אוקטובר 2022

רופא/ה, רוקח/ת נכבד/ה,

שלום רב,

<u>הנדון: עדכון עלוני התכשיר</u>

<u>Tabrecta 150 mg & Tabrecta 200 mg</u>

<u>טברקטה 150 מ"ג וטברקטה 200 מ"ג</u>

Film coated tablets / טבליות מצופות

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

התכשירים מתווים להתוויה הבאה:

TABRECTA is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an approved test.

המרכיב הפעיל:

CAPMATINIB (AS DIHYDROCHLORIDE MONOHYDRATE)

בהודעה זו מפורטים העדכונים המהותיים בלבד (ללא שינוי נוסח, עריכה, אדמיניסטרציה וכו'). למידע מלא על התרופה יש לעיין בעלון לרופא ובעלון לצרכן העדכניים של התכשיר .

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום נוברטיס ישראל בע"מ.

בברכה,

אסתר תירוש
רוקחת ממונה
נוברטיס ישראל בע"מ

Novartis Israel Ltd.
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

נוברטיס ישראל בע"מ
רח' תוצרת הארץ 6
ת.ד. 7126 תל אביב
טלפון: 03-9201123 פקס: 03-9229331

NOVARTIS

שינויים בעלון לרופא:

...

WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis, which can be fatal, occurred in patients treated with TABRECTA *[see Adverse Reactions (6.1)]*. ILD/pneumonitis occurred in 4.~~5~~8% of patients treated with TABRECTA in GEOMETRY mono-1, with 1.~~8~~9% of patients experiencing Grade 3 ILD/pneumonitis and one patient experiencing death (0.3%). ~~Eight~~Nine patients (2.4%) discontinued TABRECTA due to ILD/pneumonitis. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 1.48 months (range: 0.2 months to 1.~~2~~7 years).

Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold TABRECTA in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified *[see Dosage and Administration (2.3)]*.

5.2 Hepatotoxicity

Hepatotoxicity occurred in patients treated with TABRECTA *[see Adverse Reactions (6.1)]*. Increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in ~~13~~15% of patients treated with TABRECTA in GEOMETRY mono-1. Grade 3 or 4 increased ALT/AST occurred in ~~6~~7% of patients. Three patients (0.~~9~~8%) discontinued TABRECTA due to increased ALT/AST. The median time-to-onset of Grade 3 or higher increased ALT/AST was 1.~~4~~8 months (range: 0.5 to 46.4~~.1~~ months).

Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of TABRECTA, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue TABRECTA *[see Dosage and Administration (2.3)]*.

...

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Metastatic Non-Small Cell Lung Cancer

The safety of TABRECTA was evaluated in GEOMETRY mono-1 *[see Clinical Studies (14)]*. Patients received TABRECTA 400 mg orally twice daily until disease progression or unacceptable toxicity (N = ~~334~~373). Among patients who received TABRECTA, ~~31~~37% were exposed for at least 6 months and ~~16~~22% were exposed for at least one year.

Serious adverse reactions occurred in ~~51~~53% of patients who received TABRECTA. Serious adverse reactions in ≥ 2% of patients included dyspnea (7%), pneumonia (~~4.8~~7%), pleural effusion (4.3~~.6~~%), musculoskeletal pain (3.8%), general physical health deterioration (~~3%),~~ 2.9%), ILD/pneumonitis (2.7%), and vomiting (2.4~~%), and nausea (2.1%). A fatal~~%). Fatal adverse ~~reaction~~reactions occurred in ~~one patient~~0.5% of patients who received TABRECTA, including pneumonitis (0.3%) ~~due to pneumonitis.~~and death, not otherwise specified (0.3%).

Permanent discontinuation of TABRECTA due to an adverse reaction occurred in ~~16~~17% of patients. The most frequent adverse reactions (≥ 1%) leading to permanent discontinuation of TABRECTA were ~~peripheral edema (1.8%),~~ ILD/pneumonitis (~~1.8%), and~~ 2.4%), edema (2.4%), fatigue (1.~~5~~3%), and pneumonia (1.1%).

