מרץ 2024

רופא/ה, רוקח/ת נכבד/ה,

Takhyzro (163-47-35885-00)

הרחבת ההתוויה ותוספת פרזנטציה של PFS 1 מ"ל

חברת טקדה ישראל בע"מ מבקשת לידע כי אושרה **הרחבת ההתוויה של התכשיר וכן הוספה פרזנטציה** של מזרק מוכן לשימוש (PFS) 1 מ"ל.

העלונים של התכשיר התעדכנו בהתאם ונוסף עלון לצרכן בעקבות העדכונים לפיכך, לתכשיר בצורת PFS קיימים שני עלונים לצרכן בנוסף לעלון לרופא:

1. עלון לצרכן עבור PFS בגודל של 1 מ"ל למזרק עבור גיל שנתיים עד גיל 12 שנים (חדש)
2. עלון לצרכן עבור PFS בגודל של 2 מ"ל למזרק עבור גיל 12 שנים ומעלה (מעודכן)
3. עלון לרופא עבור כל הפרזנטציות (מעודכן).

התוויה המורחבת המאושרת לתכשיר זה:

Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 years and older.

מרכיב פעיל: Lanadelumab 150 mg/ml

בעמוד הבאים מפורטים עיקרי השינויים שבוצעו בעלון.
למידע נוסף, יש לעיין במאגר התרופות שבאתר משרד הבריאות.

העלונים העדכניים של התכשיר מפורסמים במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פניה לחברת טקדה ישראל בע"מ, רח' אפעל 25, פתח תקוה, 03-3733140.

בברכה,
טקדה ישראל בע"מ

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להלן פירוט השינויים העיקריים בעלון לרופא (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה, טקסט המהווה החמרה מודגש בצהוב):

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One unit (pre-filled syringe) contains 150 mg of lanadelumab* in 1 ml solution.

One unit (~~vial or~~ pre-filled syringe or vial) contains 300 mg of lanadelumab* in 2 ~~mL~~ ml solution.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged ~~12~~ 2 years and older.

4.2 Posology and method of administration

This medicinal product should be initiated under the supervision of a physician experienced in the management of patients with hereditary angioedema (HAE).

Posology

Adults

The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction ~~of~~ to 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.

Adolescents 12 to less than 18 years of age

The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction to 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.

Children 6 to less than 12 years of age

The recommended starting dose is 150 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction to 150 mg lanadelumab every 4 weeks, may be considered.

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Children 2 to less than 6 years of age
The recommended dose is 150 mg lanadelumab every 4 weeks.

TAKHZYRO is not intended for treatment of acute HAE attacks (see section 4.4)

Missed doses

~~If a dose of TAKHZYRO is missed, the patient should be instructed to administer the dose as soon as possible ensuring at least 10 days between doses.~~

If a dose of TAKHZYRO is missed, the patient or caregiver should be instructed to administer the dose as soon as possible. The subsequent dosing schedule may need adjustment according to the intended dosing frequency to ensure

- at least 10 days between doses for patients on every 2 weeks dosing regimen,
- at least 24 days between doses for patients on every 4 weeks dosing regimen.

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Paediatric population

The safety and efficacy of TAKHZYRO in children aged less than ~~12~~ 2 years have not been established. No data are available.

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Method of administration

For adults and adolescents (12 to less than 18 years of age), TAKHZYRO may be self-administered or administered by a caregiver only after training on subcutaneous~~SC~~ injection technique by a healthcare professional.

For children (2 to less than 12 years of age), TAKHZYRO should only be administered by a caregiver after training on subcutaneous injection technique by a healthcare professional.

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4.8 Undesirable effects

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Safety data available from the HELP study extension are consistent with the safety data from the HELP study (described in Table 1).

