

יוני 2017

רופא/ה נכבד/ה
רוקח/ת נכבד/ת

ברצוננו להביא לידיעתכם כי משרד הבריאות אישר את תוספת ההתוויה ומשטר המינון הבאים לתכשיר **IMBRUVICA**:

נוסח ההתוויה החדשה כפי שאושר על ידי משרד הבריאות הינו :

IMBRUVICA is indicated for the first line treatment of adult patients, 65 years of age or older, with chronic lymphocytic leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)

התוויה זו נוספת להתוויות הבאות המאושרות לתכשיר :

The treatment of adult patients with MCL (Mantle Cell Lymphoma) who have received at least one prior therapy.

Imbruvica is indicated for the treatment of adult patients with Chronic Lymphocytic Leukemia (CLL) who have received at least one prior therapy.

IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) /Small Lymphocytic Lymphoma (SLL) with 17p deletion

Imbruvica is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

תוספת משטר המינון :

For patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma, without del(17p), who have received at least one prior therapy The recommended dose of IMBRUVICA when used in combination with bendamustine and rituximab (administered every 28 days for up to 6 cycles) is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

J-C Health Care Ltd.

כמו כן, ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא ולצרכן של התכשיר.

השינויים מסומנים בעלונים המצורפים כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק בכחול נגרע ממנו.

העלונים מפורסמים במלואם במאגר התרופות שבאתר משרד הבריאות.

כמו כן, ניתן לקבל את העלונים המודפסים בפניה אלינו לטלפון 09-9591111 .

להלן העדכונים.

בברכה,

צפריר כהן
רוקח ממונה

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

IMBRUVICA is indicated for the treatment of adult 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 of clinical benefit in confirmatory trials [see *Clinical Studies (14.1)*].

1.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

IMBRUVICA is indicated for the first line treatment of adult patients, 65 years of age or older, with chronic lymphocytic leukemia (CLL)/SLL [see *Clinical Studies (14.2)*].

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy [see *Clinical Studies (14.2)*].

1.3 Chronic Lymphocytic Leukemia /Small Lymphocytic Lymphoma with 17p deletion

IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) /Small Lymphocytic Lymphoma with 17p deletion [see *Clinical Studies (14.2)*].

1.4 Waldenström's Macroglobulinemia

IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) [see *Clinical Studies (14.3)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

Administer IMBRUVICA orally once daily at approximately the same time each day. Swallow the capsules whole with water. Do not open, break, or chew the

capsules.

2.2 Dosage

Mantle Cell Lymphoma

The recommended dose of IMBRUVICA for MCL is 560 mg (four 140 mg capsules) orally once daily **until disease progression or unacceptable toxicity**.

Chronic Lymphocytic Leukemia/ **Small Lymphocytic Lymphoma** and Waldenström's Macroglobulinemia

The recommended dose of IMBRUVICA for CLL/**SLL** and WM is 420 mg (three 140 mg capsules) orally once daily **until disease progression or unacceptable toxicity**.

For patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma, without del(17p), who have received at least one prior therapy The recommended dose of IMBRUVICA when used in combination with bendamustine and rituximab (administered every 28 days for up to 6 cycles) is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity.

2.3 Dose Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or greater non-hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA.

Recommended dose modifications are described below:

Toxicity Occurrence	MCL Dose Modification After Recovery Starting Dose = 560 mg	CLL/ SLL and WM 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 IMBRUVICA	Discontinue IMBRUVICA

2.4 Dose Modifications for Use with CYP3A Inhibitors

Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone, ~~eobieista~~) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting IMBRUVICA therapy until the CYP3A inhibitor is no longer needed [*see Drug Interactions (7.1)*].

Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, ~~amiodarone, dronedarone~~ and ciprofloxacin) [*see Drug Interactions (7.1)*].

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity.

2.5 Dose Modifications for Use in Hepatic Impairment

For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule). Avoid the use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) [*see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

2. 6 Missed Dose

If a dose of IMBRUVICA is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of IMBRUVICA should not be taken to make up for the missed dose.

3 DOSAGE FORMS AND STRENGTHS

140 mg capsules

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

~~Use of preparations containing St. John's Wort is contraindicated in patients treated with IMBRUVICA.~~

5 WARNINGS AND PRECAUTIONS

5.1 Haemorrhage

Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial haemorrhage, [including subdural hematoma], gastrointestinal bleeding, hematuria and post procedural haemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising, epistaxis and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies **and patients should be monitored for signs of bleeding.**

~~Patients were excluded from participation in IMBRUVICA phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA. Supplements such as fish oil and vitamin E preparations should be avoided.~~

~~Patients with congenital bleeding diathesis have not been studied.~~

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post- surgery depending upon the type of surgery and the risk of bleeding [see *Clinical Studies (14)*].

5.2 Infections

Fatal and non-fatal infections **have occurred with IMBRUVICA therapy**~~(including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) have occurred with IMBRUVICA therapy. Some of these infections have been associated with hospitalization and death. Most patients with fatal infections also had neutropenia.~~

Grade 3 or greater infections occurred in 14% to ~~26%~~ **29%** of patients. [See *Adverse Reactions (6.1), (6.2)*]. Cases of progressive multifocal leukoencephalopathy (PML) **and Pneumocystis jirovecii pneumonia (PJP)** have occurred in patients treated with IMBRUVICA. **Evaluate** ~~Monitor~~ patients for fever, **neutropenia** and infections and **treat appropriately** ~~evaluate promptly~~.

5.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, ~~49-13~~ to 29%) thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to ~~913~~%) **based on laboratory measurements** occurred in patients treated with **single agent** IMBRUVICA.

Monitor complete blood counts monthly.

5.4 Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, **hypertension**, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients

clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see Dosage and Administration (2.3)].

~~In patients with preexisting atrial fibrillation requiring anticoagulant therapy, alternative treatment options to IMBRUVICA should be considered. In patients who develop atrial fibrillation on therapy with IMBRUVICA a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to IMBRUVICA are non-suitable, tightly controlled treatment with anticoagulants should be considered.~~

5.5 Hypertension

Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

5.6 Second Primary Malignancies

Other malignancies (range, 5.3 to 16% 14%) including non-skin carcinomas (range, 1 to 4% 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4.2 to 13% 11%).

5.7 Tumor Lysis Syndrome

Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (eg, high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate. ~~take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).~~

5.8 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. ~~Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures.~~ Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient

should be apprised of the potential hazard to a fetus [see *Use in Specific Populations* (8.1)].

~~5.8 5.9 — Leukostasis~~

~~Cases of leukostasis have been reported in patients treated with IMBRUVICA. A high number of circulating lymphocytes (> 400,000/mcL) may confer increased risk. Consider temporarily holding IMBRUVICA. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.~~

~~5.9 5.10 — Effects on the QT interval~~

~~In a phase 2 study, ECG evaluations showed IMBRUVICA produced a mild decrease in QTcF interval (mean 7.5 ms). Although the underlying mechanism and safety relevance of this finding is not known, clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (e.g., Congenital Short QT Syndrome or patients with a family history of such a syndrome).~~

~~5.10 5.11 — Effects on ability to drive and use machines~~

~~Fatigue, dizziness and asthenia have been reported in some patients taking IMBRUVICA and should be considered when assessing a patient's ability to drive or operate machines~~

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage [see *Warnings and Precautions* (5.1)]
- Infections [see *Warnings and Precautions* (5.2)]
- Cytopenia [see *Warnings and Precautions* (5.3)]
- Atrial Fibrillation [see *Warnings and Precautions* (5.4)]
- **Hypertension [see *Warnings and Precautions* (5.5)]**
- Second Primary Malignancies [see *Warnings and Precautions* (5.6)]
- Tumor Lysis Syndrome [see *Warnings and Precautions* (5.7)]

~~Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.~~

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma

The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions ($\geq 20\%$) 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 (See Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions ($\geq 5\%$) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of $\geq 10\%$ are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in $\geq 10\%$ of Patients with Mantle Cell Lymphoma (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1

General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

~~The data described below reflect exposure to IMBRUVICA in an open label clinical trial (study 1) that included 48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.~~

The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

~~The most commonly occurring adverse reactions in Study 1 and Study 2 ($\geq 20\%$) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea and pyrexia.~~

