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יוני 2019

רופא/ה, רוקח/ת נכבד/ה,

חברת פייזר שמחה להודיעך על תוספת התוויה עבור התכשיר Bosulif:
newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).

ברצוננו להודיעך על עדכון בעלון לרופא ובעלונים לצרכן של **Bosulif 100 mg** ו- **Bosulif 500 mg:**

<u>המרכיב הפעיל:</u>

Bosutinib 100 mg; Bosutinib 500 mg

<u>Indicated for:</u>
Bosulif is indicated for the treatment of adult patients with:

- newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

<u>להלן העדכונים העיקריים בעלון לרופא:</u>

4.1 Therapeutic indications

Bosulif is indicated for the treatment of adult patients with:

- <u>newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).</u>
- chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML.

<u>Posology</u>

<u>Newly-diagnosed CP Ph+ CML</u>
<u>The recommended dose is 400 mg bosutinib once daily.</u>

<u>CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy</u>
The recommended dose is 500 mg bosutinib once daily.

In clinical trials <u>for both indications</u>, treatment with bosutinib continued until disease progression or ~~until it was no longer tolerated by the patient~~<u>intolerance to therapy</u>.

<u>Dose adjustments</u>

~~*In the Phase 2 clinical trial of adult patients with previously treated Ph+ leukaemia, dose escalation to 600 mg once daily with food was allowed in patients who did not experience severe or persistent moderate adverse reactions, under any of the following circumstances. A total of 85 patients (15.2%) who started treatment at </= 500 mg (n= 558) received dose escalations to 600 mg of bosutinib.*~~
In the Phase 1/2 clinical study in patients with CML who were resistant or intolerant to prior therapy, dose escalations from 500 mg to 600 mg once daily with food were allowed in patients who failed to demonstrate complete haematological response (CHR) by Week 8 or complete cytogenetic response (CCyR) by Week 12 and did not have Grade 3 or higher adverse events possibly-related to the investigational product. Whereas, in the Phase 3 study in patients with newly-diagnosed CP CML treated with bosutinib 400 mg, dose escalations by 100 mg increments to a maximum of 600 mg once daily with food were permitted if the patient failed to demonstrate breakpoint cluster region-Abelson (BCR-ABL) transcripts ≤ 10% at Month 3, did not have a Grade 3 or 4 adverse reaction at the time of escalation, and all Grade 2 non-haematological toxicities were resolved to at least Grade 1.

In the Phase 1/2 clinical study in patients with CML who were resistant or intolerant to prior therapy who started treatment at ≤ 500 mg, 93 (93/558; 16.7%) patients had dose escalations to 600 mg daily.

In the Phase 3 study in patients with newly-diagnosed CP CML who started bosutinib treatment at 400 mg, a total of 46 patients (17.2%) received dose escalations to 500 mg. In addition, 5.6% of patients in the bosutinib treatment group had further dose escalations to 600 mg.

~~Circumstances for dose escalation~~
~~- *Failure to achieve complete haematologic response (CHR) by Week 8*~~
~~- *Failure to achieve complete cytogenetic response (CCyR) by Week 12*~~

Doses greater than 600 mg/day have not been studied and therefore should not be given.

Dose adjustments for adverse reactions
~~*Dose adjustments for non-haematologic*~~
Non-haematological adverse reactions
If clinically significant moderate or severe non-haematological toxicity develops, bosutinib should be interrupted, and may be resumed at ~~400~~a dose reduced by 100 mg taken once daily ~~once~~after the toxicity has resolved. If clinically appropriate, re-escalation ~~of~~to the dose ~~to 500 mg~~prior to the dose reduction taken once daily should be considered (see section 4.4). Doses less than 300 mg/day have been used in patients; however, efficacy has not been established.

Elevated liver transaminases: If elevations in liver transaminases > 5- × institutional upper limit of normal (ULN) occur, bosutinib should be interrupted until recovery to ≤ 2.5 × ULN and may be resumed at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinuation of bosutinib should be considered. If transaminase elevations ≥ 3 × ULN occur concurrently with bilirubin elevations > 2 × ULN and alkaline phosphatase < 2 × ULN, bosutinib should be discontinued (see section 4.4).

Diarrhoea: For NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade 3-4 diarrhoea, bosutinib should be interrupted and may be resumed at 400 mg once daily upon recovery to grade ≤ 1 (see section 4.4).

~~*Dose adjustments for haematologic*~~*Haematological adverse reactions*
Dose reductions are recommended for severe or persistent neutropenia and thrombocytopenia as described in Table 1:

Table 1 – Dose adjustments for neutropenia and thrombocytopenia

ANC[a] < 1.0×10^9/L and/or Platelets < 50×10^9/L	Hold bosutinib until ANC ≥ 1.0×10^9/L and platelets ≥ 50×10^9/L. Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for > 2 weeks, upon recovery reduce dose by 100 mg and resume treatment. If cytopoenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses less than 300 mg/day have been used; however, efficacy has not been ~~evaluated~~established.

