ינואר 2020

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון:
Vitrakvi 25mg, Vitrakvi 100mg,
ויטראקבי 25 מ"ג, ויטראקבי 100 מ"ג
Capsules
Larotrectinib (as sulfate) 25mg, 100mg

Vitrakvi 20 mg/ml oral solution
Solution
Larotrectinib (as sulfate) 20mg/ml

אנו מבקשים להודיעכם שהעלון לרופא והעלון לצרכן של התכשירים שבנדון עודכנו.

ההתוויה המאושרת לתכשיר:
Vitrakvi as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,
• Who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
• Who have no satisfactory treatment options

בהודעה זו כלולים העידכונים המהותיים בלבד, בפירוט שלהלן מופיע, רק המידע שהתעדכן. תוספת טקסט מודגש בצבע אדום ומסומן בקו תחתון.

לתשומת ליבכם, המידע בפרק 5 בעלון הרופא (**PHARMACOLOGICAL PROPERTIES**) התעדכן לאור הצטברות מידע נוסף לאור מחקרים שבוצעו, המידע במלואו מופיע בעלון לרופא ולצרכן אשר נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp
כמו כן, ניתן לקבלם מודפסים ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700

העדכונים בעלון לרופא:

Effect of larotrectinib on substrates of PXR regulated enzymes
In vitro studies indicate that larotrectinib is a weak ~~may~~ inducer of PXR regulated enzymes (e.g. CYP2C family and UGT). Co-administration of larotrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

4.8 Undesirable effects

Summary of the safety profile

~~The safety of VITRAKVI was evaluated in 125 patients with TRK fusion-positive cancer in one of three clinical trials, Studies 1, 2 ("NAVIGATE"), and 3 ("SCOUT"). Median time on treatment for the overall safety population was 7.4 months (range: 0.03 to 40.7). The safety population characteristics were comprised of patients with a median age of 45 years (range: 0.1, 80) with 30% of patients being paediatric patients.~~ The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were ~~fatigue (32%),~~ increased ALT (~~31~~32%), fatigue (30%), constipation (29%), increased AST (27%), dizziness (~~30~~26%), ~~increased AST (29%), constipation (29%),~~ vomiting (23%), ~~nausea (26%),~~ anaemia (~~24~~23%), and ~~nausea (22%)vomiting (20%)~~.

The majority of adverse reactions were Grade 1 or 2. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (1~~.6~~%) ~~and~~ ALT increased (~~<~~ 1%), and AST increased (<1%). The highest reported grade was Grade 3 for adverse reactions anaemia, weight increased, fatigue, ~~increased AST,~~ dizziness, paraesthesia, muscular weakness, ~~-~~nausea, myalgia, gait disturbance, vomiting, and leukocyte count decreased. All the reported Grade 3 adverse reactions occurred in less than 5% of patients, with the exception of anaemia (~~7~~8%).
Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions, regardless of attribution occurred in ~~3~~5% of patients (one case each of ALT increased, AST increased, bile duct adenocarcinoma, gait disturbance, intestinal perforation, jaundice, malignant neoplasm progression, neutrophil count decreased, small intestinal obstruction, spinal cord compression, and viral infection).
The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

Tabulated list of adverse reactions

The safety of VITRAKVI was evaluated in 196 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 ("NAVIGATE"), and 3 ("SCOUT"). The safety population characteristics were comprised of patients with a median age of 37.5 years (range: 0.1, 84) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=196) was 9.3~~tt~~ months (range: 0.10, 51.6)
The adverse drug reactions reported in patients (n=196) treated with VITRAKVI are shown in Table 2 and Table 3.