~~Approximately five percent of patients receiving IMBRUVICA in Study 1 and Study 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.~~

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA ($\geq 20\%$) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1

Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=~~48~~ 51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL

occurring at a rate of $\geq 10\%$ with a median duration of treatment of 15.6 months are presented in Table 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in $\geq 10\%$ of Patients with CLL/SLL (N=~~51~~ 48) in study 1

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	63 59	4
	Constipation	23 22	2
	Nausea	21 20	2
	Stomatitis	21 20	0
	Vomiting	19 18	2
	Abdominal pain	15 14	0
	Dyspepsia	13 12	0
Infections and infestations	Upper respiratory tract infection	48 47	2
	Sinusitis	21 22	6
	Skin infection	17 16	6
	Pneumonia	10 12	8 10
	Urinary tract infection	10 12	0 2
General disorders and administration site conditions	Fatigue	31 33	4 6
	Pyrexia	25 24	2
	Peripheral edema	23 22	0
	Asthenia	13 14	4 6
	Chills	13 12	0
Skin and subcutaneous tissue disorders	Bruising	54 51	2
	Rash	27 25	0
	Petechiae	17 16	0
Respiratory, thoracic and mediastinal disorders	Cough	19 22	0
	Oropharyngeal pain	15 14	0
	Dyspnea	10 12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	27 25	6
	Arthralgia	23 24	0
	Muscle spasms	19 18	2
Nervous system disorders	Dizziness	21 20	0
	Headache	19 18	2
	Peripheral neuropathy	10	0
Metabolism and nutrition disorders	Decreased appetite	17 16	2

Neoplasms benign, malignant, unspecified	Second malignancies*	10 *- 12 *	0
Injury, poisoning and procedural complications	Laceration	10	2
Psychiatric disorders	Anxiety	10	0
	Insomnia	10	0
Vascular disorders	Hypertension	17 -16	8

*One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=~~51~~ ~~48~~) in study 1

	Percent of Patients (N= 51 48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71 -69	10 -12
Neutrophils Decreased	54 -53	27 -26
Hemoglobin Decreased	44 -43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions

STUDY 2

Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2 in patients with previously treated CLL/SLL.

Table 5: ~~Non-Hematologic~~ Adverse Reactions Reported in ≥ 10% of patients and at least 2% Greater in the IMBRUVICA Treated Arm in Patients Reported in Study 2

Body system Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				

Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Fatigue	28	2	30	2
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

* Based on laboratory measurements per IWCLL criteria

Study 3

Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil of 7.1 months in Study 3.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3

Body system Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4

Body system Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

Study 4

Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients in Study 4

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16

Skin and subcutaneous tissue disorders				
Rash *	32	4	25	1
Bruising *	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain *	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension *	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

<1 used for frequency above 0 and below 0.5%

* Includes multiple ADR terms

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

Waldenström's Macroglobulinemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial ($\geq 20\%$) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 9: Non-Hematologic Adverse Reactions in $\geq 10\%$ of Patients with Waldenström's Macroglobulinemia (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and Administration site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0

Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The system organ class and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Additional Important Adverse Reactions

Diarrhea

Diarrhea of any grade occurred at a rate of 43% (range, 36% to 63%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 15%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 12 days (range, 0 to 627), of Grade 2 was 37 days (range, 1 to 667) and of Grade 3 was 71 days (range, 3 to 627). Of the patients who reported diarrhea, 83% had complete resolution, 1% had partial improvement and 16% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance

Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to

414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days). ~~Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 88 days (range, 1 to 414 days). Of the patients with visual disturbance, 64% had complete resolution and 36% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 281 days).~~

6. 2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary disorders: ~~Severe liver toxicities, such as~~ hepatic failure (includes multiple terms)

Respiratory disorders: interstitial lung disease (includes multiple terms)

Metabolic and nutrition disorders: tumor lysis syndrome [see *Warnings & Precautions* (5.7)]

- Immune system disorders: anaphylactic shock, angioedema, urticaria

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasia

~~Skin and subcutaneous tissue disorders: Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema~~

~~Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported. Severe liver toxicities, such as hepatic failure, have also been reported.~~

~~Additional adverse events:~~

~~Dry mouth (common)~~

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A).

In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng·hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity [see *Dosage and Administration* (2.4)].

~~Simulations using clinically relevant fasted conditions suggested that the mild CYP3A4 inhibitors azithromycin and fluvoxamine may increase the AUC of ibrutinib by < 2-fold. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed.~~

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A [see *Dosage and Administration* (2.4), and *Clinical Pharmacology* (12.3)].

7.2 CYP3A Inducers

Administration of IMBRUVICA with rifampin, a strong CYP3A inducer decreased ibrutinib C_{max} and AUC by approximately 13 and 10- fold, respectively.

~~Co-administration of CYP3A4 inducers may lead to decreased IMBRUVICA exposure and consequently a risk for lack of efficacy.~~

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction [see Clinical Pharmacology (12.3)]. ~~efficacy. Mild inducers may be used concomitantly with IMBRUVICA, however, patients should be monitored for potential lack of efficacy.~~

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

~~Women of child bearing potential/Contraception in females~~

~~Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months after ending treatment. Therefore, women of child bearing potential must use highly effective contraceptive measures while taking IMBRUVICA and for three months after stopping treatment. It is currently unknown whether ibrutinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method~~

IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations [see Data].

~~Pregnancy~~

If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Animal Data

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at ~~oral~~ doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased ~~resorptions and~~ post-implantation loss. The dose of 80 mg/kg/day in ~~animals rats~~ is

approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in ~~animals~~ rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternbrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

8.2 Lactation

~~It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.~~

Risk Summary

There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 3 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking IMBRUVICA and for three months after stopping treatment. It is currently unknown whether ibrutinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

8.4 Pediatric Use

The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

8.5 Geriatric Use

~~Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis), gastrointestinal events (diarrhea, constipation and dehydration), anaemia and dizziness occurred more frequently among elderly patients.~~

~~Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) [see Clinical Studies (14.2)].~~

~~Of the 63 patients treated for WM, 59% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), and infections (pneumonia and urinary tract infection) occurred more frequently among elderly patients.~~

Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age,

while 21% were ≥ 75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

8.6 Renal Impairment

~~Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CL_{cr}) > 25 mL/min. Hydration should be maintained and serum creatinine levels monitored periodically. Administer IMBRUVICA to patients with severe renal impairment (< 30 mL/min Creatinine clearance) only if the benefit outweighs the risk and monitor patients closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis [see Clinical Pharmacology (12.3)].~~

8.6 Hepatic Impairment

Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function.

~~The safety of IMBRUVICA has not been evaluated in patients with hepatic impairment.~~
The safety of IMBRUVICA has not been evaluated in cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)].

8.8 Females and Males of Reproductive Potential

~~Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm [see Use in Specific Populations (8.1)].~~

~~Women of childbearing potential must use a highly effective method of contraception while taking IMBRUVICA.~~

8.9 Severe cardiac disease

~~Patients with severe cardiovascular disease were excluded from IMBRUVICA clinical studies.~~

8.7 Plasmapheresis

Management of hyperviscosity in patients with WM may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

10 OVERDOSAGE

Symptoms and signs

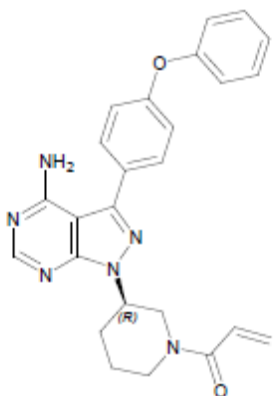
~~There are limited data on the effects of IMBRUVICA overdose. No Maximum-Tolerated Dose was reached in the Phase 1 study in which patients received up to 12.5 mg/kg/day (1400 mg/day). In a separate study, one healthy subject who received a dose of 1680 mg experienced reversible Grade 4 hepatic enzyme increases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. There is no specific antidote for IMBRUVICA. Patients who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment~~

There is no specific experience in the management of ibrutinib overdose in patients. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Closely monitor patients who ingest more than the recommended dosage and provide appropriate supportive treatment.

11 DESCRIPTION

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula C₂₅H₂₄N₆O₂ and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water.

