30 אוגוסט 2021

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

שלום רב,

הנדון : <u>עדכוני בטיחות בעלוני התכשיר</u>

Kisqali 200 mg /קיסקלי 200 מ"ג

Film Coated Tablets /טבליות מצופות

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלונים לרופא ולצרכן של התכשיר Kisqali 200 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.

התוויות התכשיר:

Kisqali is indicated in combination with:

- a non-steroidal aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, as initial endocrine-based therapy; or
- fulvestrant for the treatment of men and postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

חומר פעיל:

Ribociclib (as succinate) 200 mg

העלונים לרופא ולצרכן עודכנו באוגוסט 2021. להלן העדכונים המהווים עדכון בסעיף משטר מינון ובמידע בטיחותי בעלונים (טקסט מודגש בצהוב) :

בעלון לרופא:

4.2 Posology and method of administration

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Table 5 Dose modification and management – ILD/pneumonitis

	Grade 1* (asymptomatic)	**Grade 2*** (symptomatic)	**Grade 3 or 4*** (severe)
ILD/pneumonitis	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade ≤1, then resume Kisqali at the next lower dose level**.	Discontinue Kisqali
*Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events) **An individualised benefit-risk assessment should be performed when considering resuming Kisqali ILD = interstitial lung disease			

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Table 6Dose modification and management – Other toxicities*

Other toxicities	Grade 1 or 2**	Grade 3**	Grade 4**
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade ≤1, then resume Kisqali at the same dose level. If grade 3 recurs, resume Kisqali at the next lower dose level.	Discontinue Kisqali.
* Excluding neutropenia, hepatotoxicity, QT interval prolongation and ILD/pneumonitis ** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)			

4.4 Special warnings and precautions for use

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Interstitial lung disease/pneumonitis

ILD/pneumonitis has been reported with CDK4/6 inhibitors including Kisqali. In the 3 phase III clinical studies (MONALEESA-2 [A2301], MONALEESA-7 [E2301-NSAI] and MONALEESA-3 [F2301]), ILD (any grade 0.3%, including 0.1% grade 3) was reported in the Kisqali-treated group, with no cases in the placebo-treated group. Pneumonitis was reported in both the Kisqali- and the placebo-treated groups (any grade 0.4%, with no grade 3 or 4 in either treatment group).
Based on the severity of the ILD/pneumonitis, which may be fatal, Kisqali may require dose interruption, reduction or discontinuation as described in Table 5 (see section 4.2).

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough and dyspnoea and dose modifications should be managed in accordance with Table 5 (see section 4.2).

5.3 Preclinical safety data

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Carcinogenesis

Ribociclib was assessed for carcinogenicity in a 2-year study in rats.

Oral administration of ribociclib for 2 years resulted in an increased incidence of endometrial epithelial tumours and glandular and squamous hyperplasia in the uterus/cervix of female rats at doses ≥300 mg/kg/day as well as an increased incidence in follicular tumours in the thyroid glands of male rats at a dose of 50 mg/kg/day. Mean exposure at steady state (AUC_{0-24h}) in female and male rats in whom neoplastic changes were seen was 1.2- and 1.4-fold that achieved in patients at the recommended dose of 600 mg/day, respectively. Mean exposure at steady state (AUC_{0-24h}) in female and male rats in whom neoplastic changes were seen was 2.2- and 2.5-fold that achieved in patients at a dose of 400 mg/day, respectively.

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Additional non-neoplastic proliferative changes consisted of increased liver altered foci (basophilic and clear cell) and testicular interstitial (Leydig) cell hyperplasia in male rats at doses of ≥5 mg/kg/day and 50 mg/kg/day, respectively.

The effects on the uterus/cervix and on the testicular interstitial (Leydig) cells may be related to prolonged hypoprolactinemia secondary to CDK4 inhibition of lactotrophic cell function in the pituitary gland, altering the hypothalamus-pituitary-gonadal axis.

Potential mechanisms for the thyroid findings in males include a rodent-specific microsomal enzyme induction in the liver and/or a dysregulation of the hypothalamus-pituitary-testis-thyroid axis secondary to a persistent on-target hypoprolactinemia.

Any potential increase of oestrogen/progesterone ratio in humans by this mechanism would be compensated by an inhibitory action of concomitant anti-oestrogen therapy on oestrogen synthesis as in humans Kisqali is indicated in combination with oestrogen-lowering agents.

Considering important differences between rodents and humans with regard to synthesis and role of prolactin, this mode of action is not expected to have consequences in humans.

בעלון לצרכן:

ספר לרופא שלך או לרוקח אם אחד מהבאים חל עליך במהלך הטיפול בקיסקלי:

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- אתה חווה בעיות נשימה, שיעול וקוצר נשימה (עלולים להיות סימנים לבעיות ריאה או נשימה).

במידת הצורך, ייתכן שהרופא ירשום לך מינון נמוך יותר, יעצור את הטיפול בקיסקלי, או יפסיק אותו לצמיתות.

בברכה,

קרין שוורץ

רוקחת ממונה

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