The adverse drug reactions are classified according to the System Organ Class.
Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), and not known (cannot be estimated from available data).
Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population, n=~~125~~196)

System organ class	Frequency	All grades	Grades 3 and 4
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	
	Common		Anaemia Neutrophil count decreased (Neutropenia)[a] ~~Leukocyte count decreased (Leukopenia)~~
	Uncommon		Leukocyte count decreased (Leukopenia)
Nervous system disorders	Very common	Dizziness ~~Paraesthesia~~	
	Common	Gait disturbance Paraesthesia	Dizziness Paraesthesia
	Uncommon		Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting	
	Common	Dysgeusia[b]	~~Nausea~~
	Uncommon		Nausea Vomiting
Musculoskeletal and connective tissue disorders	Very common	Myalgia ~~Muscular weakness~~	
	Common	Muscular weakness	Myalgia Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	
	Common		Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)	
	Common	Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased[a] Aspartate aminotransferase (AST) increased[a] Weight increased (Abnormal weight gain)

[a] Grade 4 reactions were reported

[b] ADR dysgeusia includes the preferred terms "dysgeusia" and "taste disorder"

Table 3: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=~~37~~73); all Grades

System organ class	Frequency	Infants and toddlers (n=~~14~~29)[a]	Children (n=~~15~~30)[b]	Adolescents (n=~~8~~14)[c]	Paediatric patients (n=~~37~~73)
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)
Nervous system disorders	Very common			Dizziness ~~Paraesthesia~~	
	Common		Dizziness Paraesthesia Gait disturbance	Paraesthesia	Dizziness Paraesthesia Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting	Nausea Constipation Vomiting	Nausea Vomiting	Nausea Constipation Vomiting
	Common		Dysgeusia	Constipation	Dysgeusia
Musculoskeletal and connective tissue disorders	~~Very common~~ Common		Myalgia Muscular weakness	~~Myalgia~~ ~~Muscular weakness~~ Myalgia Muscular weakness	Myalgia Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	Fatigue	Fatigue	Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased ~~Weight increased (Abnormal weight gain)~~ Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased

	Common	~~Blood alkaline phosphatase increased~~	Weight increased (Abnormal weight gain)	Weight increased (Abnormal weight gain)	

[a] Infant/toddlers (28 days to 23 months): ~~one~~ two Grade 4 Neutrophil count decreased (Neutropenia) reactions reported. Grade 3 reactions included ~~two~~ seven cases of Neutrophil count decreased (Neutropenia), ~~and one~~ three cases of ~~anaemia~~Anaemia, ~~,~~three cases of Weight increased (Abnormal weight gain), and one case each of ALT increased and Vomiting. [b]

[b] Children (2 to 11 years): no Grade 4 reactions were reported. ~~One~~ Three reported Grade 3 cases ~~each~~ of Neutrophil count decreased (Neutropenia), and one case each of Paraesthesia and ~~,~~ Myalgia~~, Weight increased (Abnormal weight gain).~~

[c] Adolescents (12 to <18 years): no Grades 3 and 4 reactions were reported.

Description of selected adverse reactions

Neurologic reactions

In the overall safety database (n=~~125~~196), the maximum grade neurologic reaction observed was Grade 3 which was observed in ~~three~~ five (~~2~~3%) patients and included dizziness (~~one~~ two patients, ~~<~~1%), ~~and~~ paraesthesia (two patients, 1~~.6~~%). and gait disturbance (one patient, <1%). The overall incidence was ~~30~~26% for dizziness, ~~10~~8% for paraesthesia and ~~3~~4% for gait disturbance. Neurologic reactions leading to dose modification included dizziness (2%)~~.~~, paraesthesia (1%), and gait disturbance (<1%). One patient permanently discontinued the treatment due to Grade 3 gait disturbance. ~~None of these adverse reactions led to treatment discontinuation.~~ In all cases~~,~~ except of one, patients with evidence of anti-tumour activity who required a dose reduction were able to continue dosing at a reduced dose and/or schedule (see section 4.4).

Transaminase elevations

In the overall safety database (n=~~125~~196), the maximum grade transaminase elevation observed was Grade 4 ALT increase in ~~1~~ 2 patients (~~<~~1%) and AST increase in 1 patient (<1%). Grade 3 ALT and AST increases in ~~3~~ 4 (2%) and 2 (~~2~~1%) of patients, respectively. Majority of Grade 3 elevations were transient appearing in the first or second month of treatment and resolving to Grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in ~~9~~ 10 (~~7~~5%) and ~~6~~ 8 (~~5~~4%) of patients, respectively, and Grade 1 ALT and AST increases were observed in ~~26~~ 47 (~~21~~24%) and ~~28~~ 41 (~~22~~21%) of patients, respectively.

