אוקטובר 2024

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

חברת אלי לילי ישראל מבקשת להודיעכם על אישור התוויה חדשה לטיפול ב-CLL/SLL עבור התכשירים:

Jaypirca 50 mg **ג'ייפירקה 50 מ"ג**

Jaypirca 100 mg **ג'ייפירקה 100 מ"ג**

צורת מינון: Film Coated Tablets

החומר הפעיל: Pirtobrutinib

ההתוויות המאושרות לתכשיר בישראל:

- Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

- Jaypirca is indicated for the treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

בהודעה זו מצויינים העדכונים העיקריים בעלונים לרופא ולצרכן. קיימים עדכונים נוספים.
טקסט שהתווסף מסומן בכחול בקו תחתון.
העלונים המעודכנים מפורסמים במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום: אלי לילי ישראל בע"מ, השיזף 4, רעננה, טל': 09-9606234.

בברכה,
רונן שוורץ
רוקח ממונה
אלי לילי ישראל בע"מ

להלן העדכון העיקריים בעלון לרופא:

2 INDICATIONS AND USAGE

2.1 Mantle Cell Lymphoma

JAYPIRCA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

2.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

JAYPIRCA is indicated for the treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

6 WARNINGS AND PRECAUTIONS

6.1 Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients treated with JAYPIRCA. In the clinical trial, Grade 3 or higher infections occurred in 24% of 593 patients, most commonly pneumonia (14%), with fatal infections occurring in 4.4% of patients. Sepsis occurred in 6% of patients and febrile neutropenia in 4%.

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In patients with CLL/SLL, Grade 3 or higher infections occurred in 32% of patients, with fatal infections occurring in 8%. Opportunistic infections after treatment with JAYPIRCA have included, but are not limited to, *Pneumocystis jirovecii* pneumonia and fungal infection *[see Adverse Reactions (7.1)]*.
[…]

7 ADVERSE REACTIONS

7.1 Clinical Trials Experience

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

BRUIN
The safety of JAYPIRCA was evaluated in the BRUIN trial in 110 patients with CLL/SLL, with 98% receiving at least two prior lines of systemic therapy including a BTK inhibitor and a BCL-2 inhibitor *[see Clinical Studies (14.2)]*. The trial required a platelet count ≥ 50 x 10^9/L, absolute neutrophil count ≥ 0.75 x 10^9/L, hepatic transaminases ≤ 2.5 times upper limit of normal (ULN), and an ECOG performance status of 0 to 2. The trial excluded patients with active central nervous system (CNS) involvement by lymphoma, significant cardiovascular disease, major bleeding, uncontrolled or symptomatic arrhythmias, prolonged QTc interval, or need for a strong CYP3A inhibitor or inducer or strong P-gp inhibitor.

Patients received JAYPIRCA 200 mg orally once daily until disease progression or unacceptable toxicity (N = 110); 60% were exposed for at least 1 year and 14% were exposed for at least two years. The median age was 68 years (range: 41 to 88 years) and 67% of patients were male. Race was reported in 110 (100%) patients; of these patients, 89% were White, 4.5% were Black, 1.8% were Asian, and 1.8% were Hispanic or Latino. The median number of prior therapies was 5 (range: 1-11).

Serious adverse reactions occurred in 56% of patients who received JAYPIRCA. Serious adverse reactions that occurred in ≥ 5% of patients were pneumonia (18%), COVID-19 (9%), sepsis (7%), and febrile neutropenia (7%). Fatal adverse reactions within 28 days of the last dose of JAYPIRCA occurred in 11% of patients, most commonly due to infections (10%), including sepsis (5%) and COVID-19 (2.7%).

Adverse reactions led to dose reductions in 3.6%, treatment interruption in 42%, and permanent discontinuation of JAYPIRCA in 9%. Adverse reactions which resulted in dose reductions of JAYPIRCA in > 1% of patients included neutropenia. Adverse reactions which resulted in treatment interruptions of JAYPIRCA in > 5% of patients included pneumonia, neutropenia, febrile neutropenia, and COVID-19. Adverse reactions which resulted in permanent discontinuation of JAYPIRCA in > 1% of patients included second primary malignancy, COVID-19, and sepsis.