The chemical name for ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:



IMBRUVICA (ibrutinib) capsules for oral administration are supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient. Each capsule also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink. Each white opaque capsule is marked with “ibr 140 mg” in black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibrutinib is a small-molecule inhibitor of 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.

12.2 Pharmacodynamics

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

In healthy subjects, at a single dose 3 times the maximum recommended dose (1680 mg), ibrutinib did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Ibrutinib is absorbed after oral administration with a median T_{max} of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean \pm standard deviation) observed in patients at 560 mg is 953 ± 705 ng·h/mL and in patients at 420 mg is 680 ± 517 ng·h/mL. Absolute bioavailability in fasted condition ($n = 8$) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. Administration with food increases ibrutinib C_{max} and AUC by approximately 2 to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting.

Distribution

Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution (V_d) was 683 L, and the apparent volume of distribution at steady state ($V_{d,ss}/F$) was approximately 10000 L.

Metabolism

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.

Elimination

Intravenous clearance was 62 and 76 L/h in fasted and fed conditions, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed conditions, respectively. The half-life of ibrutinib is 4 to 6 hours.

Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

Age

In older patients (67 to 81 years), there is a 14% higher ibrutinib exposure predicted. Dose adjustment by age is not warranted.

Gender

Gender does not alter ibrutinib systemic clearance.

Renal Impairment

Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is < 10% of the dose. Creatinine clearance > 25 mL/min had no influence on the exposure to IMBRUVICA. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or in patients on dialysis.

Hepatic Impairment

Ibrutinib is metabolized in the liver.

In a hepatic impairment trial, a single dose of 140 mg of IMBRUVICA was administered in non-cancer subjects. Ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold, respectively, in subjects with mild (n=6), moderate (n=10) and severe (n=8) hepatic impairment relative to subjects with normal liver function. Ibrutinib C_{max} increased 5.2-, 8.8- and 7.0-fold, respectively, in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal liver function [see *Use in Specific Populations* (8.7)].

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inhibitors

In a sequential design trial of 18 healthy, fasted volunteers, a single dose of 120 mg of IMBRUVICA was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 - 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC 29-fold and 24-fold, respectively.

Simulations using fasted conditions indicate that moderate CYP3A inhibitors diltiazem and erythromycin may increase AUC of ibrutinib by 5- to 8-fold.

Coadministration of Ibrutinib with CYP3A Inducers

PK data from a dedicated drug interaction trial showed that rifampin (a strong CYP3A inducer) decreases ibrutinib C_{max} and AUC by more than 13 and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of Ibrutinib by up to 3-fold.

Coadministration of Ibrutinib with CYP Substrates

In vitro studies indicated that ibrutinib (I/K_i < 0.07 using mean C_{max} at 560 mg) and PCI-45227 (I/K_i < 0.03) are unlikely to be inhibitors of any major CYPs at clinical doses. Both ibrutinib and the PCI-45227 are weak inducers of CYP450 isoenzymes in vitro.

Coadministration of Ibrutinib with Substrates of Transporters

In vitro studies indicated that ibrutinib is not a substrate of P-gp (p-glycoprotein) or BCRP (breast cancer resistance protein) transporters but is an in vitro inhibitor of P-gp and BCRP. Systemic ibrutinib is unlikely to be an inhibitor of P-gp at clinical doses ($[I]_1/K_i < 0.1$) but may inhibit BCRP. ~~However, it~~ Ibrutinib may have an effect on P-gp or BCRP substrates in the GI tract due to higher local concentrations after an oral dose. Co-administration of oral narrow therapeutic index P-gp or BCRP substrates (e.g., digoxin, methotrexate) with IMBRUVICA may increase their blood concentration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Rats were administered oral daily doses of ibrutinib for 4 weeks prior to pairing and during pairing in males and 2 weeks prior to pairing and during pairing in females. Treatment of female rats continued following pregnancy up to gestation day (GD) 7, and treatment of male rats continued until end of study. No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg).

~~Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.~~

14 CLINICAL STUDIES

14.1 Mantle Cell Lymphoma

The safety and efficacy of IMBRUVICA in patients with MCL who have received at least one prior therapy were evaluated in an open-label, multi-center, single-arm trial of 111 previously treated patients. 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 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplant. At baseline, 39% of subjects had at least one tumor ≥ 5 cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening.

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 11.

Table 11: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with Mantle Cell Lymphoma

	Total (N=111)
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months (95% CI)	17.5 (15.8, NR)

CI = confidence interval; CR = complete response; PR = partial response; NR = not reached

An Independent Review Committee (IRC) performed independent reading and interpretation of imaging scans. The IRC review demonstrated an ORR of 69%.

The median time to response was 1.9 months.

Lymphocytosis

Upon initiation of IMBRUVICA, a temporary increase in lymphocyte counts (i.e., $\geq 50\%$ increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 33% of patients in the MCL study. The onset of isolated lymphocytosis occurs during the first few weeks of IMBRUVICA therapy and resolves by a median of 8 weeks.

14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

The safety and efficacy of IMBRUVICA in patients with CLL/SLL ~~who have received at least one prior therapy~~ were demonstrated in one uncontrolled trial and three randomized, controlled trials.

Study 1

An open-label, multi-center trial was conducted in 48 previously treated CLL patients. The median age was 67 years (range, 37 to 82 years), 71% were male, and 94% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median

time since diagnosis was 80 months and the median number of prior treatments was 4 (range, 1 to 12 treatments). At baseline, 46% of subjects had at least one tumor ≥ 5 cm.

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The ORR and 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 ofatumumab was conducted in patients with previously treated CLL or SLL. Patients (n=391) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression, or unacceptable toxicity or ofatumumab at an initial dose of 300 mg, followed one week later by a dose of 2000 mg weekly for 7 doses and then every 4 weeks for 4 additional doses. Fifty seven patients randomized to ofatumumab crossed over following progression to receive IMBRUVICA. The median age was 67 years (range, 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The trial enrolled 373 patients with CLL and 18 patients with SLL. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range, 1 to 13 treatments). At baseline, 58% of patients had at least one tumor ≥ 5 cm. Thirty-two percent of patients had 17p deletion.

Efficacy results for Study 2 are shown in Table 12 and the Kaplan-Meier curves for PFS assessed by independent review committee (IRC) according to IWCLL criteria, and OS are shown in Figures 1 and 2, respectively.

Table 12: Efficacy Results in Study 2

Endpoint	IMBRUVICA N=195	Ofatumumab N=196
Progression Free Survival^b		
Number of events (%)	35 (17.9)	111 (56.6)
Disease progression	26	93
Death events	9	18
Median (95% CI), months	NR	8.1 (7.2, 8.3)
HR (95% CI)	0.22 (0.15, 0.32)	
Overall Survival^a		
Number of death (%)	16 (8.2)	33 (16.8)
HR (95% CI)	0.43 (0.24, 0.79)	
Overall Response Rate ^b	42.6%	4.1%

^aMedian OS not reached for either arm

^bIRC evaluated. All partial responses achieved; none of the patients achieved a complete response.

