.

6. Leblond V, Johnson S, Chevret S, et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenstrom macroglobulinemia, marginal zone lymphoma or lymphoplasmacytic lymphoma. J Clin Oncol 2013; 31: 301.

7. Dimopoulos MA, Kastritis E, Owen RG, et al. Treatment Recommendation for Patients with Waldenstrom Macroglobulinemia and Related Disorders: IWWM-7 Consensus. Blood 2014; 124: 1404.

8. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in Previously Treated Waldenstrom's Macroglobulinemia. N Engl J Med 2015; 372: 1430.

9. Imbruvica (ibrutinib) Prescribing Information. Pharmacyclics, Inc. of Sunnyvale, CA and Janssen Biotech, Inc. of Horsham, PA. Revised 3/ 2016.

10. Dimopoulos MA, Trotman J, Tedeschi A, et ak, Ibrutinib Therapy in Rituximab-Refractory Patients with Waldenström's Macroglobulinemia: Initial Results from an International, Multicenter, Open-Label Phase 3 Substudy (iNNOVATETM). Poster Presentation at American Society of Hematology (ASH) 2015. Blood 2015; 126: 2745.

11. Treon SP. How I treat Waldenstrom Macroglobulinemia. Blood 2015; 126: 721.

12. Waldenstrom's Macroglobulinema. www.cancer.org/cancer/waldenstrommacroglobulinemia/detailedguide/waldenstrom-macroglobulinemia-key-statistics-w-m. 2016. American Cancer Society, Inc.

13. Hwang JP, Somerfield MR, Alston-Johnson DE, et al. Hepatitis B Virus Screening for Patients with Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update. J Clin Oncol 2015; DOI: 10.1200/JCO.2015.61.3745

14. Burger JA, Tedeschi A, Barr PM, et al. for the RESONATE-2 Investigators. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med 2015; 373: 2425-2437.

15. Hillmen P, Robak T, Janssens A, et al. for the COMPLEMENT 1 Study Investigators. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukemia (COMPLEMENT 1): a randomized, multicenter, open-label phase 3 trial. Lancet 2015; 385: 1873-1883.

16. VHA Guidance on Determining Clinical Benefit of High Cost Oncology Drugs. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives,VHA Oncology Field Advisory Committee, and High Cost Oncology Drug Workgroup. Veterans Health Administration, Department of Veterans Affairs; May 2012

Updated Prepared March 2016. Contact person: Berni Heron, Pharm.D., BCOP
National PBM Clinical Pharmacy Program Manager