פברואר 2020

רופא/ה נכבד/ה ,רוקח/ת נכבד/ה,

<u>הנדון: הודעה לצוות הרפואי על עדכוני בטיחות בעלוני התכשיר</u>

<u>Tykerb, Film Coated Tablets</u>

<u>טייקרב, טבליות מצופות</u>

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלון לצרכן ועלון לרופא של התכשיר Tykerb.

בהודעה זו מפורטים העדכונים המהווים החמרה במידע הבטיחותי 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
טלפון: 03-92011110

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

Tykerb is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

- in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.
- TYKERB is indicated in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.
  TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

<u>חומר פעיל</u> :

Lapatinib (as ditosylate monohydrate) 250 mg

העלונים לרופא ולצרכן עודכנו בינואר 2020. להלן העדכונים המהווים החמרה במידע הבטיחותי (מסומנים בצהוב):

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

נוברטיס ישראל בע"מ.
תוצרת הארץ 6, ת.ד. 7126, תל אביב
טלפון: 03-9201111 פקס: 03-9229331

עלון לרופא:

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4.4 Special warnings and precautions for use

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Cardiac toxicity

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A concentration-dependent increase of the QTc interval was demonstrated in a dedicated placebo-controlled crossover study in subjects with advanced solid tumours.

Caution should be taken if Tykerb is administered to patients with conditions that could result in prolongation of QTc (including hypokalemia, hypomagnesemia, and congenital long QT syndrome), co-administration of other medicinal product known to cause QT prolongation, or conditions that increase the exposure of lapatinib, such as co-administration of strong CYP3A4 inhibitors). Hypokalemia or hypomagnesemia should be corrected prior to treatment. Electrocardiograms with QT measurement should be performed prior to and one to two weeks after the start of Tykerb therapy. When clinically indicated, e.g. after initiation of a concomitant treatment that might affect QT or that may interact with lapatinib, ECG measurement should also be considered.

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4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with Tykerb and for at least 5 days after the last dose.

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Breast-feeding

The safe use of Tykerb during breast-feeding has not been established. It is not known whether lapatinib is excreted in human milk. In rats, growth retardation was observed in pups which were exposed to lapatinib via breast milk. Breast-feeding must be discontinued in women who are receiving therapy with Tykerb and for at least 5 days after the last dose.

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4.8 Undesirable effects

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Immune system disorders	
Rare	Hypersensitivity reactions including anaphylaxis (see section 4.3)

Metabolism and nutrition disorders	
Very common	Anorexia
Psychiatric disorders	
Very common	Insomnia*
Nervous system disorders	
Very common	Headache†
Common	Headache*
Cardiac disorders	
Common	Decreased left ventricular ejection fraction (see section 4.2 - dose reduction – cardiac events and section 4.4).
Not known	Ventricular arrhythmias/Torsades de Pointes, electrocardiogram QT prolonged**
Vascular disorders	
Very common	Hot flush†
Respiratory, thoracic and mediastinal disorders	
Very common	Epistaxis†, cough†, dyspnoea†.
Uncommon	Interstitial lung disease/pneumonitis.
Not known	Pulmonary arterial hypertension**.
Gastrointestinal disorders	
Very common	Diarrhoea, which may lead to dehydration (see section 4.2 - dose delay and dose reduction – other toxicities and section 4.4), nausea, vomiting, dyspepsia*, stomatitis*, constipation*, abdominal pain*.
Common	Constipation†
Hepatobiliary disorders	
Common	Hyperbilirubinaemia, hepatotoxicity (see section 4.4).
Skin and subcutaneous tissue disorders	
Very common	Rash (including dermatitis acneiform) (see section 4.2 - dose delay and dose reduction – other toxicities), dry skin*†, palmar-plantar erythrodysaesthesia*, alopecia†, pruritus†.
Common	Nail disorders including paronychia.
Notknown	Serious cutaneous reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)**

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Musculoskeletal and connective tissue disorders	
Very common	Pain in extremity*†, back pain*†, arthralgia†.
General disorders and administration site conditions	
Very common	Fatigue, mucosal inflammation*, asthenia†.

* These adverse reactions were observed when lapatinib was administered in combination with capecitabine.