[a] ANC = absolute neutrophil count

Special populations

Elderly patients (≥ 65 years)
No specific dose recommendation is necessary in the elderly. Since there is limited information in the elderly, caution should be exercised in these patients.

Renal impairment
Patients with serum creatinine > 1.5×ULN were excluded from CML studies. Increasing exposure (area under curve [AUC~~)~~]) in patients with moderate and severe renal impairment during studies was observed.

Newly-diagnosed CP Ph+ CML
In patients with moderate renal impairment (creatinine clearance [CL_{Cr}] 30 to 50 mL/min, estimated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 300 mg daily with food (see sections 4.4 and 5.2).

In patients with severe renal impairment (CL_{Cr} < 30 mL/min, estimated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 200 mg daily with food (see sections 4.4 and 5.2).

Dose escalation to 400 mg once daily with food for patients with moderate renal impairment or to 300 mg once daily for patients with severe renal impairment may be considered if they do not experience severe or persistent moderate adverse reactions and if they do not achieve an adequate haematological, cytogenetic, or molecular response.

CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy
In patients with moderate renal impairment (~~creatinine clearance [Cr~~CL_{cr}~~]~~ 30 to 50 mL/min, calculated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 400 mg daily (see sections 4.4 and 5.2).

In patients with severe renal impairment (~~Cr~~CL_{cr} < 30 mL/min, calculated by the Cockroft-Gault formula), the recommended dose of bosutinib is 300 mg daily (see sections 4.4 and 5.2).

Dose escalation to 500 mg once daily for patients with moderate renal impairment or to 400 mg once daily in patients with severe renal impairment may be considered in those who did not experience severe or persistent moderate adverse reactions, and if they do not achieve an adequate haematological, cytogenetic, or molecular response~~under any of the following circumstances~~.

~~Circumstances for dose escalation~~
~~- *Failure to achieve CHR by Week 8*~~
~~- *Failure to achieve CCyR by Week 12*~~

Cardiac disorders
In clinical studies, patients with uncontrolled or significant cardiac disease (e.g., recent myocardial infarction, congestive heart failure or unstable angina) were excluded. Caution should be exercised in patients with relevant cardiac disorders (see section 4.4).

Recent or ongoing clinically significant gastrointestinal disorder
In clinical studies, patients with recent or ongoing clinically significant gastrointestinal disorder (e.g., severe vomiting and/or diarrhoea) were excluded. Caution should be exercised in patients with recent or ongoing clinically significant gastrointestinal disorder (see section 4.4).

Paediatric population
The safety and efficacy of bosutinib in children and adolescents less than 18 years of age have not been established. No data are available.

Method of administration
Bosulif should be taken orally once daily with food (see section 5.2). If a dose is missed by more than 12 hours, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

4.4 Special warnings and precautions for use
Fluid retention
Treatment with bosutinib may be associated with fluid retention including pericardial effusion, pleural effusion, pulmonary oedema and/or peripheral oedema. Patients should be monitored and managed using standard-of-care treatment. In addition, fluid retention can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see sections 4.2 and 4.8).

4.6 Fertility, pregnancy and lactation
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Fertility
Based on non-clinical findings, bosutinib has the potential to impair reproductive function and fertility in humans (see section 5.3). Men being treated with bosutinib are advised to seek advice on conservation of sperm prior to treatment because of the possibility of decreased fertility due to therapy with bosutinib.
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4.8 Undesirable effects

Summary of safety profile
A total of 1,272 leukaemia patients received at least 1 dose of single-agent bosutinib. The median duration of therapy was 13.8 months (range: 0.03 to 123.3 months). These patients were either newly diagnosed, with CP CML or were resistant or intolerant to prior therapy with chronic, accelerated, or blast phase CML or Ph+ acute lymphoblastic leukaemia (ALL). Of these patients, 268 (400 mg starting dose) and 248 (500 mg starting dose) are from the 2 Phase 3 studies in previously untreated CML patients, 570 and 63 are from 2 Phase 1/2 studies in previously treated Ph+ leukaemias, and 123 patients from a Phase 4 study in previously treated CML. The median duration of therapy was 14.1 months (range: 0.3 to 24.7 months), 61.6 months (0.03 to 99.6 months), 11.1 months (range: 0.03 to 123.3 months), 30.2 months (range: 0.3 to 85.6 months), and 5.7 months (range: 0.07 to 17.8 months), respectively. The safety analyses included data from an ongoing extension study.