The most common adverse reactions (≥ 20%), excluding laboratory terms, were fatigue, bruising, cough, musculoskeletal pain, COVID-19, diarrhea, pneumonia, abdominal pain, dyspnea, hemorrhage, edema, nausea, pyrexia, and headache. Table 4 summarizes select adverse reactions for patients treated on BRUIN.

Table 4: Adverse Reactions (≥ 10%) in Patients with CLL/SLL Who Received JAYPIRCA

	JAYPIRCA 200 mg once daily	
	N = 110	
Adverse Reactions [a]	All Grades (%)	Grade 3-4 (%)
General Disorders		
Fatigue	36	2.7
Edema	21	0
Pyrexia	20	2.7
Injury		

	JAYPIRCA 200 mg once daily N = 110	
Adverse Reactions [a]	All Grades (%)	Grade 3-4 (%)
Bruising	36	0
Fall	14	0.9
Respiratory, thoracic, and mediastinal disorders		
Cough	33	0
Dyspnea	22	2.7
Mucositis	12	0.9
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	32	0.9
Arthritis or arthralgia	19	1.8
Infections		
COVID-19	28[b]	7
Pneumonia	27[c]	16
Upper respiratory tract infections	13	2.7
Respiratory tract infection	11	1.8
Gastrointestinal Disorders		
Diarrhea	26	0
Abdominal pain	25	2.7
Nausea	21	0
Constipation	14	0
Vascular disorders		
Hemorrhage	22[d]	2.7
Hypertension	12	5
Nervous system disorders		
Headache	20	0.9
Peripheral neuropathy	16	3.6
Dizziness	15	0
Neurological changes	12[e]	2.7
Skin and subcutaneous disorders		
Rash	19	0.9
Psychiatric disorders		
Insomnia	14	0
Neoplasms benign, malignant and unspecified		
Second primary malignancy	13[f]	2.7
Renal and urinary disorders		
Renal insufficiency	12[g]	6
Metabolism and nutrition disorders		

	JAYPIRCA 200 mg once daily	
	N = 110	
Adverse Reactions [a]	All Grades (%)	Grade 3-4 (%)
Decreased appetite	12	0
Cardiac disorders		
Supraventricular tachycardia	10[h]	5

[a] Each term listed includes other related terms.

[b] Includes COVID-19 pneumonia. Includes 1 fatalities from COVID-19 and 2 fatalities from COVID-19 pneumonia

[c] Includes COVID-19 pneumonia. Includes 2 fatalities from COVID-19 pneumonia and 1 fatality from pneumonia

[d] Includes preferred terms hemorrhage, intracranial hemorrhage, and gastrointestinal hemorrhage

[e] Includes preferred terms memory impairment, confusional state, encephalopathy, mental status changes

[f] Includes preferred terms second primary malignancy and nonmelanoma skin cancers. 1 fatality from metastatic malignant melanoma

[g] Includes preferred terms renal failure, chronic kidney disease, acute kidney injury

[h] Includes preferred terms supraventricular tachycardia, sinus tachycardia, atrial fibrillation

Clinically relevant adverse reactions in < 10% include vision changes, lower respiratory tract infection, urinary tract infection, herpesvirus infection, and tumor lysis syndrome.

Table 5 summarizes laboratory abnormalities in BRUIN.

Table 5: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with CLL/SLL Who Received JAYPIRCA

	JAYPIRCA [a] 200 mg once daily	
Laboratory Abnormality	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Neutrophil count decreased	63	45
Hemoglobin decreased	48	19
Platelet count decreased	30	15
Lymphocyte count decreased	23	8
Chemistry		
Calcium decreased	40	2.8
Sodium decreased	30	0
ALT increased	23	2.8
AST increased	23	1.9
Creatinine increased	23	0
Lipase increased	21	7
Alkaline phosphatase increased	21	0

[a] The denominator used to calculate the rate varied from 83 to 108 based on the number of patients with a baseline value and at least one post-treatment value.

Grade 4 laboratory abnormalities in > 5% of patients included neutrophils decreased (23%).

