מרץ 2022

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

שלום רב,

הנדון : <u>עדכוני בטיחות בעלוני התכשיר</u>
<u>Mekinist 0.5mg and 2mg Film-Coated Tablets</u>

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלון לרופא ובעלון לצרכן של התכשירים **Mekinist 0.5mg** ו- **Mekinist 2mg**.

התוויות התכשיר:

<u>Melanoma</u>
Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy.
<u>Adjuvant treatment of melanoma</u>
Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.
<u>Non-small cell lung cancer (NSCLC)</u>
Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.
<u>Anaplastic Thyroid Cancer (ATC)</u>
Trametinib is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.

חומר פעיל:

TRAMETINIB (AS DIMETHYL SULFOXIDE) 0.5mg, 2mg

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 במרץ 2022, להלן העדכונים המהווים עדכון במידע בטיחותי (החמרה במידע בטיחותי מודגשת בצהוב):

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4.2 Posology and method of administration

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P.O.Box 7126 6 Tozeret Haaretz street, Tel Aviv
Tel: 972-3-9201111 Fax: 972-3-9229331

נוברטיס ישראל בע"מ.
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Table 2 Dose modification schedule based on the grade of any adverse reactions (excluding pyrexia)

Grade (CTC-AE)*	**Recommended trametinib dose modifications** Used as monotherapy or in combination with dabrafenib
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.
* The intensity of clinical adverse reactions graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)	

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Pyrexia
If a patient's temperature is ≥38ºC, therapy should be interrupted (trametinib when used as monotherapy, and both trametinib and dabrafenib when used in combination). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice (see section 4.4). Trametinib, or both trametinib and dabrafenib when used in combination, should be restarted if the patient is symptom free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

If treatment-related toxicities occur when trametinib is used in combination with dabrafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for ~~pyrexia,~~ uveitis, RAS mutation positive non-cutaneous malignancies (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions

~~*Pyrexia*~~
~~When trametinib is used in combination with dabrafenib and the patient's temperature is ≥38.5ºC please refer to the dabrafenib Prescribing Information (section 4.2) for dose modifications for dabrafenib. No dose modification of trametinib is required when taken in combination with dabrafenib.~~

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4.4 Special warnings and precautions for use

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Pyrexia

Fever has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib (see section 4.8). The incidence and severity of pyrexia are increased with the combination therapy (see dabrafenib Prescribing Information section 4.4). In patients receiving trametinib in combination with dabrafenib, pyrexia may be accompanied by severe rigors, dehydration, and hypotension which in some cases can lead to acute renal insufficiency.

Therapy (trametinib when used as monotherapy, and both trametinib and dabrafenib when used in combination) should be interrupted if the patient's temperature is ≥38ºC (see section 5.1). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection. Therapy can be restarted once the fever resolves. If fever is associated with other severe signs or symptoms, therapy should be restarted at a

reduced dose once fever resolves and as clinically appropriate (see section 4.2).~~When trametinib is used in combination with dabrafenib and the patient's temperature is ≥38.5ºC please refer to the dabrafenib Prescribing Information (section 4.2) for dose modifications for dabrafenib. No dose modification of trametinib is required when taken in combination with dabrafenib.~~

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5.1 Pharmacodynamic properties

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Other studies - pyrexia management analysis
Study CPDR001F2301 (COMBI-i) and Study CDRB436F2410 (COMBI-Aplus)
Pyrexia is observed in patients treated with dabrafenib and trametinib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia (fever ≥38.5°C). In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-Aplus, N=552), interruption of both medicinal products when patient's temperature is ≥38ºC (COMBI-Aplus), or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia) was advised. In COMBI-i and COMBI-Aplus there was a lower incidence of grade 3/4 pyrexia, complicated pyrexia, hospitalisation due to serious pyrexia adverse events of special interest (AESIs), the time spent in pyrexia AESIs, and permanent discontinuations from both medicinal products due to pyrexia AESIs (the latter in the adjuvant setting only) compared to COMBI-d, COMBI-v and COMBI-AD. The COMBI-Aplus study met its primary endpoint with a composite

rate of 8.0% (95% CI: 5.9, 10.6) for grade 3/4 pyrexia, hospitalisation due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to 20.0% (95% CI: 16.3, 24.1) for the historical control (COMBI-AD).

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העלון לצרכן עודכן במרץ 2021, להלן העדכונים המהווים עדכון במידע בטיחותי (החמרה במידע בטיחותי מודגשת בצהוב):

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2. לפני השימוש בתרופה

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חום
נטילת מקיניסט או שילוב של מקיניסט עם דבראפניב עלולה לגרום לחום, אם כי זה סביר יותר אם אתה נוטל את הטיפול המשולב (ראה גם סעיף 4). במקרים מסוימים, אנשים עם חום עלולים לפתח לחץ דם נמוך, סחרחורת או תסמינים אחרים.
ספר מיד לרופא אם יש לך חום מעל 38~~.5~~°C או אם אתה מרגיש שעומד לעלות לך החום בזמן שאתה לוקח תרופה זו.

בברכה,

אסתר תירוש
רוקחת ממונה

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