Paediatric population

The safety of TAKHZYRO 300 mg/2 ml was evaluated in a subgroup of 23 subjects ~~aged~~ 12 to ~~<~~less than 18 years of age in the HELP and HELP study extension~~old~~. ~~Results of the subgroup analysis were consistent with overall study results for all subjects.~~ In the SPRING study, the safety of TAKHZYRO was also evaluated at 150 mg/1 ml in 21 subjects 2 to less than 12 years of age (see section 5.1). No subject below the age of 3.5 years was receiving lanadelumab in the study. No new adverse reactions were identified. Safety and tolerability results for paediatric subjects were consistent with overall study results for all subjects.

~~Immunogenicity~~

~~Treatment with lanadelumab has been associated with development of treatment-emergent anti-drug antibodies (ADA) in 11.9% (10/84) of subjects. All antibody titres were low. The ADA response was transient in 20% (2/10) of ADA-positive subjects. 2.4% (2/84) of lanadelumab-treated subjects tested positive for neutralizing antibodies.~~

~~The development of ADA including neutralising antibodies against TAKHZYRO did not appear to adversely affect the pharmacokinetic (PK) and pharmacodynamics (PD) profiles or clinical response.~~

5.1 Pharmacodynamic properties

Pharmacodynamic effects

In adult and adolescent (12 to less than 18 years of age) patients, c~~C~~oncentration-dependent inhibition of plasma kallikrein, measured as reduction of cHMWK levels, was demonstrated after subcutaneous ~~SC~~ administration of TAKHZYRO 150 mg every 4 weeks, 300 mg every 4 weeks or 300 mg every 2 weeks in subjects with HAE.

The PK-PD relationship between TAKHZYRO and cHMWK is described by an indirect exposure-response pharmacological model. The cHMWK formation rate was maximally reduced by 53.7% with an IC_{50} of 5705 ng/ml.

For children aged 2 to less than 6 years (150 mg every 4 weeks) and 6 to less than 12 years (150 mg every 2 weeks), the observed mean percent change from baseline in cHMWK levels was similar to that observed in adult and adolescent (12 to less than 18 years of age) patients.

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HELP study extension

Long-term safety and efficacy, pharmacokinetics (PK), and impact on health-related quality of life (HRQoL) of TAKHZYRO for prophylaxis to prevent HAE attacks were~~as~~ evaluated in an open-label uncontrolled HELP study extension.

A total of 212 adult and adolescent (≥ 12 years) subjects with symptomatic type I or II HAE received at least one dose of lanadelumab 300 mg every 2 weeks in this study, including 109 subjects who entered as rollover subjects from the HELP study. Rollover subjects, regardless of randomisation group in the HELP Study, received a single dose of lanadelumab 300 mg at study entry and did not receive additional treatment until the occurrence of an HAE attack. After the first HAE attack, all subjects received open-label treatment with lanadelumab 300 mg every 2 weeks. ~~and~~ The study also included 103 new or non-rollover subjects (including 19 subjects from Phase1b study) who had an historical baseline attack rate of ≥1 attack per 12 weeks. The non-rollover subjects received lanadelumab 300 mg every 2 weeks at study entry. Subjects were allowed to initiate self-administration after receiving the first 2 doses from a health care professional in clinic and completing appropriate training. ~~Interim analysis indicates that the effect was sustained up to one year of treatment.~~

The majority of subjects (173/212; 81.6%) who were treated in this study completed at least 30 months of treatment (either as a rollover or non-rollover subjects). The mean (SD) time in the HELP study extension was 29.6 (8.20) months. The majority of subjects self-administered lanadelumab (60.6% of 8,018 injections).

There was a sustained reduction in attack rates compared to baseline during the HELP study extension, with a similar response to TAKHZYRO observed in both rollover (92.4%) and non-rollover groups (82.0%) and an overall reduction rate of 87.4%. Though the magnitude of the attack rate reduction in the HELP study limited the potential for further reductions in the HELP extension study, mean attack rates for the rollover subjects decreased further at the time of the final analysis and ranged from 0.08 to 0.26 attacks per month. In addition, the mean (SD) percentage of attack-free days was 97.7 (6.0)% and the mean (SD) duration of the attack-free period was 415.0 (346.1) days. The

proportion of patients with a maximum attack-free period of 6 months or more or 12 months or more was 81.8% and 68.9%, respectively.