**Lymphocytosis: Upon initiation of JAYPIRCA, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count increased ≥ 50% from baseline and a post-baseline value ≥ 5,000/µL) occurred in 64% of CLL/SLL patients in BRUIN. The median time to onset of lymphocytosis was 1.1 weeks, with 75% of cases occurring within 1.1 weeks, and the median duration was 19 weeks.

9.5 Geriatric Use

Of the patients with MCL who received the 200 mg dose of JAYPIRCA in BRUIN, 93 (78%) were 65 years of age and older and 39 (33%) were 75 years and older [see Clinical Studies (14.1)]. Clinical studies of JAYPIRCA did not include sufficient numbers of patients with MCL who were less than 65 years of age to determine whether older patients respond differently from younger adult patients. Of the patients with CLL/SLL who received the 200 mg once daily dose of JAYPIRCA in BRUIN, 68 (63%) were 65 years of age and older and 21 (19%) were 75 years and older [see Clinical Studies (14.2)]. No overall differences in effectiveness were observed between younger and older patients.

14.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The efficacy of JAYPIRCA in patients with CLL/SLL was evaluated in BRUIN [NCT03740529], an open-label, international, single-arm, multicohort study of JAYPIRCA as monotherapy. Efficacy was based on 108 patients with CLL/SLL treated with JAYPIRCA who were previously treated with at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor. JAYPIRCA was given orally at a dose of 200 mg once daily and was continued until disease progression or unacceptable toxicity. The trial required a platelet count ≥ 50 x 10^9/L, absolute neutrophil count ≥ 0.75 x 10^9/L, hepatic transaminases ≤ 2.5 times upper limit of normal (ULN), and an ECOG performance status of 0 to 2. The trial excluded patients with significant cardiovascular disease, major bleeding, uncontrolled or symptomatic arrhythmias, prolonged QTc interval, or need for a strong CYP3A inhibitor or inducer or strong P-gp inhibitor. Patients with active central nervous system (CNS) involvement by lymphoma or allogeneic hematopoietic stem cell transplantation (HSCT) within 60 days were excluded.

The median age was 68 years (range: 41 to 88 years); 69% were male; 89% were White, 4.6% Black or African American, 1.9% Asian and 1.9% were Hispanic or Latino. Baseline ECOG performance status was 0 or 1 in 91% of patients and 48% of patients had Rai stage III or IV disease. Among those patients with central testing available, 42% (37 of 88 patients) had a C481 BTK mutation, 54% (43 of 79 patients) had 17p deletion and/or TP53 mutation, 93% (77 of 83 patients) had unmutated IGHV, and 22% (16 of 72 patients) had 11q deletion. Patients received a median number of 5 prior lines of therapy (range: 2 to 11). The most common prior BTK inhibitors received were ibrutinib (97%), acalabrutinib (9%), and zanubrutinib (0.9%). Seventy-seven percent of patients discontinued the last BTK inhibitor for refractory or progressive disease, 13% discontinued for toxicity, and 10% discontinued for other reasons.

Efficacy was established based on overall response rate (ORR) and duration of response (DOR), as assessed by an independent review committee (IRC) using 2018 iwCLL criteria. Efficacy results are shown in Table 7. The median time to response was 3.7 months (range: 1.7, 27.9 months).

Table 7: Efficacy Results per IRC in Patients with CLL/SLL Previously Treated with a BTK Inhibitor and a BCL-2 inhibitor

Outcome	JAYPIRCA 200 mg once daily (N = 108)
Overall Response Rate	
ORR, n	78 (72%)
(95% CI, %)	63, 80
PR, n	78 (72%)
Duration of Response [a]	
Median DOR, months (95% CI)	12.2 (9.3, 14.7)

CI, confidence interval; PR, partial response.

[a] Based on Kaplan-Meier estimation. Estimated median follow-up was 15.7 months.

להלן העדכונים העקריים בעלון לצרכן:

1. למה מיועדת התרופה?