ALT and AST increases leading to dose modifications occurred in ~~7~~ 10 (~~6~~5%) patients and ~~6~~ 8 (~~5~~4%) patients, respectively (see section 4.4). No patient permanently discontinued the treatment due to Grade 3-4 ALT and AST increases.

Additional information on special populations

Paediatric patients

Of the ~~125~~ 196 patients treated with VITRAKVI, ~~37~~ 73 (~~30~~37%) patients were from 28 days to 18 years of age. Of these ~~37~~ 73 patients, ~~38~~40% were 28 days to < 2 years (n=~~14~~29), 41% were 2 years to < 12 years (n=~~15~~30), and ~~22~~19% were 12 years to < 18 years (n=~~8~~14). The safety profile in the paediatric population (< 18 years) was consistent in types of reported adverse reactions to those observed in the adult population. The majority of adverse reactions were Grade 1 or 2 in severity (see Table 3) and were resolved without VITRAKVI dose modification or discontinuation. The adverse reactions of vomiting (~~35~~38% versus ~~14~~15% in adults), leucocyte count decrease (~~22~~16% versus ~~9~~11% in adults), neutrophil count decrease (~~30~~27% versus 7% in adults), and blood alkaline phosphatase increased (~~14~~12% versus ~~2~~4% in adults) ~~and transaminase elevations (ALT 41% versus 27% in adults and AST 35% versus 26% in adults)~~ were more frequent in paediatric patients compared to adults.

Elderly
Of the ~~125~~ 196 patients in the overall safety population who received VITRAKVI, ~~28~~ 35 (~~22~~18%) patients were 65 years or older and ~~8~~ 10 (~~6~~5%) patients were 75 years or older. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients ~~(< 65 years)~~. The adverse reaction~~s~~ gait disturbance (~~17~~11% versus ~~3~~5% ~~in under 65 years~~ in all adults)~~, and blood alkaline phosphatase increased (4% versus 2% in under 65 years) were~~ was more frequent in patients of 65 years or older.

העדכונים בעלון לצרכן:

4. תופעות לוואי

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

עליך לפנות **לרופא באופן מיידי** אם אתה סובל מאחת **מתופעות הלוואי החמורות** שלהלן:
- תחושת סחרחורת, ~~עקצוץ, תחושת נימול או תחושת צריבה בכפות הידיים ובכפות הרגליים~~ (תופעת לוואי שכיחה מאוד, עלולה להשפיע על יותר מ-1 מתוך 10 משתמשים), עקצוץ, תחושת נימול, או תחושת צריבה בכפות הידיים ובכפות הרגליים, קושי ללכת באופן נורמלי (תופעת לוואי שכיחה, עלולה להשפיע על עד 1 מתוך 10 משתמשים). אלה עלולים להיות תסמינים של **בעיות במערכת העצבים**.

ייתכן כי הרופא יחליט להפחית את המינון, או להשהות או להפסיק את הטיפול.

תופעות לוואי נוספות
שכיחות מאוד (עלולות להשפיע על יותר מ-1 מתוך 10 משתמשים):
- אתה עלול להיראות חיוור ולהרגיש את פעימות הלב שלך; אלה עלולים להיות תסמיני רמה נמוכה של תאי הדם האדומים (אנמיה)
- תסמינים דמויי שפעת לרבות חום; אלה עלולים להיות תסמיני רמה נמוכה של תאי הדם הלבנים (נויטרופניה, לויקופניה)
- בחילות או הקאות
- עצירות
- כאב שרירים (מיאלגיה)
- ~~חולשת שרירים~~
- תחושת עייפות (תשישות)
- רמה גבוהה של אנזימי כבד בבדיקות דם
- עלייה במשקל.

שכיחות (עלולות להשפיע על עד 1 מתוך 10 משתמשים):
- שינוי בחוש הטעם (דיסגאוזיה)
- חולשת שרירים
- רמה גבוהה של "פוספטאז בסיסי" בבדיקות דם (תופעה שכיחה מאוד בילדים).

בברכה,
באייר ישראל