נובמבר 2020

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

שלום רב,

הנדון : **<u>עדכוני בטיחות בעלוני התכשיר</u>**
Jakavi 5/10/15/20 mg
ג'קאבי 5/10/15/20 מ"ג

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלון לרופא של התכשירים **Jakavi 5/10/15/20 mg**.

התוויות התכשיר:

<u>Myelofibrosis (MF)</u>

Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

<u>Polycythaemia vera (PV)</u>

Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

חומר פעיל:

Ruxolitinib (as phosphate) 5/10/15/20 mg

בהודעה זו מפורטים העדכונים המהווים עדכון במידע בטיחותי בלבד .למידע מלא יש לעיין בעלוני התכשיר.
העלונים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות ,וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום:
נוברטיס ישראל בע"מ.
תוצרת הארץ 6, ת.ד. 7126, תל אביב

העלון לרופא עודכן בנובמבר 2020, להלן העדכונים המהווים עדכון במידע בטיחותי (החמרה במידע בטיחותי מודגשת בצהוב):

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8. Undesirable effects

<u>Summary of the safety profile</u>

<u>Myelofibrosis</u>

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia.

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events

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[CTCAE] grade) included anaemia (83.8%), thrombocytopenia (80.5%) and neutropenia (20.8%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (33.3%), other bleeding (including epistaxis, post-procedural haemorrhage and haematuria) (24.3%) and dizziness (21.9%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (40.7%), raised aspartate aminotransferase (31.5%) and hypertriglyceridaemia (25.2%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypertriglyceridaemia, or raised aspartate aminotransferase, nor CTCAE grade 4 raised alanine aminotransferase or hypercholesterolaemia were observed.

Discontinuation due to adverse events, regardless of causality, was observed in 30.0% of patients.

Polycythaemia vera

Haematological adverse reactions (any CTCAE grade) included anaemia (61.8%) and thrombocytopenia (25.0%). Anaemia and thrombocytopenia CTCAE grade 3 or 4 were reported in respectively 2.9% and 2.6%.

The three most frequent non-haematological adverse reactions were weight gain (20.3%), dizziness (19.4%) and headache (17.9%) .

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) identified as adverse reactions were raised alanine aminotransferase (45.3%) raised aspartate aminotransferase (42.6%), and hypercholesterolaemia (34.7%). No CTCAE grade 4 raised alanine aminotransferase or hypercholesterolaemia, and one CTCAE grade 4 raised aspartate aminotransferase were observed.

Discontinuation due to adverse events, regardless of causality, was observed in 19.4% of patients.

Tabulated list of adverse drug reactions from clinical studies

Safety in MF patients was evaluated using the long-term follow-up data from two phase 3 studies (COMFORT-I and COMFORT-II) including data from patients initially randomised to ruxolitinib (n=301) and patients who received ruxolitinib after crossing over from control treatments (n=156). The median exposure upon which the ADR frequencies categories for MF patients are based was 30.5 months (range 0.3 to 68.1 months).

Safety in PV patients was evaluated using the long-term follow-up data from two phase 3 studies (RESPONSE, RESPONSE 2) including data from patients initially randomised to ruxolitinib (n=184) and patients who received ruxolitinib after crossing over from control treatments (n=156). The median exposure upon which the ADR frequencies categories for PV patients are based was 41.7 months (range 0.03 to 59.7 months).

In the clinical study programme the severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1 = mild, grade 2 = moderate, grade 3 = severe and grade 4=life-threatening.

Adverse drug reactions from clinical studies (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on

the following convention: 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).

Table 1 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE, RESPONSE 2)

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Infections and infestations		
Urinary tract infections[a,d]	Very common	Very common
Herpes zoster[a,d]	Very common	Very common
Pneumonia	Very common	Common
Sepsis	Common	Uncommon
Tuberculosis[e]	Uncommon	Unknown[f]
Blood and lymphatic system disorders[b,d]		
Anaemia[b]		
CTCAE[c] grade 4 (<6.5g/dl)	Very common	Uncommon
CTCAE[c] grade 3 (<8.0 – 6.5g/dl)	Very common	Common
Any CTCAE[c] grade	Very common	Very common
Thrombocytopenia[b]		
CTCAE[c] grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (50,000 – 25,000/mm^3)	Very common	Common
Any CTCAE[c] grade	Very common	Very common
Neutropenia[b]		
CTCAE[c] grade 4 (<500/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (<1,000 – 500/mm^3)	Common	Uncommon
Any CTCAE[c] grade	Very common	Very common
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	Very common	Very common
Bruising	Very common	Very common
Gastrointestinal bleeding	Very common	Common
Intracranial bleeding	Common	Uncommon
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Very common	Very common