לימפומה של תאי מעטפת (MCL – Mantle Cell Lymphoma)

ג'ייפירקה כטיפול יחיד, מיועדת לטיפול במבוגרים עם לימפומה של תאי מעטפת (MCL) נשנית או עמידה לטיפול אשר טופלו בעבר במעכב BTK (Bruton's tyrosine kinase inhibitor).

לוקמיה לימפוציטית כרונית/ לימפומה של לימפוציטים קטנים (CLL - Chronic Lymphocytic Leukemia/ SLL - Small Lymphocytic Lymphoma)

ג'ייפירקה מיועדת לטיפול במבוגרים עם לוקמיה לימפוציטית כרונית או לימפומה של לימפוציטים קטנים (CLL/SLL) אשר טופלו בעבר בלפחות שני קווי טיפול, הכוללים מעכב BTK ומעכב BCL-2.

4. תופעות לוואי

תופעות לוואי נוספות שנצפו במחקרים קליניים

[...]

לוקמיה לימפוציטית כרונית/ לימפומה של לימפוציטים קטנים (CLL/SLL)

- **תופעות הלוואי השכיחות ביותר שהופיעו אצל 20% או יותר מהחולים ב-CLL/SLL המטופלים בג'ייפירקה:** עייפות, חבורות, שיעול, כאבי שרירים ושלד, וירוס הקורונה (COVID-19), שלשול, דלקת ריאות, כאב בטן, קוצר נשימה, דימום, בצקת, בחילה, חום וכאב ראש.
- **תופעות הלוואי שהופיעו אצל 10% או יותר מהחולים ב-CLL/SLL המטופלים בג'ייפירקה:**
  - **הפרעות כלליות:** עייפות, בצקת וחום.
  - **פציעה:** חבורות, נפילה.
  - **הפרעות בדרכי הנשימה וחלל בית החזה:** שיעול, קוצר נשימה ודלקת ברירית חלל הפה והלשון (mucositis).
  - **הפרעות שרירים ושלד ורקמות חיבור:** כאבי שרירים ושלד, דלקת מפרקים או כאב במפרקים (ארתרלגיה).
  - **זיהומים:** וירוס הקורונה (COVID-19), דלקת ריאות, זיהומים בדרכי הנשימה העליונות וזיהום בדרכי הנשימה.
  - **הפרעות במערכת העיכול:** שלשול, כאב בטן, בחילה ועצירות.
  - **הפרעות בכלי הדם:** דימום ויתר לחץ דם.
  - **הפרעות במערכת העצבים:** כאב ראש, נוירופתיה היקפית, סחרחורת, שינויים נוירולוגיים.
  - **הפרעות בעור וברקמות תת עוריות:** פריחה.
  - **הפרעות פסיכיאטריות:** נדודי שינה.
  - **ניאופלזמות שפירות, ממאירות ולא מוגדרות:** התפתחות גידול סרטני ראשוני נוסף.
  - **הפרעות בכליות ובדרכי השתן:** אי ספיקת כליות.
  - **הפרעות במטבוליזם ובתזונה:** תיאבון מופחת.
  - **הפרעות לב:** דופק מהיר (supraventricular tachycardia).
- **תופעות לוואי רלוונטיות מבחינה קלינית שהופיעו אצל פחות מ-10% מהחולים ב-CLL/SLL המטופלים בג'ייפירקה:** שינויים בראייה, זיהום בדרכי הנשימה התחתונות, זיהום בדרכי השתן, זיהום בנגיף הרפס ותסמונת פירוק הגידול (tumor lysis syndrome).
- **תוצאות חריגות נבחרות בבדיקות מעבדה (≥ 20%) שהחמירו בחולים ב-CLL/SLL המטופלים בג'ייפירקה:**
  - **בדיקות המטולוגיות בדם:** ירידה בספירת נויטרופילים, ירידה בהמוגלובין, ירידה בספירת טסיות, ירידה בספירת לימפוציטים.
  - **בדיקות כימיה בדם:** ירידה ברמת הסידן, ירידה ברמת הנתרן, עלייה באנזימי כבד (ALT ו-AST), עלייה בקריאטינין, עלייה ברמת הליפאז, עלייה ברמת אלקליין פוספטאז.

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