# הודעה על החמרה (מידע בטיחות) בעלון לרופא
# (מעודכן 05.2013)

**תאריך: 2.1.2014**

**שם תכשיר באנגלית ומספר הרישום:**

**Jakavi 5mg, 15mg, 20mg tablets [33747, 33748, 33750]**

**שם בעל הרישום: Novartis Pharma Services AG**

טופס זה מיועד לפרוט ההחמרות בלבד !

| ההחמרות המבוקשות | | |
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| **טקסט חדש** | **טקסט נוכחי** | **פרק בעלון** |
| …<br>Posology<br>…<br>*Special populations*<br>*Renal impairment*<br>…<br>There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis.<br>Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for patients with ESRD on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for patients with platelet count between 100,000/mm3 and 200,000/mm3. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for patients with platelet count of >200,000/mm3. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session. These dose recommendations are based on simulations and any dose modification in | …<br>Posology<br>…<br>*Special populations*<br>*Renal impairment*<br>…<br>There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Available data in this population suggest that the starting dose for patients with ESRD on haemodialysis is a single dose of 15 mg or 20 mg, to be administered after haemodialysis has been completed and only on the day of haemodialysis. A single dose of 15 mg is for patients with platelet count between 100,000/$mm^3$ and 200,000/$mm^3$ or a single dose of 20 mg for patients with platelet count of >200,000/$mm^3$. Subsequent doses should be administered once daily on haemodialysis days following each dialysis session. Dosing only on dialysis days, applying a dialysis frequency of 3 times a week, is estimated to result in a low STAT3 inhibitory effect 24-48 hours post dose (see section 5.2). Other dosing regimens may be more suitable from an efficacy perspective. However, due to | 4.2 Posology and method of administration |

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| ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).<br>… | increased metabolite exposure and lack of knowledge on the potential safety consequences of these exposures, dose modification should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).<br>… | |
| …<br>Infections<br>Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi for myelofibrosis. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.<br>Jakavi therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly (see section 4.8).<br>… | …<br>Infections<br>Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi for myelofibrosis. Attention should be given to the possibility of latent or active tuberculosis.<br>Jakavi therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly (see section 4.8).<br>… | 4.4 Special warnings and precautions for use |
| …<br>Progressive multifocal leukoencephalopathy<br>Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for myelofibrosis. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric | …<br>Progressive Multifocal Leukencephalopathy<br>Progressive Multifocal leukencephalopathy (PML) has been reported with ruxolitinib treatment for myelofibrosis. Physicians should be alert for neuropsychiatric symptoms suggestive of PML.<br>… | 4.4 Special warnings and precautions for use |

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| symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.<br>… | | |
| …<br><br><u>Special populations</u><br>*Renal impairment*<br>The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose should be based on platelet counts (see section 4.2). Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy (see sections 4.2 and 5.2).<br>… | …<br><br><u>Special populations</u><br>*Renal impairment*<br>The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose should be based on platelet counts (see section 4.2). Subsequent doses (single administration) should be administered on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy (see sections 4.2 and 5.2).<br>… | 4.4 Special warnings and precautions for use |
| …<br>As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3-year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivotal phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.<br>… | … | 4.8 Undesirable effects |

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| **Table 1 Percentage of patients with adverse drug reactions in clinical studies*** | **Table 1 Percentage of patients with adverse drug reactions in clinical studies*** | 4.8 Undesirable effects |
| אנא ראו טבלה מצורפת בנספח 2 | אנא ראו טבלה מצורפת בנספח 1 | |

**Table 1 Percentage of patients with adverse drug reactions in clinical studies***

| Adverse drug reaction | Ruxolitinib – myelofibrosis patients N=301* | | |
|---|---|---|---|
| | All CTCAE grades[c] (%) | CTCAE grade 3/4[c] (%) | Frequency category |
| **Infections and infestations** | | | |
| Urinary tract infections[a,d] | 12.3 | 1.0 | Very common |
| Herpes zoster[a,d] | 4.3 | 0.3 | Common |
| **Blood and lymphatic system disorders[b,d]** | | | |
| Anaemia | 82.4 | 42.5 | Very common |
| Thrombocytopenia | 69.8 | 11.3 | Very common |
| Neutropenia | 15.6 | 6.6 | Very common |
| Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding) | 32.6 | 4.7 | Very common |
| Intracranial bleeding | 1.0 | 1.0 | Common |
| Gastrointestinal bleeding | 5.0 | 1.3 | Common |
| Bruising | 21.3 | 0.3 | Very common |
| Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria) | 13.3 | 2.3 | Very common |
| **Metabolism and nutrition disorders** | | | |
| Weight gain[a] | 10.0 | 1.3 | Very common |
| Hypercholesterolaemia[b] | 16.6 | 0 | Very common |
| **Nervous system disorders** | | | |
| Dizziness[a] | 15.0 | 0.3 | Very common |
| Headache[a] | 13.9 | 0.5 | Very common |
| **Gastrointestinal disorders** | | | |
| Flatulence[a] | 2.9 | 0 | Common |
| **Hepatobiliary disorders** | | | |
| Raised alanine aminotransferase[b] | 26.9 | 1.3 | Very common |
| Raised aspartate aminotransferase[b] | 19.3 | 0 | Very common |

* Myelofibrosis patients randomised to and treated with ruxolitinib from the phase 3 pivotal COMFORT-I and COMFORT-II studies

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.