Novartis Israel Ltd.
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

נוברטיס ישראל בע"מ
רח' תוצרת הארץ 6
ת.ד. 7126 תל אביב
טלפון: 03-9201123 פקס: 03-9229331

NOVARTIS

Dose interruptions due to an adverse reaction occurred in ~~54~~57% of patients who received TABRECTA. Adverse reactions requiring dosage interruption in > 2% of patients who received TABRECTA included ~~peripheral~~ edema, increased blood creatinine, nausea, increased lipase, vomiting, increased ~~lipase, increased~~ ALT, dyspnea, pneumonia, fatigue, increased amylase, increased AST, musculoskeletal pain, abdominal pain, and increased blood bilirubin~~, fatigue, and pneumonia~~.

Dose reductions due to an adverse reaction occurred in ~~23~~26% of patients who received TABRECTA. Adverse reactions requiring dosage reductions in > 2% of patients who received TABRECTA included ~~peripheral~~ edema, increased ALT~~,~~ and increased blood creatinine~~, and nausea~~.

The most common adverse reactions (≥ 20%) in patients who received TABRECTA were ~~peripheral~~ edema, nausea, musculoskeletal pain, fatigue, vomiting, dyspnea, cough, and decreased appetite.

Table 3 summarizes the adverse reactions in GEOMETRY mono-1.

Table 3: Adverse Reactions (≥ 10%) in Patients Who Received TABRECTA in GEOMETRY mono-1

Adverse ~~Reactions~~reactions	**TABRECTA (N = ~~334~~373)**	
	Grades 1 to 4 (%)	**Grades 3 to ~~4~~[a]4 (%)**
General disorders and administration-site conditions		
~~Peripheral edema~~[b]Edema[a]	~~52~~59	~~9~~13
Musculoskeletal pain[b]	40	4.3
Fatigue[c]	~~32~~34	8
~~Non-cardiac chest pain~~[d]	~~15~~	~~2.1~~
~~Back pain~~Pyrexia[d]	14	0.~~9~~8
~~Pyrexia~~[e]	~~14~~	~~0.6~~
Weight decreased	~~10~~11	0.~~6~~5
Gastrointestinal disorders		
Nausea	~~44~~46	2.~~7~~4
Vomiting	28	2.4
Constipation	~~18~~19	0.~~9~~8
Diarrhea	~~18~~19	0.~~3~~5
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	~~24~~25	~~7~~[a]7
~~Cough~~Cough[c]	~~16~~21	0.~~6~~5
Pneumonia[f]	13	6
Metabolism and nutrition disorders		
Decreased appetite	21	~~0.9~~1.1
Skin and subcutaneous tissue disorders		
Rash[g]	12	0.5
Nervous system disorders		
Dizziness[h]	13	0.5

[a] ~~Only~~[a]Edema includes ~~Grade 3 adverse reactions with exception of dyspnea. Grade 4 dyspnea was reported in 0.6% of patients.~~

[b] ~~Peripheral~~ edema ~~includes~~ peripheral ~~swelling,~~ , generalized edema, face edema, edema, localized edema, edema genital, eyelid edema, peripheral swelling, scrotal edema, and ~~fluid overload~~penile edema.

[c] ~~Fatigue includes fatigue and asthenia.~~

[d] ~~Non-cardiac chest~~[b]Musculoskeletal pain includes ~~chest discomfort,~~ arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, ~~and chest~~pain in extremity, pain in jaw, spinal pain.

Novartis Israel Ltd.
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

נוברטיס ישראל בע"מ
רח' תוצרת הארץ 6
ת.ד. 7126 תל אביב
טלפון: 03-9201123 פקס: 03-9229331

[e]~~Pyrexia~~[c]Fatigue includes fatigue and asthenia.
[d]Pyrexia includes pyrexia and body temperature increased.
[c]Cough includes upper airway cough syndrome, and productive cough.
[f]Pneumonia includes pneumonia aspiration, pneumonia, pneumonia influenzal, pneumonia bacterial, lower respiratory tract infection, and lung abscess.
[g]Rash includes rash, dermatitis acneiform, rash maculo-papular, eczema, erythema multiforme, rash macular, dermatitis, rash erythematous, rash pustular, dermatitis bullous, and rash vesicular.
[h]Dizziness includes dizziness, vertigo, and vertigo positional.

Clinically relevant adverse reactions occurring in < 10% of patients treated with TABRECTA included pruritus (including allergic ~~and generalized~~pruritus), ILD/pneumonitis, cellulitis, acute kidney injury (including renal failure), urticaria, and acute pancreatitis.