Paediatric population

SPRING study
The safety and efficacy of TAKHZYRO for prophylaxis to prevent HAE attacks in children were evaluated in an open-label, multicenter, Phase 3 SPRING study. Dosing regimens were based on the following pre-defined age groups: children from 2 to less than 6 years of age were to receive lanadelumab 150 mg every 4 weeks and children from 6 to less than 12 years of age were to receive lanadelumab 150 mg every 2 weeks. The overall treatment period was 52 weeks, equally divided into Treatment Period A and B. The study enrolled 21 paediatric subjects who had a baseline attack rate of ≥ 1 attack per 3 months (12 weeks) and a confirmed diagnosis of type I or II HAE.

In Treatment Period A, subjects aged 2 to < 6 years (n=4) and 6 to < 12 years (n=17) received lanadelumab 150 mg every 4 weeks and 150 mg every 2 weeks, respectively. The youngest patient included in the study was 3.5 years old.

In Treatment Period B, subjects receiving lanadelumab 150 mg every 2 weeks (i.e., subjects 6 to less than 12 years of age) could reduce dosing to 150 mg every 4 weeks if they were well-controlled (e.g., attack free) for 26 weeks with lanadelumab treatment. Seven subjects in the 6 to less than 12 years age group switched to 150 mg every 4 weeks during Treatment Period B, and one subject (enrolled in the 2 to less than 6 years age group) turned 6 years of age during Treatment Period A and switched to 150 mg every 2 weeks during Treatment Period B after experiencing recurrent attacks.

The total exposure was 5.5 patient-years in the "every 4 weeks"- dosing regimen group (age range 3.5-10.4 years) and 14.47 patient-years in the "every 2 weeks"-dosing regimen group (age range 6-10.9 years).

The TAKHZYRO dose regimen in both age groups produced reduction in mean HAE attack rate compared to baseline and an increased percentage of attack-free subjects in Treatment Period A (Table 5). Similar results were observed for the overall, 52-week treatment period.

Table 5. Results of efficacy measures

Criteria	TAKHZYRO		
	150 mg every 4 weeks[a]	150 mg every 2 weeks[a]	Total
Treatment Period A (26 weeks)			
N	4	17	21
Baseline attack rate, mean (SD)	1.9 (1.0)	1.8 (1.6)	1.8 (1.5)
Attack rate (attacks/month[b]), mean (SD)	0.2 (0.3)	0.1 (0.2)	0.1 (0.2)
Attack-free subjects N (%)	3 (75.0)	14 (82.4)	17 (81.0)

[a] The actual treatment received during the given study period.
[b] Month is defined as 28 days. Calculated over the 26-week treatment period.

Immunogenicity

Anti-drug antibodies (ADA) were very commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

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5.2 Pharmacokinetic properties

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Special populations

No dedicated studies have been conducted to evaluate the pharmacokinetics of lanadelumab in special patient populations including gender, ~~age,~~ or pregnant women ~~or the presence of renal or hepatic impairment~~.

~~In a p~~Population pharmacokinetic analyses~~analysis~~, ~~after~~ showed that age, gender and race did not meaningfully influence the pharmacokinetics of lanadelumab. ~~correcting for b~~Body weight~~, no influence of gender or age (12 to 75 years) was apparent on the~~ was identified as an important covariate describing the variability of clearance ~~or~~ and volume of distribution of lanadelumab.