CI= confidence interval; HR= hazard ratio; NR= not reached

Figure 1: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study 2

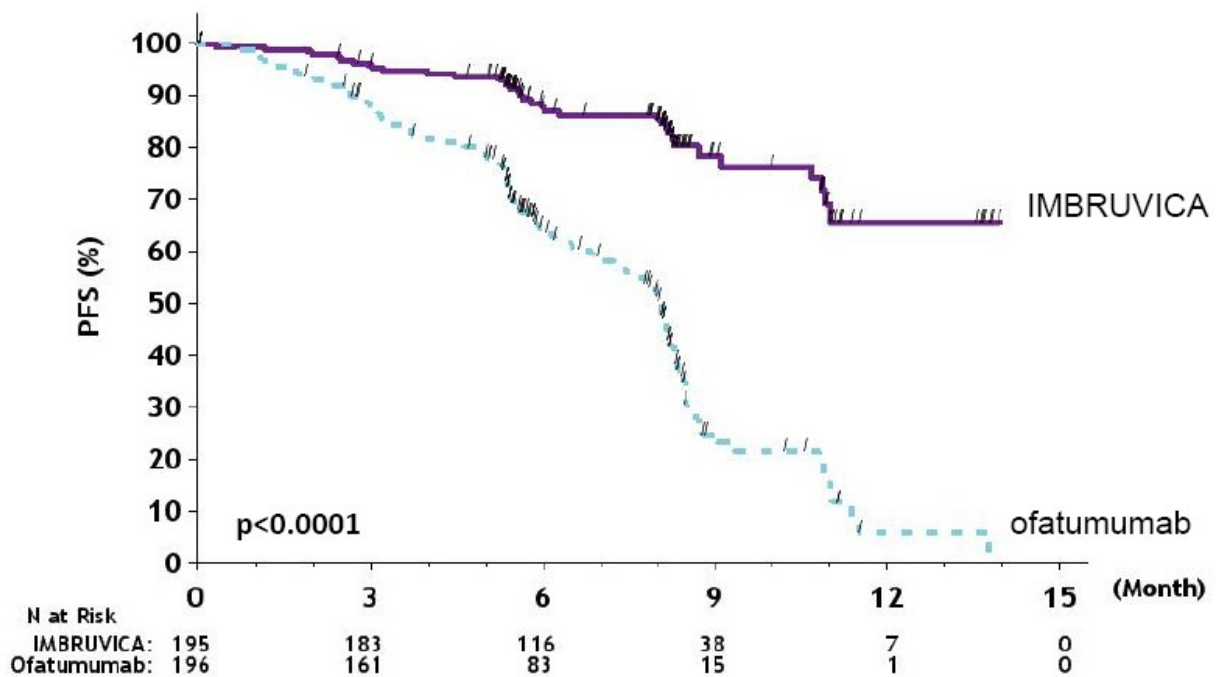
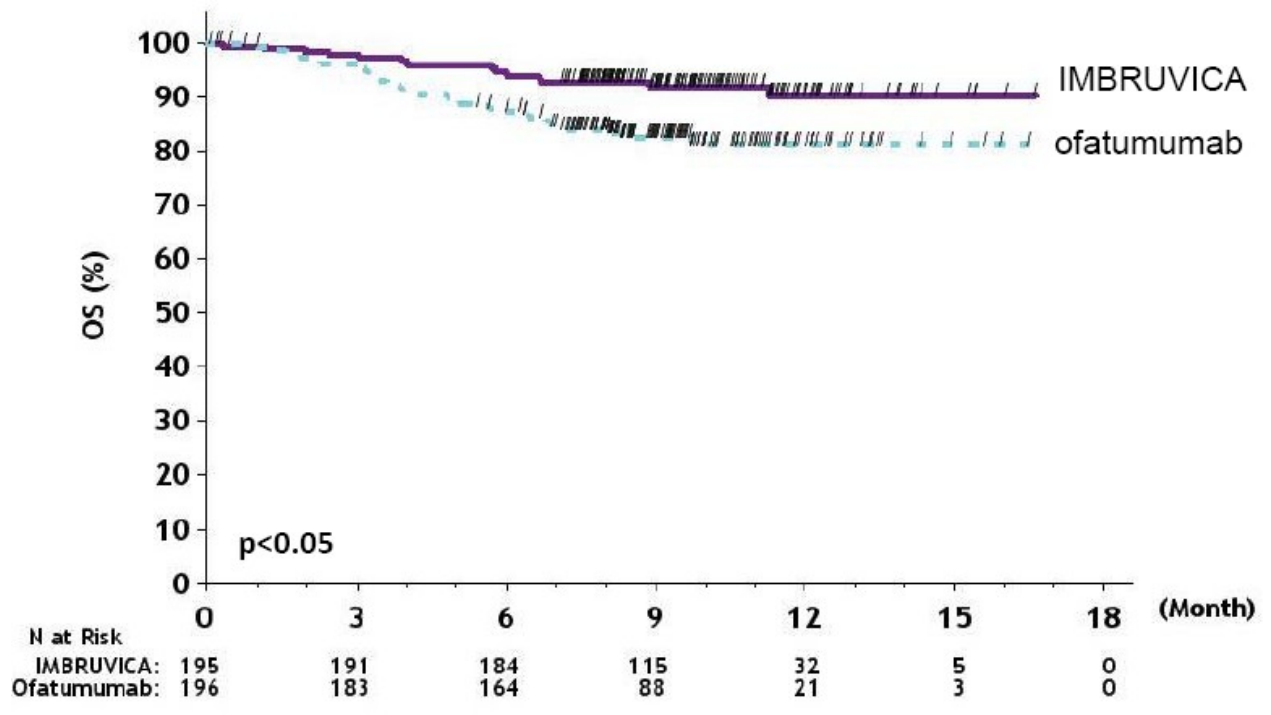


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study 2



CLL with 17p deletion (del 17p CLL/SLL) in study 2

Study 2 included 127 patients with del 17p CLL/SLL. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for del 17p CLL are shown in Table-13.

Table 13.: Efficacy Results in Patients with del 17p CLL/SLL in study 2

Endpoint	IMBRUVICA N=63	Ofatumumab N=64
Progression Free Survival		
Number of events (%)	16 (25.4)	38 (59.4)
<u>Disease progression</u>	<u>12</u>	<u>31</u>
<u>Death events</u>	<u>4</u>	<u>7</u>
Median (95% CI), months	NR	5.8 (5.3, 7.9)
HR (95% CI)	0.25 (0.14, 0.45)	
Overall Response Rate ^a	47.6%	4.7%

^aIRC evaluated. All partial responses achieved; none of the patients achieved a complete response.
CI= confidence interval; HR= hazard ratio; NR= not reached

Study 3

A randomized, multi-center, open-label study of IMBRUVICA versus chlorambucil was conducted in patients with treatment naïve CLL or SLL who were 65 years of age or older. Patients (n = 269) 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, with an allowance for inpatient dose increases up to 0.8 mg/kg based on tolerability.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety one percent of patients had a baseline ECOG performance status of 0 or 1 and 9% had an ECOG performance status of 2. The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic lymphadenopathy (37%), progressive or symptomatic splenomegaly (30%), fatigue (27%) and night sweats (25%).

With a median follow-up of 28.1 months, there were 32 observed death events [11 (8.1%) and 21 (15.8%) in IMBRUVICA and chlorambucil treatment arms, respectively]. With 41% of patients switching from chlorambucil to IMBRUVICA, the overall survival analysis in the ITT patient population resulted in a statistically significant HR of 0.44 [95% CI (0.21, 0.92)] and 2-year survival rate estimates of 94.7% [95% CI (89.1, 97.4)] and 84.3% [95% CI (76.7, 89.6)] in the IMBRUVICA and chlorambucil arms, respectively.

Efficacy results for Study 3 are shown in Table 14 and the Kaplan-Meier curve for PFS, assessed by independent review committee (IRC) according to IWCLL criteria is shown in Figure 3.

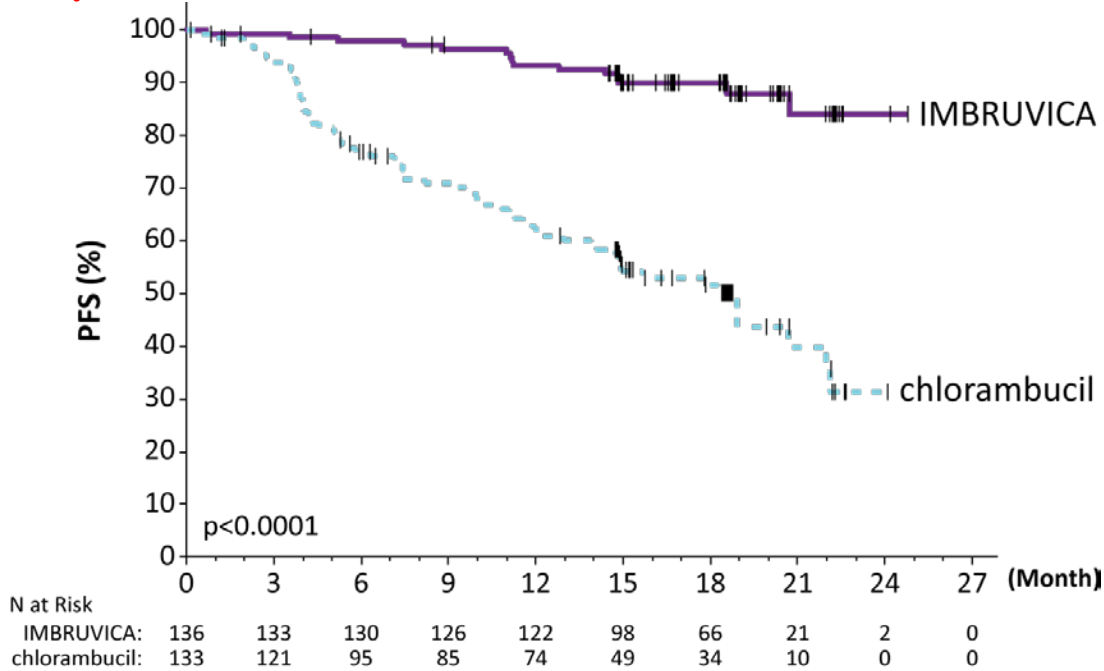
Table 14: Efficacy Results in Study 3

Endpoint	IMBRUVICA N=136	Chlorambucil N=133
Progression Free Survival^a		
Number of events (%)	15 (11.0)	64 (48.1)
Disease progression	12	57
Death events	3	7
Median (95% CI), months	NR	18.9 (14.1, 22.0)
HR ^b (95% CI)	0.161 (0.091, 0.283)	
Overall Response Rate^a (CR + PR)	82.4%	35.3%
P-value	<0.0001	