**Table 1 Percentage of patients with adverse drug reactions in clinical studies***

| Adverse drug reaction | Ruxolitinib – myelofibrosis patients N=301* | | |
|---|---|---|---|
| | All CTCAE grades[c] (%) | CTCAE grade 3/4[c] (%) | Frequency category |
| **Infections and infestations** | | | |
| Urinary tract infections[a,d] | 12.3 | 1.0 | Very common |
| Herpes zoster[a,d] | 4.3 | 0.3 | Common |
| Tuberculosis[e] | 0.27 | 0.27 | Uncommon |
| **Blood and lymphatic system disorders[b,d]** | | | |
| Anaemia | 82.4 | 42.5 | Very common |
| Thrombocytopenia | 69.8 | 11.3 | Very common |
| Neutropenia | 15.6 | 6.6 | Very common |
| Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding) | 32.6 | 4.7 | Very common |
| Intracranial bleeding | 1.0 | 1.0 | Common |
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| **Metabolism and nutrition disorders** | | | |
| Weight gain[a] | 10.0 | 1.3 | Very common |
| Hypercholesterolaemia[b] | 16.6 | 0 | Very common |
| **Nervous system disorders** | | | |
| Dizziness[a] | 15.0 | 0.3 | Very common |
| Headache[a] | 13.9 | 0.5 | Very common |
| **Gastrointestinal disorders** | | | |
| Flatulence[a] | 2.9 | 0 | Common |
| **Hepatobiliary disorders** | | | |
| Raised alanine aminotransferase[b] | 26.9 | 1.3 | Very common |
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| * | Myelofibrosis patients randomised to and treated with ruxolitinib from the phase 3 pivotal COMFORT-I and COMFORT-II studies |
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| b | Frequency is based on laboratory values.<br>- A subject with multiple occurrences of an ADR is counted only once in that ADR category.<br>- 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 trials (N=4755) |

**מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.**

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

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# הודעה על החמרה (מידע בטיחות) בעלון לצרכן
# (מעודכן 05.2013)

**תאריך: 2.1.2014**

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| ההחמרות המבוקשות | | |
|---|---|---|
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **לפני השימוש בתרופה** | ...<br>**! לפני השימוש בג'קאבי, ספר לרופא** אם אחד המצבים הבאים רלבנטי אליך:<br>במידה ויש לך זיהום כלשהו. יתכן ויהיה צורך לטפל בזיהום לפני תחילת הטיפול בג'קאבי.<br>... | ...<br>**! לפני השימוש בג'קאבי, ספר לרופא** אם אחד המצבים הבאים רלבנטי אליך:<br>• במידה ויש לך זיהום כלשהו. יתכן ויהיה צורך לטפל בזיהום לפני תחילת הטיפול בג'קאבי. חשוב שתאמר לרופא שלך אם אי-פעם היתה לך שחפת או אם היית במגע קרוב עם מישהו שיש לו או שהיתה לו שחפת. הרופא שלך עשוי לבצע בדיקות כדי לגלות אם יש לך שחפת.<br>... |
| **לפני השימוש בתרופה** | ...<br>**! במהלך הטיפול עם ג'קאבי, יש ליידע את הרופא שלך או הרוקח:**<br>• ...<br>• אם יש לך אחד מהסימפטומים הבאים או אם מישהו קרוב אליך מבחין שיש לך את אחד מהסימפטומים האלו: בלבול או קשיים בחשיבה, איבוד שווי-משקל או קושי בהליכה, גמלוניות, קושי לדבר, ירידה בכוח או חולשה בצד אחד של גופך, ראייה מטושטשת ו/או אובדן ראייה (אלו הם סימנים של progressive multifocal leukoencephalopathy).<br>... | ...<br>**! במהלך הטיפול עם ג'קאבי, יש ליידע את הרופא שלך או הרוקח:**<br>• ...<br>• אם יש לך אחד מהסימפטומים הבאים או אם מישהו קרוב אליך מבחין שיש לך את אחד מהסימפטומים האלו: בלבול או קשיים בחשיבה, איבוד שווי-משקל או קושי בהליכה, גמלוניות, קושי לדבר, ירידה בכוח או חולשה בצד אחד של גופך, ראייה מטושטשת ו/או אובדן ראייה. אלו יכולים להיות סימנים של זיהום חמור במוח והרופא שלך עשוי להציע בדיקות נוספות ומעקב.<br>... |

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| **כיצד תשתמש בתרופה?** | **...**<br>**אין לעבור על המנה המומלצת.**<br>...<br>אם אתה מטופל בדיאליזה, קח מנה אחת של ג'קאבי בימי הדיאליזה, לאחר שהדיאליזה הושלמה. הרופא יאמר לך כמה טבליות לקחת בכל מנה.<br>... | **...**<br>**אין לעבור על המנה המומלצת.**<br>...<br>אם אתה מטופל בדיאליזה, קח מנה אחת של ג'קאבי או שתי מנות נפרדות של ג'קאבי רק בימי הדיאליזה, לאחר שהדיאליזה הושלמה. הרופא יאמר לך אם אתה צריך לקחת מנה אחת או שתי מנות וכמה טבליות לקחת בכל מנה.<br>... |

**מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.**
שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.