† These adverse reactions were observed when lapatinib was administered in combination with letrozole.

** Adverse reactions from spontaneous reports and literature

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Description of selected adverse reactions

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Decreased left ventricular ejection fraction and QT interval prolongation

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A concentration dependent increase in QTcF (maximum mean ΔΔQTcF 8.75 ms; 90% CI 4.08, 13.42) was observed in a dedicated QT study in patients with advanced solid tumours (see section 4.4).

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5.1 Pharmacodynamic properties

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Cardiac electrophysiology

The effect of lapatinib on the QT-interval was evaluated in a single-blind, placebo-controlled, single sequence (placebo and active treatment) crossover study in patients with advanced solid tumours (EGF114271) (n=58). During the 4-day treatment period, three doses of matching placebo were administered 12 hours apart in the morning and evening on Day 1 and in the morning on Day 2. This was followed by three doses of lapatinib 2000 mg administered in the same way. Measurements, including electrocardiograms (ECGs) and pharmacokinetic samples, were taken at baseline and at the same time points on Day 2 and Day 4.

In the evaluable population (n=37), the maximum mean ΔΔQTcF (90% CI) of 8.75 ms (4.08, 13.42) was observed 10 hours after ingestion of the third dose of lapatinib 2000 mg. The ΔΔQTcF exceeded the 5 ms threshold and the upper bound 90% CIs exceeded the 10 ms threshold at multiple time points. The results for the pharmacodynamics population (n=52) were consistent with those from the evaluable population (maximum ΔΔQTcF (90% CI) of 7.91 ms (4.13, 11.68) observed 10 hours after ingestion of the third dose of lapatinib 2000 mg).

There is a positive relationship between lapatinib plasma concentrations and ΔΔQTcF. Lapatinib produced a maximum mean concentration of 3920 (3450-4460) ng/ml (geometric mean/95% CI), exceeding the geometric mean $C_{max.ss}$ and 95% CI values observed following the approved dosing regimens. An additional increase in peak exposure of lapatinib can be expected when lapatinib is taken repeatedly with food (see sections 4.2 and 5.2) or concomitantly with strong CYP3A4 inhibitors. When lapatinib is taken in combination with strong CYP3A4 inhibitors the QTc interval can be expected to be prolonged by 16.1 ms (12.6-20.3 ms) as demonstrated in a model-based prediction (see section 4.4).

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<u>עלון לצרכן:</u>

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הריון, הנקה ופוריות

ההשפעה של טייקרב במהלך הריון אינה ידועה. אל תקחי טייקרב אם את בהריון, אלא אם כן הרופא שלך המליץ על כך במפורש.

- **אם את בהריון** או מתכננת להיכנס להריון, **ספרי על כך לרופא.**
- **השתמשי באמצעי מניעה אמין** כדי למנוע הריון במהלך תקופת הטיפול בטייקרב ולפחות חמישה ימים לאחר המנה האחרונה.
- **אם את נכנסת להריון** במהלך תקופת הטיפול בטייקרב, **ספרי על כך לרופא שלך.**

לא ידוע אם טייקרב עוברת לחלב אם. אל תניקי במהלך תקופת הטיפול בטייקרב ולפחות חמישה ימים לאחר המנה האחרונה.

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4. <u>תופעות לוואי</u>

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תופעות לוואי שכיחות (תופעות שמופיעות ב- 1-10 משתמשים מתוך 100):

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- תוצאות של בדיקות דם המצביעות על שינויים בתפקוד הכבד (בדרך כלל שינויים קלים וזמניים).

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תופעות לוואי ששכיחותן אינה ידועה (תופעות ששכיחותן טרם נקבעה)**:**

- קצב לב לא סדיר (שינוי בפעילות החשמלית של הלב)
- תגובה עורית חריפה שעשויה לכלול: פריחה, עור אדום, שלפוחיות בשפתיים, בעיניים או בפה, קילוף בעור, חום או שילוב כלשהו של אלו
- יתר לחץ דם ריאתי (עליה בלחץ הדם בעורקים (כלי הדם) של הריאות)

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בברכה,

לריסה חייקין

רוקחת ממונה

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