^a IRC evaluated; five subjects (3.7%) in the IMBRUVICA arm and two subjects (1.5%) in the Chlorambucil arm achieved complete response

^b HR = hazard ratio; NR = not reached

Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study 3



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 median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to

11 treatments). At baseline, 56% of patients had at least one tumor > 5 cm and 26% presented with del11q.

Efficacy results for Study 4 are shown in Table 15 and the Kaplan-Meier curves for PFS are shown in Figure 4.

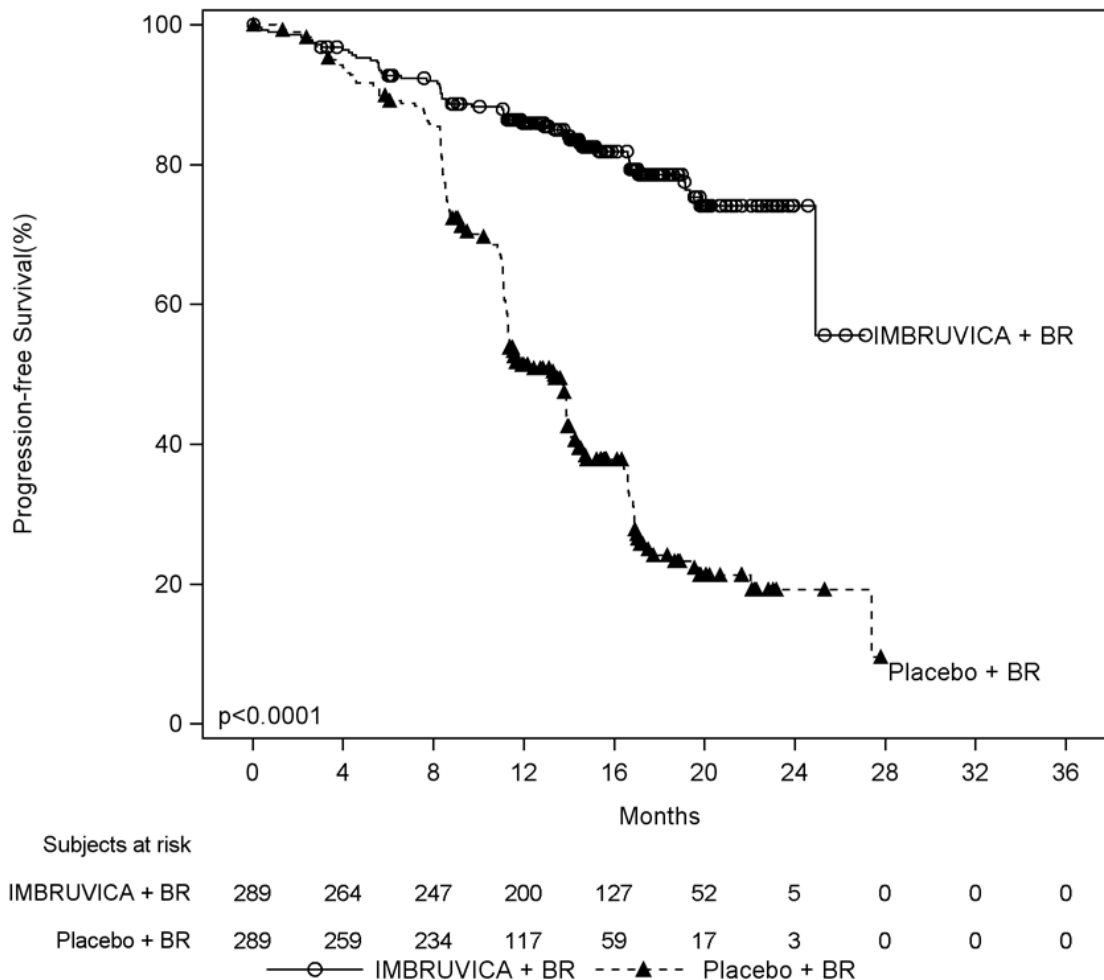
Table 15: Efficacy Results in Study 4

<u>Endpoint</u>	<u>IMBRUVICA + BR</u> <u>N=289</u>	<u>Placebo + BR</u> <u>N=289</u>
<u>Progression Free Survival^a</u>		
<u>Number of events (%)</u>	<u>56 (19.4)</u>	<u>183 (63.3)</u>
<u>Median (95% CI), months</u>	<u>Not reached</u>	<u>13.3 (11.3, 13.9)</u>
<u>HR (95% CI)</u>	<u>0.20 (0.15, 0.28)</u>	
<u>Overall Response Rate^a</u>	<u>82.7%</u>	<u>67.8%</u>

^a IRC evaluated, Twenty four subjects (8.3%) in the IMBRUVICA + BR arm and six subjects (2.1%) in the placebo + BR arm achieved complete response

BR = bendamustine and rituximab; CI = confidence interval; HR = hazard ratio

Figure 4: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study 4



Lymphocytosis

Upon initiation of IMBRUVICA, an increase in lymphocyte counts (i.e., $\geq 50\%$ increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 66% of patients in the CLL studies. The onset of isolated lymphocytosis occurs during the first month of IMBRUVICA therapy and resolves by a median of 14 weeks (range 0.1 – 104 weeks). When IMBRUVICA was administered with chemoimmunotherapy, lymphocytosis was 7% with IMBRUVICA + BR versus 6% with placebo + BR.

14.3 Waldenström's Macroglobulinemia

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 Independent Review Committee (IRC) using criteria adopted from the International Workshop of Waldenström's Macroglobulinemia. Responses, defined as partial response or better, per IRC are shown in Table 14.

Table 16.: Overall Response Rate (ORR) and Duration of Response (DOR) Based on IRC Assessment in Patients with WM

	Total (N=63)
Response rate (CR+VGPR+PR), (%)	61.9
95% CI (%)	(48.8, 73.9)
Complete Response (CR)	0
Very Good Partial Response (VGPR), (%)	11.1
Partial Response (PR), (%)	50.8
Median duration of response, months (range)	NR (2.8+, 18.8+)

CI = confidence interval; NR = not reached

The median time to response was 1.2 months (range: 0.7-13.4 months).

16 HOW SUPPLIED/STORAGE AND HANDLING

The white opaque 140 mg capsules marked with “ibr 140 mg” in black ink are available in white HDPE bottles with a child-resistant closure:

- 90 capsules per bottle
- 120 capsules per bottle

Store bottles at room temperature 20°C to 25°C .Excursions are permitted between 15°C and 30°C. Retain in original package until dispensing.