At least 1 adverse reaction of any toxicity grade was reported for 1,240 (97.5%) patients. The most frequent adverse reactions reported for ≥ 20% of patients were diarrhoea (78.1%), nausea (40.8%), thrombocytopenia (34.9%), abdominal pain (34.0%), vomiting (33.0%), rash (31.5%), anaemia (25.6%), pyrexia (21.8%), fatigue (21.4%), and ALT increased (25.0%). At least 1 Grade 3 or Grade 4 adverse reaction was reported for 814 (63.9%) patients. The Grade 3 or Grade 4 adverse reactions reported for ≥ 5% of patients were thrombocytopenia (20.3%), anaemia (10.2%), neutropenia (10.5%), ALT increased (12.7%), diarrhoea (9.6%), rash (5.0%), lipase increased (8.2%), and AST increased (5.8%).

Tabulated list of adverse reactions

The following adverse reactions were reported in patients in bosutinib clinical studies (Table 2). These represent an evaluation of the adverse reaction data from 1,272 patients with either newly-diagnosed CP CML or with chronic, accelerated, or blast phase CML resistant or intolerant to prior therapy or Ph+ ALL who have received at least 1 dose of single-agent bosutinib. These adverse reactions are presented by system organ class and frequency. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 - Adverse reactions for bosutinib

Infections and infestations	
Very common	Respiratory tract infection (including Lower respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection, Viral upper respiratory tract infection), Nasopharyngitis
Common	Pneumonia (including Atypical pneumonia), Influenza, Bronchitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Uncommon	Tumour lysis syndrome**
Blood and lymphatic system disorders	
Very common	Thrombocytopenia (including Platelet count decreased), Neutropenia (including Neutrophil count decreased), Anaemia (including haemoglobin decreased)
Common	Leukopenia (including White blood cell count decreased)
Uncommon	Febrile neutropenia, Granulocytopenia
Immune system disorders	
Uncommon	Anaphylactic shock, Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Dehydration, Hyperkalaemia, Hypophosphataemia
Nervous system disorders	
Very common	Headache
Common	Dizziness, Dysgeusia
Ear and labyrinth disorders	
Common	Tinnitus
Cardiac disorders	
Common	Pericardial effusion, Electrocardiogram QTc prolonged (including Long QTc syndrome)
Uncommon	Pericarditis
Vascular disorders	
Common	Hypertension (including Blood pressure increased, Blood pressure systolic increased, Essential hypertension, Hypertensive crisis)
Respiratory, thoracic and mediastinal disorders	
Very common	Dyspnoea, Cough
Common	Pleural effusion
Uncommon	Pulmonary hypertension, Respiratory failure, Acute pulmonary oedema
Gastrointestinal disorders	
Very common	Diarrhoea, Vomiting, Nausea, Abdominal pain (including Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Gastrointestinal pain)
Common	Gastritis, Gastrointestinal haemorrhage (including Anal haemorrhage, Gastric haemorrhage, Intestinal haemorrhage, Lower gastrointestinal haemorrhage, Rectal haemorrhage)
Uncommon	Pancreatitis (including Pancreatitis acute)

Hepatobiliary disorders	
Very common	Alanine aminotransferase increased, Aspartate aminotransferase increased
Common	Hepatotoxicity (including Hepatitis, Hepatitis toxic, Liver disorder), Hepatic function abnormal (including Liver function test abnormal, Liver function test increased, Transaminases increased), Blood bilirubin increased (including Hyperbilirubinaemia), Gamma-glutamyltransferase increased
Uncommon	Liver injury (including Drug-induced liver injury)
Skin and subcutaneous tissue disorders	
Very common	Rash (including Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic)
Common	Urticaria, Acne, Pruritus
Uncommon	Exfoliative rash, Drug eruption
Rare	Erythema multiforme
Unknown	Stevens-Johnson Syndrome**, Toxic epidermal necrolysis**
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, Back pain
Common	Myalgia
Renal and urinary disorders	
Common	Acute kidney injury, Renal failure, Renal impairment
General disorders and administration site conditions	
Very common	Pyrexia, Asthenia, Oedema (including Face oedema, Localised oedema, Oedema peripheral), Fatigue (including Malaise)
Common	Chest pain (including Chest discomfort), Pain
Investigations	
Very common	Lipase increased (including Hyperlipasaemia)
Common	Blood creatinine increased, Amylase increased, Blood creatine phosphokinase increased

** Adverse reaction identified post marketing.

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להלן העדכונים העיקריים בעלון לצרכן:

1. למה מיועדת התרופה?

בוסוליף מיועדת לטיפול בחולים מבוגרים עם:

- שלב כרוני של לוקמיה מיאלואידית כרונית עם כרומוזום פילדלפיה חיובי אשר מאובחנים לראשונה
- שלב כרוני, שלב מואץ ושלב בלאסטי של לוקמיה מיאלואידית כרונית עם כרומוזום פילדלפיה חיובי אשר טופלו בעבר עם מעכב טירוזין קינאז אחד או יותר ועבור מי שטיפול עם אימטיניב (imatinib), נילוטיניב (nilotinib) ודסטיניב (dasatinib) אינו נחשב לאפשרות טיפולית מתאימה.

