יוני 2022

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 של התכשירים שבנדון עודכן.

**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://israeldrugs.health.gov.il/#!/byDrug
כמו כן, ניתן לקבלם מודפסים ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700

**העדכונים בעלון לרופא:**

**4.8 Undesirable effects**

Summary of the safety profile

The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were increased ALT (312%), increased AST (29%), vomiting (29%), constipation (28%), fatigue (3026%), ~~constipation (29%),increased AST (27%),~~ nausea (25%), anaemia (24%), dizziness (236%), ~~vomiting (23%), anaemia (23%),~~ and myalgia (20%) ~~nausea (22%)~~.
The majority of adverse reactions were Grade 1 or 2. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (21%) ALT increased (1%) ~~and~~ AST increased, leucocyte count decreased and blood alkaline phosphatase increased (each in <1%).The highest reported grade was Grade 3 for adverse reactions anaemia, weight increased, fatigue, dizziness, paraesthesia, muscular weakness, nausea, myalgia, gait disturbance, and vomiting ~~and leukocyte count decreased~~. All the reported Grade 3 adverse reactions occurred in less than 5% of patients, with the exception of anaemia (78%).

Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions, regardless of attribution occurred in 25% 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 248196 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 327.5 years (range: 0.1, 84) with 397% of patients being paediatric patients. Median time on treatment for the overall safety population (n=248196) was 12.59.3 months (range: 0.103, 571.56).
The adverse drug reactions reported in patients (n=196248) 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=196248)**

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

[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=7398); all Grades**

| System organ class | Frequency | Infants and toddlers (n=2935)[a] | Children (n=3045)[b] | Adolescents (n=184)[c] | Paediatric patients (n=7398) |
|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | Very common | Anaemia<br>Neutrophil count decreased (Neutropenia)<br>Leukocyte count decreased (Leukopenia) | Anaemia<br>Neutrophil count decreased (Neutropenia)<br>Leukocyte count decreased (Leukopenia) | Neutrophil count decreased (Neutropenia)<br>Leukocyte count decreased (Leukopenia) | Anaemia<br>Neutrophil count decreased (Neutropenia)<br>Leukocyte count decreased (Leukopenia) |
| | Common | | | Anaemia | |
| **Nervous system disorders** | Very common | | | Dizziness | |
| | Common | Dizziness | Dizziness<br>Paraesthesia<br>Gait disturbance | Paraesthesia | Dizziness<br>Paraesthesia<br>Gait disturbance |
| **Gastrointestinal disorders** | Very common | Nausea<br>Constipation<br>Vomiting | Nausea<br>Constipation<br>Vomiting | Nausea<br>Vomiting | Nausea<br>Constipation<br>Vomiting |
| | Common | | Dysgeusia | Constipation | Dysgeusia |
| **Musculoskeletal and connective tissue disorders** | Common | | Myalgia<br>Muscular weakness | Myalgia<br>Muscular weakness | Myalgia<br>Muscular weakness |
| **General disorders and administration site conditions** | Very common | Fatigue | Fatigue | Fatigue | Fatigue |
| **Investigations** | Very common | Alanine aminotransferase (ALT) increased<br>Aspartate aminotransferase (AST) increased<br>Weight increased (Abnormal weight gain)<br>Blood alkaline Phosphatase increased | Alanine aminotransferase (ALT) increased<br>Aspartate aminotransferase (AST) increased<br>~~Blood alkaline phosphatase~~<br>Weight increased (Abnormal weight gain) | Alanine aminotransferase (ALT) increased<br>Aspartate aminotransferase (AST) increased<br>Blood alkaline phosphatase increased<br>Weight increased (Abnormal weight gain) | Alanine aminotransferase (ALT) increased<br>Aspartate aminotransferase (AST) increased<br>Weight increased (Abnormal weight gain)<br>Blood alkaline phosphatase increased |
| | Common | | ~~Weight increased (Abnormal weight gain)~~<br>Blood alkaline phosphatase increased | ~~Weight increased (Abnormal weight gain)~~ | |

[a] Infant/toddlers (28 days to 23 months): ~~two~~ four Grade 4 Neutrophil count decreased (Neutropenia) reactions and one Blood alkaline phosphatase increased reported. Grade 3 reactions included ~~seven~~ ten cases of Neutrophil count decreased (Neutropenia), three cases of Anaemia,

three cases of Weight increased (Abnormal weight gain), and one case each of ALT increased and Vomiting.

[b] Children (2 to 11 years): ~~no~~ One Grade 4 Leucocytes count decreased~~reactions were~~ reported. ~~Three~~ Six reported Grade 3 cases of Neutrophil count decreased (Neutropenia), two cases of Anaemia and one case each of ALT increased, AST increased, Gait disturbance, Vomiting, Paraesthesia and Myalgia

[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=~~196~~248 ), the maximum grade neurologic adverse reaction observed was Grade 3 which was observed in five ( 3%) patients and included dizziness (two patients, 1%), paraesthesia (~~two~~ three patients, 1%). and gait disturbance (one patient, <1%). The overall incidence was ~~26~~23% for dizziness, ~~8~~7% for paraesthesia and 4% for gait disturbance. Neurologic reactions leading to dose modification included dizziness (~~2~~1%) and, paraesthesia (1%), ~~and gait disturbance (<1%)~~. One patient permanently discontinued the treatment due to Grade 3 gait disturbance 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=~~196~~248), the maximum grade transaminase elevation observed was Grade 4 ALT increase in ~~2~~3 patients (1%) and AST increase in ~~1~~2 patients (<1%) Grade 3 ALT and AST increases in ~~4~~11 (~~2~~4%) and 10~~2~~ (~~1~~4%) of patients, respectively. Majority of Grade 3 elevations were transient appearing in the first three~~or second~~ months of treatment and resolving to Grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 1~~8~~9 (~~5~~7%) and ~~8~~20 (~~8~~4%) of patients, respectively, and Grade 1 ALT and AST increases were observed in ~~47~~122 (~~2~~9%) and 4115 (~~21~~46%) of patients, respectively.

ALT and AST increases leading to dose modifications occurred in 1~~3~~0 (5%) patients and ~~8~~12 (~~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 ~~196~~248 patients treated with VITRAKVI, ~~73~~98 (~~37~~40%) patients were from 28 days to 18 years of age. Of these ~~73~~98 patients, ~~40~~36% were 28 days to < 2 years (n=~~29~~35), 4~~6~~1% were 2 years to < 12 years (n=~~30~~45), and ~~19~~18% were 12 years to < 18 years (n=184). 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 (~~38~~48% versus 1~~6~~5% in adults), leucocyte count decrease (176% versus ~~1~~9% in adults), neutrophil count decrease (~~27~~31% versus ~~6~~7% in adults), and blood alkaline phosphatase increased (1~~3~~2% versus ~~4~~5% in adults) were more frequent in paediatric patients compared to adults.

*Elderly*

Of the ~~196~~248 patients in the overall safety population who received VITRAKVI, ~~35~~40 (1~~6~~8%) patients were 65 years or older and 1~~1~~0 (~~4~~5%) patients were 75 years or older. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients. The adverse reaction dizziness (48% versus 35% in all adults), anaemia (38% versus 24% in all adults), muscular weakness (23% versus 12% in all adults), and gait disturbance (1~~0~~1% versus 5% in all adults) ~~was~~ were more frequent in patients of 65 years or older.

בברכה,
באייר ישראל