After first opening the package, Imbruvica should be used within 45 days

17 PATIENT COUNSELING INFORMATION

● ~~Hemorrhage:~~

~~Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions (5.1)].~~

~~● **Infections:**~~

~~Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions (5.2)].~~

~~● **Atrial Fibrillation:**~~

~~Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see Warnings and Precautions (5.4)].~~

~~● **Second primary malignancies:**~~

~~Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions (5.5–5.6)].~~

~~● **Tumor lysis syndrome:**~~

~~Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions (5.6–5.7)].~~

~~● **Embryo-fetal toxicity:**~~

~~Advise women of the potential hazard to a fetus and to avoid becoming pregnant [see Warnings and Precautions (5.7–5.8)].~~

~~● **Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day [see Dosage and Administration (2.1)].**~~

~~● **Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose [see Dosage and Administration (2.5–2.6)].**~~

~~● **Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions (6)]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.**~~

~~● **Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over the counter drugs, vitamins, and herbal products [see Drug Interactions (7)].**~~

~~● **Advise patients that they may experience loose stools or diarrhea, and should contact**~~

~~their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.~~
~~Active ingredient made in China.~~

Manufacturer: Catalent CTS, Inc. 10245 Hickman Mills Drive, Kansas City, MO 64137 USA

Registration holder: J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel

This insert was checked and approved by the Israeli MoH in Mar2017

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו-1986

התרופה משווקת על פי מרשם רופא בלבד

אימברוביקה, כמוסות

IBRUTINIB 140mg

איברוטיניב 140 מ"ג

חומרים בלתי פעילים ואלרגניים בתכשיר - ראה סעיף 6 "מידע נוסף"

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך שאלות נוספות, פנה אל הרופא או אל הרוקח.

תרופה זו נרשמה לטיפול במחלתך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מחלתם דומה.

התרופה אינה מיועדת לשימוש בילדים ובמתבגרים מתחת לגיל 18. יעילות ובטיחות התרופה לא נבדקו באוכלוסייה זו.

1. למה מיועדת התרופה?

התרופה מיועדת לטיפול במחלת MCL (Mantle Cell Lymphoma) במבוגרים שקיבלו לפחות טיפול קודם אחד.

התרופה מיועדת לטיפול במחלת [SLL \(Small lymphocytic lymphoma\)](#) / [CLL \(Chronic lymphocytic leukemia\)](#) במבוגרים, שקיבלו לפחות טיפול קודם אחד.

התרופה מיועדת לטיפול בקו ראשון במחלת [CLL/SLL \(Small lymphocytic lymphoma\)](#) / [CLL \(Chronic lymphocytic leukemia\)](#) במבוגרים מגיל 65 ומעלה.

התרופה מיועדת לטיפול במחלת CLL (Chronic lymphocytic leukemia) במבוגרים עם החסרת מקטע על כרומוזום 17 (17p deletion).

התרופה מיועדת לטיפול במחלת Waldenström's macroglobulinemia (WM)

קבוצה תרופוטית: מעכבי BTK (Bruton's Tyrosine Kinase)

2. לפני השימוש בתרופה:

אין להשתמש בתכשיר אם:

- אתה רגיש (אלרגי) לחומר הפעיל איברוטיניב או לאחד מהמרכיבים הנוספים אשר מכילה התרופה אימברוביקה. לרשימת המרכיבים הנוספים ראה סעיף 6 "מידע נוסף".
- אתה נוטל תרופה צמחית הנקראת פרע (St. John's Wort), המשמשת לטיפול בדיכאון). אם אתה לא בטוח- היוועץ ברופא, ברוקח או באחות טרם נטילת התרופה.

אזהרות מיוחדות הנוגעות בשימוש בתרופה:

לפני הטיפול באימברוביקה, ספר לרופא אם:

- עברת ניתוח לאחרונה או שאתה מתכנן לעבור ניתוח. ~~במיוחד אם הניתוח עלול להשפיע על ספיגת מזון ותרופות במערכת העיכול.~~ יתכן והרופא יפסיק את הטיפול באימברוביקה לפני הליך רפואי, ניתוח או טיפול שיניים מתוכנן.
 - הנך סובל מבעיות של דימום, ~~אי פעם היו לך שטפי דם או דימומים חריגים או אם אתה נוטל תרופות ותוספי מזון המעלים את הסיכון לדימומים (ראה להלן).~~
 - הנך סובל, או סבלת בעבר, מבעיות בקצב הלב, אם הנך מעשן או אם הנך סובל ממצב רפואי כלשהוא העלול להגביר את הסיכון שלך למחלת לב, כגון: לחץ דם גבוה, כולסטרול גבוה או סוכרת ~~או מכשול לבבי חמור.~~
 - הנך סובל מזיהום.
 - הנך סובל מבעיות בכבד או בכליה ~~או בכליה.~~
 - הנך בהריון או מתכננת להכנס להריון. אימברוביקה עלול להזיק לעובר. ~~אין להיכנס להריון בזמן הטיפול באימברוביקה. במידה ואת בגיל הפוריות הרופא המטפל יפנה אותך לבצע בדיקת הריון לפני תחילת הטיפול באימברוביקה.~~
 - **נשים:** יש להמנע מכניסה להריון בזמן הטיפול ו **3 חודשים** לאחר נטילת המנה האחרונה של אימברוביקה.
 - **גברים:** יש להימנע מלהכניס את בת הזוג להריון בזמן הטיפול ו**חודש** לאחר נטילת המנה האחרונה של אימברוביקה. (ראה סעיף "הריון והנקה")
 - הנך מניקה או מתכננת להניק. יש להחליט בהתייעצות עם הרופא המטפל האם להניק או ליטול אימברוביקה. (ראה סעיף "הריון והנקה") ~~אין להניק ולטול אימברוביקה במקביל.~~
- אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.** נטילת אימברוביקה במקביל לתרופות אחרות עלולה להשפיע על פעילות אימברוביקה ~~ועלולה לגרום לתופעות לוואי וכן נטילת אימברוביקה עלולה להשפיע על פעילותן של תרופות אחרות.~~
- אימברוביקה עלולה לגרום לך לדמם בקלות יתר. עליך לספר לרופא, לפני נטילת אימברוביקה, אם אתה נוטל תרופות נוספות המגבירות את הסיכון לדמם, כגון:
 - ~~אספירין ונוגדי דלקת שאינם סטרואידים (NSAIDs) כדוגמת איבופרופן או נפרקסן.~~
 - ~~מדללי דם כדוגמת קומדין, הפרין ותרופות נוספות למניעת קרישים.~~
 - ~~תוספי תזונה שעלולים להגביר את הסיכון לדימומים כדוגמת שמן דגים, ויטמין E או זרעי פשתן.~~
 - תרופות שעלולות להשפיע על פעילות אימברוביקה או שפעילותן עלולה להיות מושפעת, כתוצאה משימוש בו זמני עם אימברוביקה:
 - אנטיביוטיקות לטיפול בזיהומים חידקיים- קלריתרומיצין, טליטרומיצין, ציפרופלוקסצין, אריתרומיצין, ריפמפיצין.
 - תרופות לטיפול בזיהומים פטרייתיים- קטוקונזול, איטרקונזול, פלוקונזול, ווריקונזול. **פוסקונזול**
 - תרופות לזיהומי HIV- ריטונאוור, קוביקסטאט, אינדינאוור, נלפינוויר, סקווינאוור,

אמפרנוויר, אטאזאנוויר, דרנוויר, פוסאמפרנוויר. בוספרנוויר, טלפרנוויר

- תרופות למניעת בחילות והקאות כתוצאה מטיפול בכמותרפיה-אפרפיטאנט.
- תרופות לטיפול בדיכאון- נפאזודון.
- תרופות לטיפול בסרטן ממשפחת מעכבי הקינאזות- קריזוטיניב, אימטיניב.
- תרופות לטיפול ביתר לחץ דם ובכאבים בחזה ממשפחת מעכבי תעלות סידן- דיילטיאזם, וורפמיל.

~~○ תרופות לטיפול ברמות גבוהות של כולסטרול- רוזובסטאטין~~

~~○ תרופות לטיפול בבעיות לבביות ובקצב לב לא סדיר- אמיודרון, דרונדרון.~~

- תרופות למניעת פרכוסים, לטיפול באפילפסיה ולטיפול בנוירלגיה של העצב המשולש (trigeminal neuralgia)- קרבמזפין, פניטואין.

- אם אתה נוטל דיגוקסין, תרופה הניתנת לבעיות לבביות, או מתותרקסאט, תרופה הניתנת לסוגי סרטן אחרים ולהפחתת פעילות מערכת החיסון (לדוגמה בדלקת מפרקים שגרנית או פסוריאזיס), יש ליטול את הדיגוקסין או מתותרקסאט לפחות 6 שעות לפני או 6 שעות אחרי נטילת אימברוביקה.