2. לפני השימוש בתרופה

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הריון והנקה

אין להשתמש בבוסוליף במהלך ההיריון, אלא אם כן יש צורך ברור, בגלל שבוסוליף עלולה לפגוע בעובר.
פני לרופא לקבלת ייעוץ לפני נטילת בוסוליף אם את בהריון או עלולה להרות.

לנשים הנוטלות בוסוליף מומלץ להשתמש באמצעי מניעה יעילים במהלך הטיפול. הקאות או שלשולים יכולים להפחית את היעילות של גלולות למניעת הריון.

קיים סיכון כי הטיפול עם בוסוליף יגרום לירידה בפוריות. ניתן לפנות לקבלת יעוץ לגבי שימור פוריות ו\או שימור זרע לפני תחילת הטיפול.

יש ליידע את הרופא אם את מניקה. אין להניק במהלך הטיפול עם בוסוליף מאחר והתרופה עלולה לפגוע בתינוק.

3. כיצד תשתמש בתרופה?

~~תמיד~~ יש להשתמש בתכשיר תמיד בהתאם ~~לפי~~ להוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן נטילת התכשיר.
המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.

- המינון המקובל בדרך כלל הוא 400 מ"ג פעם ביום בחולים שאובחנו לראשונה עם CML . המינון המקובל בדרך כלל הוא 500 מ"ג פעם ביום בחולים שטיפולים קודמים ל- CML לא התאימו או לא היו יעילים עבורם.

אם אתה סובל מבעיות בתפקוד הכליה, יתכן והרופא יוריד לך את המינון. הרופא יכול להתאים לך את המינון בהתאם למצבך הרפואי, ~~התגובה~~ לתגובה שלך לטיפול או לתופעות הלוואי אותן ~~אתה~~ אולי תחווה~~תחווה~~.
תרופה זו אינה מיועדת לילדים ולמתבגרים מתחת לגיל 18.

אין לעבור על המנה המומלצת!

4. תופעות לוואי

כמו בכל תרופה, השימוש בבוסוליף עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי, יתכן ולא תסבול מאף אחת מהן.
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תופעות לוואי נוספות:
תופעות לוואי שכיחות מאוד (עשויות להופיע ביותר מ-1 מכל 10 אנשים):
ירידה במספר הטסיות, תאי הדם האדומים ו/או נויטרופילים (סוג של תאי דם לבנים), שלשולים, הקאות, כאבי בטן, בחילות, חום, נפיחות של הידיים, הרגליים או הפנים, עייפות, חולשה, זיהום בדרכי הנשימה, דלקת של האף והלוע, שינויים בבדיקות דם כדי לקבוע האם בוסוליף משפיעה על הכבד ו\או הלבלב שלך, ירידה בתיאבון, כאבי מפרקים, כאב גב, כאב ראש, פריחה בעור העלולה לגרד או להתפשט, שיעול, קוצר נשימה.

תופעות לוואי שכיחות (עשויות להופיע בעד 1 מכל 10 אנשים):
ספירה נמוכה של תאי דם לבנים (לויקופניה), דלקת בקיבה, דימום מהקיבה או מהמעי, כאב, כאבים בחזה, נזק טוקסי לכבד, הפרעה בתפקוד הכבד כולל תפקוד לקוי, , דלקת ריאות, שפעת, דלקת הסמפונות, בעיות בקצב הלב שמובילות לעילפון, לסחרחורת ולדפיקות לב, עליה בלחץ דם, רמה גבוהה של אשלגן בדם, רמה נמוכה של זרחן בדם, התייבשות, כאבי שרירים, חוסר יציבות (סחרחורת), שינויים בחוש הטעם, כשל כלייתי חריף (אקוטי), כשל כלייתי, תפקוד לקוי של הכליות נוזלים סביב הריאות (תפליט פלאורלי), נוזלים סביב הלב (תפליט פריקרדיאלי), צלצולים באוזניים (טינטון), גרד, סרפדת ואקנה.

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא צוינה בעלון, עליך להתייעץ עם הרופא.

השינויים המודגשים ברקע צהוב מהווים החמרה. כמו כן, בוצעו שינויים נוספים הכוללים תוספת מידע, השמטת מידע ועדכוני נוסח שאינם מהווים החמרה. העלונים המעודכנים זמינים באתר משרד הבריאות.

https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h

לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פרמצבטיקה ישראל בע"מ, שנקר 9, ת.ד. 12133 הרצליה פיתוח, 46725.

בברכה,
מרגריטה פולישצ'וק
רוקחת ממונה