Table 4 summarizes the laboratory abnormalities in GEOMETRY mono-1.

Table 4: Select Laboratory Abnormalities (≥ 20%) Worsening F~~f~~rom Baseline in Patients Who Received TABRECTA in GEOMETRY mono-1

Laboratory ~~Abnormalities~~abnormalities	TABRECTA[a]	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
Chemistry		
Decreased albumin	~~68~~72	1.~~8~~9
Increased creatinine	~~62~~65	0.~~3~~5
Increased alanine aminotransferase	~~37~~39	~~8~~9
Increased ~~alkaline phosphatase~~amylase	~~32~~34	~~0.3~~4.7
Increased ~~amylase~~alkaline phosphatase	~~31~~32	~~4.4~~0.6
Increased gamma-glutamyltransferase	~~29~~30	~~7~~6
Increased lipase	~~26~~29	~~7~~9
Increased aspartate aminotransferase	~~25~~28	~~4.9~~6
Decreased ~~sodium~~phosphate	~~23~~26	~~6~~4.4
Increased potassium~~Decreased phosphate~~	~~23~~25	4.~~6~~1
Decreased sodium~~Increased potassium~~	~~23~~24	~~3.1~~6
Decreased glucose	~~21~~23	0.3
Hematology		
Decreased lymphocytes	~~44~~45	14
Decreased leukocytes	25	1.7
Decreased hemoglobin	24	2.8
~~Decreased leukocytes~~	~~23~~	~~0.9~~

[a]~~The~~[a]The denominator used to calculate the rate varied from ~~320~~359 to ~~325~~364 based on the number of patients with a baseline value and at least one post-treatment value.

...

8.2 Geriatric Use

In GEOMETRY mono-1, ~~57~~61% of the ~~334~~373 patients were 65 years or older and ~~16~~18% were 75 years or older. No overall differences in the safety or effectiveness were observed between these patients and younger patients.

Novartis Israel Ltd.
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

נוברטיס ישראל בע"מ
רח' תוצרת הארץ 6
ת.ד. 7126 תל אביב
טלפון: 03-9201123 פקס: 03-9229331

שינויים בעלון לצרכן:

תופעות לוואי
כמו בכל תרופה, השימוש בטברקטה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן שלא תסבול מאף אחת מהן.

תופעות לוואי שכיחות מאוד (very common) (עשויות להשפיע על יותר ממשתמש אחד מתוך 10 משתמשים):
....

- נפיחות בידיים או בכפות הרגליים
- הקאות
- בחילות
- כאב בשריר או בעצם
- אובדן תיאבון
- עייפות וחולשה
- קושי בנשימה
- ~~קוצר נשימה~~
- דלקת ריאות
- ~~כאב בחזה שמקורו אינו בלב~~
- ~~כאב גב~~
- עליית חום הגוף
- ירידה במשקל
- עצירות
- שלשול
- שיעול
- פריחה בעור
- סחרחורות
- שינויים בבדיקות דם מסוימות:

כימיה
רמה נמוכה של אלבומין
רמה גבוהה של קריאטינין
רמה גבוהה של אלקליין פוספטאז
רמה גבוהה של עמילאז
רמה גבוהה של גמא-גלוטמיל טרנספראז
רמה גבוהה של ליפאז
רמה נמוכה של נתרן
רמה נמוכה של זרחן
רמה גבוהה של אשלגן
רמה נמוכה של גלוקוז
המטולוגיה
רמה נמוכה של לימפוציטים
רמה נמוכה של המוגלובין
רמה נמוכה של לויקוציטים

...
כיצד נראית התרופה ומה תוכן האריזה
טברקטה 150 מ"ג: טבליה מצופה בצבע כתום-חום בהיר, אליפטית, מקומרת עם קצוות משופעים, עם הטבעה של DU בצד אחד ו-NVR בצד השני. כל אריזה מכילה 120 טבליות מצופות.
טברקטה 200 מ"ג: טבליה מצופה בצבע צהוב, אליפטית, מקומרת עם קצוות משופעים, עם הטבעה של LO בצד אחד ו-NVR בצד השני. כל אריזה מכילה 120 טבליות מצופות.

נוברטיס ישראל בע"מ
רח' תוצרת הארץ 6
ת.ד. 7126 תל אביב
טלפון: 03-9201123 פקס: 03-9229331

Novartis Israel Ltd.
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331