נטילת אימברוביקה ומזון

בזמן הטיפול באימברוביקה אין לאכול אשכוליות או תפוזי חושש (Seville orange) המשמשים רבות בהכנת ריבות. כמו כן אין לשתות מיץ אשכוליות או מיץ תפוזי חושש, או ליטול כל מאכל או תוסף שעשוי להכיל אותם. מוצרים אלה עלולים להעלות את רמת התרופה בדם.

ילדים ומתבגרים:

תרופה זו אינה מיועדת לילדים ומתבגרים, מאחר והשימוש בגילאים אלה לא נבדק.

הריון והנקה

- ידעי את הרופא אם הנך בהריון, חושבת שאת בהריון או מתכננת להיכנס להריון. אימברוביקה עלול להזיק לעובר. אין להיכנס להריון בזמן הטיפול באימברוביקה.
- נשים בגיל פוריות חייבות להשתמש בשיטה יעילה מאוד למניעת הריון במהלך הטיפול באימברוביקה ובמשך תקופה של 3 חודשים לאחר הפסקת נטילתה. אם את משתמשת באמצעי מניעה הורמונליים, כגון גלולות למניעת הריון או התקנים תוך רחמיים, עליך להשתמש גם באמצעי מניעה מכני (כגון קונדום).
- ידעי את הרופא אם הנך מניקה או מתכננת להניק. יש להחליט בלוחי הרופא המטפל האם להניק או לטול אימברוביקה. אין להניק ולטול אימברוביקה במקביל.

הריון:

- יש ליידע את הרופא אם הנך בהריון או מתכננת להיכנס להריון. אימברוביקה עלול להזיק לעובר. במידה ואת בגיל הפוריות, הרופא המטפל יפנה אותך לבצע בדיקת הריון לפני תחילת הטיפול באימברוביקה.
- נשים: יש להימנע מכניסה להריון בזמן הטיפול ו-3 חודשים לאחר נטילת המנה האחרונה של אימברוביקה. נשים בגיל פוריות חייבות להשתמש בשיטה יעילה מאוד למניעת הריון במהלך הטיפול באימברוביקה ובמשך תקופה של 3 חודשים לאחר הפסקת נטילתה. אם את משתמשת באמצעי מניעה הורמונליים, כגון גלולות למניעת הריון או התקנים תוך רחמיים, עליך להשתמש גם באמצעי מניעה מכני (כגון קונדום).

- **גברים:** יש להימנע מלהכניס את בת הזוג להריון בזמן הטיפול **וחדש** לאחר נטילת המנה האחרונה של אימברוביקה.

הנקה:

יש ליידע את הרופא אם הינך מניקה או מתכננת להניק. יש להחליט בהתייעצות עם הרופא המטפל האם להניק או ליטול אימברוביקה. אין להניק ולטול אימברוביקה במקביל.

נהיגה ושימוש במכוונות

אתה עלול להרגיש עייפות או סחרחורת, אשר עלולים להשפיע על היכולת שלך לנהוג או להפעיל מכוונות מסוכנות.

3. כיצד תשתמש בתרופה:

יש לטול אימברוביקה בדיוק לפי הוראות הרופא.

עליך לבדוק עם הרופא או הרוקח אם אינך בטוח.

המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.

המינון המקובל הוא:

Mantle Cell Lymphoma (MCL) - 4 כמוסות (560 מ"ג), פעם ביום.

Chronic Lymphocytic Leukaemia (CLL) - 3 כמוסות (420 מ"ג), פעם ביום.

Waldenström's macroglobulinemia (WM) - 3 כמוסות (420 מ"ג), פעם ביום.

יתכן והרופא יתאים לך מינון שונה.

אין לעבור על המנה הממומלצת.

יש ליטול אימברוביקה פעם אחת ביום בזמן קבוע ככל שניתן, בכל יום. יש לבלוע את הכמוסה

בשלמותה עם כוס מים. אין לפתוח, לשבור או ללעוס את הכמוסה.

אין לקחת אימברוביקה עם מיץ אשכוליות. במהלך הטיפול באימברוביקה אין לשתות מיץ אשכוליות, לאכול אשכוליות או תפוז חושש (seville oranges) המשמש לרוב בהכנת ריבות.

בדיקות ומעקב

Tumour lysis syndrome (TLS) - תסמונת הנגרמת על ידי פירוק תאי גידול סרטני . בשל רכיביהם

המפורקים של תאי הגידול, יתכנו רמות לא תקינות של כימיקלים בדם במהלך הטיפול וגם במהלך

המחלה ללא טיפול, העלולות להוביל לשינויים בתפקודי הכליות, קצב לב לא תקין או פרכוסים. הרופא

המטפל עשוי להפנותך לבצע בדיקות דם ל TLS.

לימפוציטוזיס – בדיקות מעבדה עלולות להראות עליה ברמות תאי הדם הלבנים (מסוג לימפוציטים)

בדמך, בשבועות הראשונים לטיפול. תופעה זו צפויה ועלולה להימשך מספר חודשים. עליה ברמת תאי

דם לבנים אלה אינה מעידה בהכרח על החמרה במחלת הסרטן. הרופא יפנה אותך לבצע ספירת דם

לפני הטיפול ובמהלכו ובמקרים נדירים יהיה צורך בתרופה נוספת.

אם נטלת מנת יתר או אם בטעות בלע ילד מן התרופה, פנה מיד לרופא או לחדר מיון של בית חולים

והבא את אריזת התרופה איתך.

אם שכחת ליטול את התרופה יש ליטול אותה באותו היום בזמן שנזכרת. יש לקחת את המנה הבאה בזמן הרגיל, למחרת. אין ליטול מנה כפולה ביום אחד, על מנת לפצות על מנה שנשכחה. אם אינך בטוח כיצד לנהוג התייעץ ברופא, או ברוקח לגבי מועד נטילת המנה הבאה

יש להתמיד בטיפול כפי שהומלץ על ידי הרופא.
גם אם חל שיפור במצב בריאותך, אין להפסיק את הטיפול ללא התייעצות עם הרופא.
אין ליטול תרופות בחושך! בדוק את התווית והמנה בכל פעם שהינך נוטל תרופה. הרכב משקפיים אם הינך זקוק להם.
אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.

4. תופעות לוואי

כמו לכל תרופה, השימוש באימברוביקה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן.

יש להפסיק את השימוש ולפנות מיד לרופא אם אתה חש אחת מתופעות הלוואי הבאות: פריחה בולטת ומגרדת, קשיי נשימה, נפיחות של הפנים, השפתיים, הלשון או הגרון- תופעות אלו עלולות להעיד על תגובה אלרגית לתרופה.

אימברוביקה עלולה לגרום לתופעות לוואי חמורות, הכוללות:

- **בעיות דימום – שכיח.** דימומים עלולים להתרחש במהלך הטיפול באימברוביקה (~~בשכיחות של יותר ממשתמש אחד מעשרה~~) ועלולים להיות חמורים ולהוביל אף למוות. הסיכון לדימום עלול לעלות אם הנך נוטל במקביל תרופות מדללות דם. יש לפנות לרופא באופן מיידי במידה ואתה חווה סימני דימום הכוללים:
דם בצואה או, צואה שחורה (נראית כזפת), שתן ורוד או חום, ~~דימום ווסתי מוגבר, דימום מהאף, דימום בלתי צפוי, דימום בלתי צפוי, דימום חמור או דימום שאינו ניתן לשליטה, הקאה דמית או הקאה דמוית פולי קפה, שיעול דמי או שיעול עם קרישי דם, נטייה מוגברת לחבלות, פתמים אדומים או סגולים קטנים הנגרמים על ידי דימום תחת העור, תחושת סחרחורת או חולשה, בלבול, שינוי בדיבור או כאב ראש הנמשך זמן רב.~~
- **זיהומים – שכיח.** זיהומים שונים (~~נגיפים, חיידקים או פטרייתים~~) עלולים להתרחש במהלך הטיפול באימברוביקה (~~בשכיחות של יותר ממשתמש אחד מעשרה~~). ~~זיהומים אלה יכולים להיות דלקת ריאות, זיהום באף, בסינוסים או דלקת גרון (דלקת של דרכי הנשימה העליונות), דלקת בדרכי השתן, בסינוס הכליה או דלקת בעור.~~ הזיהומים עלולים להיות חמורים ולהוביל למוות. יש ליידע את הרופא באופן מיידי במידה ואתה סובל מחום, צמרמורות, כאבים, עייפות, חולשה, בלבול, ~~בלבול, תסמינים דמויי שפעת, קוצר נשימה או כל סימן או תסמין אחר לזיהום, במהלך הטיפול באימברוביקה.~~
- **ירידה בספירת דם – ירידה בספירת דם (תאי דם לבנים, טסיות ותאי דם אדומים) הינה תופעה שכיחה בטיפול באימברוביקה אך עלולה להיות גם חמורה.** הרופא המטפל צריך להפנות אותך לבצע

ספירת דם כל חודש.