~~Although body weight was identified as an important covariate describing the variability of clearance, a 300 mg q2wks dose regimen provided sufficient exposure for the indication (see section 5.1).~~

Paediatric population

Following subcutaneous administration of 150 mg every 4 weeks (2 to less than 6 years of age) and 150 mg every 2 weeks (6 to less than 12 years of age), the overall exposure (i.e., $C_{avg,ss}$) to lanadelumab was similar compared with adult and adolescent (12 to less than 18 years of age) patients who received TAKHZYRO 300 mg every 2 weeks (ratio to adults ranged from 0.8 to 1.11).

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6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the solution (~~vial or~~ pre-filled syringe or vial) in the outer carton in order to protect from light.

The solution (~~vial or~~ pre-filled syringe or vial) may be stored below 25°C for a single period of 14 days, but not beyond the expiry date. Do not return TAKHZYRO to refrigerated storage after storage at room temperature.

When one pre-filled syringe from a multi-pack is removed from refrigeration, return the remaining pre-filled syringes to the refrigerator until future use when needed.

For storage conditions after first opening of the product in vial, see section 6.3.

6.5 Nature and contents of container

TAKHZYRO 150 mg solution for injection in pre-filled syringe

1 ml of solution in pre-filed syringe with a bromobutyl stopper, 27G x 13 mm staked needle and rigid needle cap. TAKHZYRO is available as unit packs containing 1 or 2 pre-filled syringes and in multipacks containing 6 (3 packs of 2) pre-filled syringes.

TAKHZYRO 300 mg solution for injection in pre-filled syringe

2 ml of solution in pre-filled syringe with a bromobutyl stopper, 27G x 13 mm staked needle and rigid needle cap. TAKHZYRO is available as unit packs containing 1 or 2 pre-filled syringes and in multipacks containing 6 (3 packs of 2) pre-filled syringes.

TAKHZYRO 300 mg solution for injection in v~~V~~ial~~:~~

6.6 Special precautions for disposal and other handling

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Administration steps

TAKHZYRO 150 mg solution for injection in pre-filled syringe
After removing the single use pre-filled syringe from the refrigerator, wait 15 minutes before injecting to allow the solution to reach room temperature. Caregiver should inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm (see section 4.2).

TAKHZYRO 300 mg solution for injection in pre-filled syringe

~~Vial:~~
~~Using aseptic technique, withdraw the prescribed dose of TAKHZYRO from the vial into the syringe using an 18 gauge needle.~~

~~Change the needle on the syringe to a 27 gauge needle or other needle suitable for SC injection. Inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm (see section 4.2).~~

~~Discard the vial with any unused contents.~~

~~Pre-filled syringe:~~
After removing the single use pre-filled syringe from the refrigerator, wait 15~~-30-~~ minutes before injecting to allow the solution to reach room temperature. Inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm (see section 4.2).

Each pre-filled syringe is for single use only. Discard the pre-filled syringe after injection is completed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

All needles and syringes should be disposed of in a sharps container.

TAKHZYRO 300 mg solution for injection in vial
Using aseptic technique, withdraw the prescribed dose of TAKHZYRO from the vial into the syringe using an 18 gauge needle.

Change the needle on the syringe to a 27 gauge needle or other needle suitable for subcutaneous injection. Inject TAKHZYRO subcutaneously into the abdomen, thigh, or upper arm (see section 4.2).

Discard the vial with any unused contents.

להלן פירוט השינויים העיקריים בעלון לצרכן של מזרק מוכן לשימוש של 2 מ"ל (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה, טקסט המהווה החמרה מודגש בצהוב):

1. למה מיועדת התרופה?

טאקזירו מיועד לשימוש במטופלים~~מבוגרים ובמתבגרים~~ מגיל ~~12 שנים~~שנתיים ומעלה למניעת התקפי אנגיואדמה חוזרים, במטופלים עם אנגיואדמה תורשתית (HAE).

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2. לפני השימוש בתרופה

ילדים ומתבגרים
~~לא קיים מידע לגבי בטיחות ויעילות~~ השימוש בתכשיר זה אינו מומלץ בילדים מתחת לגיל ~~12 שנים~~שנתיים מכיוון שלא נחקר בקבוצת גיל זו.