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Metabolism and nutrition disorders		
Hypercholesterolaemia[b] any CTCAE[c] grade	Very common	Very common
Hypertriglyceridaemia[b] any CTCAE[c] grade	Very common	Very common
Weight gain[a]	Very common	Very common
Nervous system disorders		
Dizziness[a]	Very common	Very common
Headache[a]	Very common	Very common
Gastrointestinal disorders		
Elevated lipase, any CTCAE[c] grade	Very common	Very common
Constipation[a]	Very common	Very common
Flatulence[a]	Common	Common
Hepatobiliary disorders		
Raised alanine aminotransferase[b]		
CTCAE[c] grade 3 (> 5x – 20 x ULN)	Common	Common
Any CTCAE[c] grade	Very common	Very common
Raised aspartate aminotransferase[b]		
Any CTCAE[c] grade	Very common	Very common
Vascular disorders		
Hypertension[a]	Very common	Very common

[a] Frequency is based on adverse event data.
- A subject with multiple occurrence of an adverse drug reaction (ADR) is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[b] Frequency is based on laboratory values.
- A subject with multiple occurrences of an ADR is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[c] Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening

[d] These ADRs are discussed in the text.

[e] Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)

[f] ADR derived from post-marketing experience

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Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

Description of selected adverse drug reactions

Anaemia
In phase 3 clinical studies in MF, median time to onset of first CTCAE grade 2 or higher anaemia was 1.5 months. One patient (0.3%) discontinued treatment because of anaemia.

In patients receiving ruxolitinib mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomised, placebo-controlled study COMFORT-I 60.6% of Jakavi-treated MF patients and 37.7% of placebo-treated MF patients received red blood cell transfusions during randomised treatment. In the COMFORT-II study the rate of packed red blood cell transfusions was 53.4% in the Jakavi arm and 41.1% in the best available therapy arm.

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (40.8% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 2.7%, while in the MF patients the frequency was 42.56%.

Thrombocytopenia
In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm^3 was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving ruxolitinib and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving ruxolitinib and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm^3 to 200,000/mm^3 before starting ruxolitinib had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (16.8%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (2.7%) than in MF (11.6%) patients.

Neutropenia
In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 neutropenia, the median time to onset was 12 weeks. During the randomised period, dose holding or reductions due to neutropenia were reported in 1.0% of patients, and 0.3% of patients discontinued treatment because of neutropenia.

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In the randomised period of the phase 3 studies in PV patients, neutropenia was reported in 1.6% of patients exposed to ruxolitinib compared to 7% in reference treatments. In the ruxolitinib arm one patient developed CTCAE grade 4 neutropenia. An extended follow-up of patients treated with ruxolitinib showed 2 patients reporting CTCAE grade 4 neutropenia.

Bleeding

In the phase 3 pivotal studies in MF bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to ruxolitinib and 23.2% of patients exposed to the reference treatments (placebo or best available therapy). The frequency of grade 3-4 events was similar for patients treated with ruxolitinib or reference treatments (4.7% versus 3.1%). Most of the patients with bleeding events during the treatment reported bruising (65.3%). Bruising events were more frequently reported in patients taking ruxolitinib compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to ruxolitinib and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to ruxolitinib compared to 3.1% exposed to reference treatments. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with ruxolitinib and 10.3% treated with reference treatments.

During the long-term follow-up of phase 3 clinical studies in MF, the cumulative frequency of bleeding events increased proportionally to the increase in the follow-up time. Bruising events were the most frequently reported bleeding events (33.3%). Intracranial and gastrointestinal bleeding events were reported in 1.3% and 10.1% of patients respectively.

In the comparative period of phase 3 studies in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 16.8% of patients treated with ruxolitinib, 15.3% of patients receiving best available therapy in RESPONSE study and 12.0% of patients receiving best available therapy in RESPONSE 2 study. Bruising was reported in 10.3% of patients treated with ruxolitinib, 8.1% of patients receiving best available therapy in RESPONSE study and 2.7% of patients receiving best available therapy in RESPONSE 2 study. No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving ruxolitinib. One patient treated with ruxolitinib experienced a grade 3 bleeding event (post-procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage, gingival bleeding) were reported in 8.7% of patients treated with ruxolitinib, 6.3% of patients treated with best available therapy in RESPONSE study and 6.7% of patients treated with best available therapy in RESPONSE 2 study.

During the long-term follow-up of phase 3 studies in PV, the cumulative frequency of bleeding events increased proportionally to the increase in the follow-up time. Bruising events were the most frequently reported bleeding events (17.4%). Intracranial and gastrointestinal bleeding events were reported in 0.3% and 3.5% of patients respectively.

Infections

In the phase 3 pivotal studies in MF, grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%. In phase 3 clinical studies sepsis was reported in 3.0% of patients. An extended follow-up of patients treated with ruxolitinib showed no trends towards an increase in the rate of sepsis over time.

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In the randomised period of the phase 3 studies in PV patients, one (0.5%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was similar in PV (4.3%) patients and MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients. Pneumonia was reported in 0.5% of patients treated with ruxolitinib compared to 1.6% of patients in reference treatments. No patients in the ruxolitinib arm reported sepsis or tuberculosis.