- **בעיות בקצב הלב (פרפור פרוזדורי ורפרוף פרוזדורי).** בעיות בקצב הלב התרחשו באנשים המטופלים באימברוביקה (בשכיחות של 10-1 משתמשים מתוך 100), בייחוד אנשים בעלי סיכון מוגבר למחלות לב, אנשים עם זיהומים או אנשים שסבלו מבעיות בקצב הלב בעבר. יש ליידע את הרופא במידה ואתה סובל מתסמינים של בעיות בקצב הלב, כגון התחושה שהלב פועם בקצב מהיר ולא סדיר, סחרחורת, קוצר נשימה, אי-נוחות בחזה או עלפון.
 - **ייתר לחץ דם (יל"ד) - שכיח - הופעה או החמרה של יתר לחץ דם, התרחשו באנשים המטופלים באימברוביקה.** ייתכן והרופא המטפל יחליט לתת לך טיפול תרופתי חדש להורדת לחץ הדם או ישנה טיפול קיים.
 - **התפתחות גידול סרטני ראשוני נוסף** – גידולי סרטן חדשים התגלו בחולים שטופלו באימברוביקה, כולל סרטן העור או איברים נוספים.
 - **Tumour lysis syndrome (TLS)** - תסמונת הנגרמת על ידי פרוק מהיר של תאי הסרטן (מופיע ב-10 משתמשים מתוך 1,000). התסמונת עלולה לגרום לכשל כליתי ולצורך בטיפול דיאליזה, קצב לב לא תקין, פרכוסים ואף מוות. הרופא המטפל עשוי להנחות אותך לבצע בדיקות דם ל TLS.
- **בעיות בכליות – כשל כליתי ומוות התרחשו במטופלים במחלת MCL במהלך טיפול באימברוביקה.**
- ספר לרופא מיד אם אתה מבחין בתופעות הלואי הבאות:
- תופעות לוואי שכיחות מאד (very common) – תופעות שמופיעות ביותר ממשתמש אחד מעשרה:
- חום, צמרמורת, כאב בגוף, תחושת עייפות, צינון או תסמיני שפעת, קוצר נשימה – סימנים העלולים להעיד על זיהום (נגיפי, חיידקי או פטרייתי). זיהומים אלה יכולים להיות זיהום באף, דלקת סינוסים או דלקת גרון (דלקת דרכי נשימה עליונות), דלקת ריאות או דלקת בעור
 - חבלות או עלייה בנטייה לחבלות
- תופעות לוואי שכיחות (common) - תופעות שמופיעות ב-10-1 משתמשים מתוך 100:
- דלקות בדרכי השתן
 - דימום מהאף, כתמים אדומים או סגולים תחת העור כתוצאה מדימום
 - דם בצואה או בשתן, דימום ווסתי מוגבר, דימום מפציעה שאינו ניתן לעצירה, בלבול, כאב ראש עם קושי בדיבור או תחושת עלפון – אלה עלולים להיות סימנים לדימום פנימי חמור בקיבה, במעיים או במח
 - קצב לב מואץ, החסרה של פעימות לב, דופק חלש או לא אחיד (תסמינים של פרפור פרוזדורים)
 - עלייה במספר תאי הדם הלבנים או בחלקם היחסי, כפי שמוצג בבדיקות דם.
 - ספירת תאי דם לבנים נמוכה המלווה בחום
 - בשל פירוק מהיר של תאי סרטן **Tumor lysis syndrome (TLS)** יתכנו רמות לא תקינות של כימיקלים בדם במהלך הטיפול וגם במהלך המחלה ללא טיפול
 - סרטן עור שאינו מלנומה

- תחושת סחרחורת
 - טשטוש ראייה
 - עור אדמומי
 - יובש בפה
 - אלח דם
 - זיהומים של העור
 - התייבשות
 - רמות גבוהות של חומצה אורית בדם (כפי שמוצג בבדיקות דם), אשר עלולות לגרום לשיגדון (גאוט).
 - דלקת בריאות שעלולה להוביל לנזק קבוע
- תופעות לוואי שאינן שכיחות (uncommon) - תופעות שמופיעות ב-10-1 משתמשים מתוך 1,000:
- ספירה גבוהה מאד של תאי דם לבנים, העלולה לגרום להיווצרות צברי תאים.
 - תגובה אלרגית, לעיתים חמורה, העלולה לכלול נפיחות בפנים, בשפתיים, בפה, בלשון או בגרון, קושי בבליעה או בנשימה, פריחה מגרדת (סרפדת)

- תופעות לוואי שכיחות מאוד נוספות:
- פצעים בפה, דלקת בפה
 - קשיי עיכול
 - כאב ראש או סחרחורת
 - עצירות
 - בחילות, הקאות, כאבי בטן, ירידה בתאבון
 - שלשול - הרפא עשוי לתת לך נזלים והשלמת מלחים או תרופה נוספת
 - פריחה בעור
 - שיעול
 - כאבים בידיים וברגלים
 - כאבי גב או כאבי פרקים, דלקת פרקים
 - התכווצויות או כאבי שרירים
 - ספירה נמוכה של טסיות דם בבדיקות דם, ספירה נמוכה מאד של תאי דם לבנים בבדיקות דם, אנמיה
 - נפיחות של הידיים, הקרסוליים או כפות הרגליים.
 - כאבים בעצמות

תופעות לוואי נוספות :

פגיעה חמורה בכבד, כולל כשל כבדי

שלשול הינו תופעת לוואי נפוצה מאד בשימוש באימברוביקה. יש להקפיד על שתייה מרובה במהלך הטיפול על מנת להימנע מאיבוד נוזלים משמעותי (התייבשות) בעקבות השלשול. יש לדווח לרופא במידה ואתה סובל משלשול שאינו נפסק.

ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי,

או ע"י כניסה לקישור: <https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

במידה והנך חש באחת מתופעות הלוואי, אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא הזכרה בעלון, עליך להתייעץ עם הרופא.

5. איך לאחסן את התרופה?

- מנעי הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.
- אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי האריזה. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.
- יש לאחסן את התרופה בטמפרטורה של 20 עד 25 מעלות צלזיוס. יש לשמור על התכשיר באריזתו המקורית כשהמכסה סגור היטב.
- לאחר פתיחה ראשונה של האריזה, יש להשתמש בתוך 45 יום.

6. מידע נוסף

- נוסף על החומר הפעיל התרופה מכילה גם:
Croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, The capsule shell contains gelatin and titanium dioxide and (E171) black printing ink (pharmaceutical glaze, iron oxide black (E172), n-butyl alcohol, propylene glycol, isopropyl alcohol, 2- propanol, concentrated aqueous ammonium and ammonium hydroxide)
- כיצד נראית התרופה ומה תוכן האריזה:
אימברוביקה היא כמוסה אטומה בצבע לבן העשויה מג'לטין עליה הטבעה בצבע שחור של הכיתוב "ibr 140mg". הכמוסה מכילה אבקה בצבע לבן/לבנבן.
- גודל אריזה: בקבוקון המכיל 120 כמוסות ובקבוקון המכיל 90 כמוסות
בעל הרישום וכתובתו: ג"י סי' הלת'קר בע"מ, קיבוץ שפיים, 6099000, ישראל
שם היצרן וכתובתו: קאטלנט CTS, קנזס סיטי, מיזורי, ארצות הברית

עלון זה נבדק ואושר ע"י משרד הבריאות בתאריך: מאי 2017
מספר רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות : 151-98-34062-00

לשם הפשטות להקלת הקריאה , עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.