אוקטובר 2022

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

**הנדון:**
**Kovaltry 250 IU 250 IU קובאלטרי**
**Kovaltry 500 IU 500 IU קובאלטר**
**Kovaltry 1000 IU 1000 IU קובאלטרי**
**Kovaltry 2000 IU 2000 IU קובאלטרי**
Powder and Solvent for Solution for Injection
Recombinant Human Coagulation Factor VIII (octocog alfa).

אנו מבקשים להודיעכם שהעלון לרופא והעלון לצרכן של התכשיר עודכנו.

ההתוויה המאושרת לתכשיר:

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Kovaltry can be used for all age groups.

בהודעה זו כלולים העידכונים המהותיים בלבד. בפירוט שלהלן מופיע, מתוך כל פרק ששונה בעלונים, רק המידע שהתעדכן. תוספת טקסט מסומנת בקו תחתון.

## העדכונים בעלון לרופא

### 4. CLINICAL PARTICULARS

### 4.2 Posology and method of administration

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*Paediatric population*
A safety and efficacy study has been performed in children of 0-12 years (see section 5.1); ~~limited data are available for children below 1 year~~
The recommended prophylaxis doses are 20-50 IU/kg twice weekly, three times weekly or every other day according to individual requirements. For paediatric patients above the age of 12, the dose recommendations are the same as for adults.

### 4.8 Undesirable effects

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**Table 2: Frequency of adverse drug reactions in clinical trials**

| **MedDRA System Organ Class** | **Adverse reactions** | **Frequency** |
|---|---|---|
| **Blood and lymphatic system disorders** | Lymphadenopathy | uncommon |
| | FVIII inhibitor | very common (PUPs)* uncommon (PTPs)* |
| **Immune system disorders** | Hypersensitivity | uncommon |
| **Psychiatric disorders** | Insomnia | common |
| **Nervous system disorders** | Headache, | common |
| | Dizziness | common |
| | Dysgeusia | uncommon |
| **Cardiac disorders** | Palpitation, | uncommon |
| | Sinus tachycardia | uncommon |
| **Vascular disorders** | Flushing | uncommon |
| **Gastrointestinal disorders** | Abdominal pain, | common |
| | Abdominal discomfort | common |
| | Dyspepsia | common |
| **Skin and subcutaneous tissue disorders** | Pruritus, | common |
| | Rash***, | common |
| | Urticaria | ~~un~~common |
| | Dermatitis allergic | uncommon |
| **General disorders and administration site conditions** | Pyrexia, | Common |
| | injection site reactions ** | common |
| | Chest discomfort | uncommon |

* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients

**includes injection site extravasation, hematoma, infusion site pain, pruritus, swelling
*** rash, rash erythematous, rash pruritic, rash vesicular

Description of selected adverse reactions

A total of 236 (193 PTPs, 43 PUPs/MTPs) patients constituted the pooled safety population in the three phase III studies in previously treated patients (PTPs), previously untreated patients (PUPs) and minimal treated patients (MTPs); LEOPOLD I, LEOPOLD II, LEOPOLD Kids studies. The median time on clinical trial for pooled safety population was 558 days (range 14 to 2436 days) with a median of 183 exposure days (EDs) (range 1 to 1230 EDs).

- The most frequently reported adverse reactions in the pooled population ~~were related to potential hypersensitivity reaction including headache~~
pyrexia, headache and, rash.

- The most frequently reported adverse reactions in the PTPs were related to potential hypersensitivity reactions, including headache, pyrexia, pruritus, rash and abdominal discomfort.
- The most frequently reported adverse reaction in PUPs/MTPs was FVIII inhibitor.

*Immunogenicity*
The immunogenicity of Kovaltry was evaluated in ~~previously treated patient~~ PTPs and PUPs/MTPs.
During clinical trials with Kovaltry in approximately 200 pediatric and adult patients diagnosed with severe hemophilia A (FVIII:C < 1%) with previous exposure to factor VIII concentrates ≥ 50 ED, one case of transient low titer inhibitor (peak titer 1.0 BU/mL) occurred ~~in the ongoing LEOPOLD Kids Part A~~ a 13 year old PTP after 549 EDs. The Factor VIII recovery was normal (2.7 IU/dL per IU/kg).

*Paediatric population*
In the clinical studies no age-specific differences in ADR were observed except for FVIII inhibitor in PUPs/MTPs.
~~In completed clinical studies with 71 paediatric previously treated patients, the frequency, type and severity of adverse reactions in children were found to be similar to those in adults.~~

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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Clinical efficacy and safety

*Control and Prevention of Bleeding*
Two multi-centre, open-label, cross-over, uncontrolled, randomized studies in previously treated adults/adolescents with severe haemophilia A (< 1%) and one multicentre, open label, uncontrolled study in ~~previously treated children~~ PTPs< 12 years of age (Part A) and PUPs/MTPs <6 years of age (Part B) with severe haemophilia A were conducted.