During long-term follow-up of phase 3 studies in PV, frequently reported infections were urinary tract infections (11.8%), herpes zoster (14.7%) and pneumonia (7.1%). Sepsis was reported in 0.6% of patients. No patients reported tuberculosis in long-term follow-up.

Elevated lipase

In the randomised period of the RESPONSE study, the worsening of lipase values was higher in the ruxolitinib arm compared to the control arm, mainly due to the differences among grade 1 elevations (18.2% vs 8.1%). Grade ≥2 elevations were similar between treatment arms. In RESPONSE 2, the frequencies were comparable between the ruxolitinib and the control arm (10.8% vs 8%). During long-term follow-up of phase 3 PV studies, 7.4% and 0.9% of patients reported grade 3 and grade 4 elevation of lipase values. No concurrent signs and symptoms of pancreatitis with elevated lipase values were reported in these patients.

In phase 3 studies in MF, high lipase values were reported in 18.7% and 19.3% of patients in the ruxolitinib arms compared to 16.6% and 14.0% in the control arms in COMFORT-I and COMFORT-II studies, respectively. In patients with elevated lipase values, no concurrent signs and symptoms of pancreatitis were reported

Increased systolic blood pressure

In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0-2 mmHg on ruxolitinib versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT-II mean values showed little difference between the ruxolitinib-treated and the control-treated MF patients.

In the randomised period of the pivotal study in PV patients, the mean systolic blood pressure increased by 0.65 mmHg in the ruxolitinib arm versus a decrease of 2 mmHg in the BAT arm.

Reporting of suspected adverse reactions

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
https://sideeffects.health.gov.il

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העלון לצרכן עודכן בנובמבר 2020, להלן העדכונים המהווים עדכון במידע בטיחותי (החמרה במידע בטיחותי מודגשת בצהוב):

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2.לפני השימוש בתרופה

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אינטראקציות/תגובות בין תרופתיות

אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.

במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח את אחת מהתרופות הבאות, המכילות אחד מהחומרים הפעילים הבאים. יתכן והרופא יצטרך להתאים את מינון ג׳קאבי עבורך.

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תרופות נוספות:

- דביגטרן, ציקלוספורין, רוזובסטטין או דיגוקסין שרמתן בדם עלולה לעלות כאשר נוטלים אותן יחד עם ג׳קאבי

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4. תופעות לוואי

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יש לפנות לרופא מיד אם אתה חש באחת מתופעות הלוואי הבאות. חלקן שכיחות מאוד (very common) - תופעות העלולות להופיע ביותר מ-1 מתוך 10 מטופלים, חלקן שכיחות (common) - תופעות העלולות להופיע בעד 1 מתוך 10 מטופלים:

- כל סימן של דימום במוח, כגון: שינוי פתאומי במצב ההכרה, כאבי ראש ממושכים, חוסר תחושה, עקצוצים, חולשה או שיתוק (שכיח).
- כל סימן של דימום בקיבה או במעיים, כגון: צואה שחורה או מוכתמת בדם, או הקאה של דם (מאוד שכיח).
- חבלות ו/או דימומים לא צפויים, עייפות חריגה, קוצר נשימה במהלך פעילות גופנית או מנוחה, עור חיוור באופן חריג, או זיהומים חוזרים (תסמינים אפשריים של הפרעות בדם) (מאוד שכיח).
- פריחה כואבת בעור עם שלפוחיות (תסמינים אפשריים של שלבקת חוגרת [herpes zoster]) (מאוד שכיח).
- חום, צמרמורות או תסמינים אחרים של זיהומים (מאוד שכיח).
- רמות נמוכות של תאי דם אדומים (אנמיה), רמות נמוכות של תאי דם לבנים (נויטרופניה) או רמה נמוכה של טסיות (טרומבוציטופניה) (מאוד שכיח).

תופעות לוואי נוספות עם ג׳קאבי:

תופעות לוואי שכיחות מאוד (very common) - תופעות העלולות להופיע ביותר מ-1 מתוך 10 מטופלים:

- רמות גבוהות של כולסטרול או שומנים בדם (hypertriglyceridaemia)
- תוצאות לא תקינות של תפקוד הכבד
- סחרחורת
- כאב ראש
- דלקות בדרכי השתן
- עליה במשקל
- חום, שיעול, קשיים או כאב בנשימה, צפצופים, כאב בחזה בזמן נשימה (תסמינים אפשריים לדלקת ריאות)

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- לחץ דם גבוה, שעשוי גם להיות הסיבה לסחרחורת ולכאב ראש
- עצירות
- רמה גבוהה של ליפאז בדם

תופעות לוואי שכיחות (common) - תופעות העלולות להופיע בעד 1 מתוך 10 מטופלים:

- כמות עודפת של גזים במערכת העיכול (נפיחות)

תופעות לוואי שאינן שכיחות (uncommon) - תופעות העלולות להופיע בעד 1 מתוך 100 מטופלים:

- שחפת

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בברכה,

לריסה חייקין
רוקחת ממונה

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