A total of ~~204~~ 247 subjects (204 PTPs and 43 PUPs/MTPs) have been exposed ~~included~~ in the clinical trial program, 153 subjects ≥ 12 years and ~~51~~ 94 subjects < 12 years. Two-hundred and eight (208) subjects (174 PTPs, 34 PUPs/MTPs) ~~140 subjects~~ were treated for at least ~~12 month~~ 360 days, and ~~55~~ 98 of these subjects (78 PTPs, 20 PUPs/MTPs) for at least 720 days. ~~For a median of 24 month~~

*Paediatric population <12 years*
Part A: The paediatric trial enrolled 51 PTPs with severe haemophilia A, 26 subjects in the age group 6-12 years and 25 subjects in the age group <6 years having accumulated a median number of 73 EDs (range: 37 to 103 EDs). Subjects were treated with 2 or 3 injections per week or up to every other day at a dose of 25 to 50 IU/kg. Consumption for prophylaxis and treatment of bleeds, annualised bleed rates and success rate for bleed treatment are presented in Table 3.

Part B: A total of 43 PUPs/MTPs were enrolled and accumulated a median of 46 EDs (range 1 to 55 EDs). The median dose for treatment of bleeds in all PUPs/MTPs was 40.5 IU/kg and 78.1% of the bleeds were successfully treated with ≤ 2 infusions.
The most frequently reported adverse reaction in PUPs/MTPs was Factor VIII inhibitor (see section 4.8). FVIII inhibitors were detected in 23 of 42 patients with a median (range) of 9 (4 – 42) EDs at the time of the first positive inhibitor test. Of these, 6 patients had low-titre inhibitors (≤ 5.0 BU) and 17 patients had high-titre inhibitors.

Extension: Of the 94 treated subjects, 82 subjects entered the Leopold Kids extension study, 79 patients received treatment with Kovaltry and 67 patients received Kovaltry as prophylaxis treatment. The median time in the extension study was 3.1 years (range 0.3 to 6.4 years), the median total time in entire study (main plus extension study) was 3.8 years (range 0.8 to 6.7 years).
During the extension study, 67 of 82 subjects received Kovaltry as prophylaxis treatment. Amongst the 67 subjects, a total of 472 bleeds were treated with Kovaltry, requiring 1-

2 infusions for the majority of bleeds (83.5%), and response to treatment was good or excellent in most (87.9%) of the cases.

*Immune Tolerance Induction (ITI)*
Data on ITI has been collected in patients with haemophilia A. 11 subjects with high titer inhibitors received ITI with various treatment regimens of three times per week up to twice daily. 5 subjects completed ITI with a negative inhibitor result at the end of the study, and 1 subject had a low titer (1.2 BU/mL) at time of discontinuation.

**העידכונים בעלון לצרכן:**

## 1) תופעות לוואי

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**תופעות לוואי נוספות**
תופעות לוואי **שכיחות** (common) - תופעות שמופיעות בעד 1 מתוך 10 משתמשים
- ~~הגדלה של בלוטות לימפה (נפיחות מתחת לעור בצוואר, בית- השחי או במפשעה)~~
- ~~דפיקות לב (תחושה שהלב פועם חזק, מהר או באופן לא סדיר)~~
- ~~קצב לב מהיר~~
- כאב בטן או אי נוחות בבטן
- קשיי עיכול
  חום
- תגובות מקומיות במקום בו הוזרקה התרופה (כגון: דימום מתחת לעור, גרד עז, נפיחות, תחושת בעירה, אודם זמני)
- כאב ראש
- סחרחורת
- קשיי שינה
- סרפדת (אורטיקריה)
- פריחה/ פריחה מגרדת

תופעות לוואי **שאינן שכיחות** (uncommon) - תופעות שמופיעות בעד 1 מתוך 100 משתמשים
- הגדלה של בלוטות לימפה (נפיחות מתחת לעור בצוואר, בית- השחי או במפשעה)
- דפיקות לב (תחושה שהלב פועם חזק, מהר או באופן לא סדיר)
- קצב לב מהיר
- טעם מוזר בפה
- ~~סרפדת (פריחה מגרדת)~~
- הסמקה (אדמומיות של הפנים)

העלון לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp
ניתן לקבלם מודפסים ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700

בברכה,
באייר ישראל