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היריון, הנקה ופוריות

הנקה
לא קיים מידע בנוגע להפרשת לנדלומאב לחלב אם. תכשירים ממשפחה זו מופרשים לחלב אם במהלך הימים הסמוכים ללידה, ולאחר מכן רמתם יורדת. לכן, לא ניתן לשלול את הימצאותו של התכשיר בחלב האם בימים הסמוכים ללידה. ניתן להשתמש בלנדלומאב במהלך הנקה במקרה של צורך קליני.

נהיגה ושימוש במכונות
לתרופה זו אין השפעה או יש השפעה זניחה על יכולת נהיגה או שימוש במכונות.

3. כיצד תשתמש בתרופה?

מבוגרים:
המנה ההתחלתית המומלצת היא 300 מ"ג כל שבועיים. אם לא היה לך התקף במשך תקופה ארוכה, ייתכן שהרופא ישנה את המנה שלך ל-300 מ"ג כל 4 שבועות, בייחוד אם משקל גופך נמוך.

מתבגרים מגיל 12 עד גיל 18:
המנה ההתחלתית המומלצת היא 300 מ"ג כל שבועיים. אם לא היה לך התקף במשך תקופה ארוכה, ייתכן שהרופא ישנה את המנה שלך ל-300 מ"ג כל 4 שבועות, בייחוד אם משקל גופך נמוך.

מגיל 6 עד 12 שנים:
המנה ההתחלתית המומלצת היא 150 מ"ג כל שבועיים. אם לא היה לילד התקף במשך תקופה ארוכה, ייתכן שהרופא ישנה את המנה שלו ל-150 מ"ג כל 4 שבועות.

מגיל שנתיים עד 6 שנים:
המנה המומלצת היא 150 מ"ג כל 4 שבועות.

כיצד להזריק את התרופה
אם אתה מזריק את התרופה בעצמך או אם אדם המטפל בך מזריק אותה, אתה או המטפל חייבים לקרוא ביסודיות ולעקוב אחרי ההוראות בסעיף 7, "הוראות שימוש".

- טאקזירו מיועד להזרקה מתחת לעור ("הזרקה תת-עורית").
- למטופלים מגיל 12 ומעלה ניתן להזריק את התרופה באופן עצמאי או שמטפל יכול להזריק לך אותה.
- למטופלים מגיל שנתיים עד 12, ההזרקה יכולה להתבצע או על ידי הצוות הרפואי או על ידי מטפל הילד.

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- מרווח של לפחות 10 ימים בין מנה למנה למטופלים המקבלים מנה כל שבועיים.
- מרווח של לפחות 24 ימים בין מנה למנה למטופלים המקבלים מנה כל 4 שבועות.
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5. איך לאחסן את התרופה?

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תנאי אחסון
- יש לאחסן את המזרק המוכן לשימוש במקרר (2°C-8°C). **אין להקפיא**. יש לשמור את המזרק מוכן לשימוש באריזת הקרטון החיצונית על מנת להגן מאור.
- ניתן לאחסן את המזרק המוכן לשימוש מתחת ל-25°C לתקופה בודדת של 14 יום, אך לא אחרי תאריך התפוגה. אל תחזיר את טאקזירו לאחסון במקרר לאחר אחסון בטמפרטורת החדר.
- כשמוציאים מהמקרר מזרק המוכן לשימוש אחד מאריזה של כמה מזרקים, יש להחזיר את שאר המזרקים המוכנים לשימוש למקרר עד השימוש בהם.
- יש לזרוק את המזרק המוכן לשימוש במידה ולא היה מאוחסן במקרר, הוקפא או שאינו נשמר באריזתו המקורית כאשר הוא מוגן מפני האור.
- **אין** לנער את טאקזירו.

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7. הוראות שימוש

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הזרקה עצמית אינה מומלצת במטופלים בגיל שנתיים עד גיל 12.

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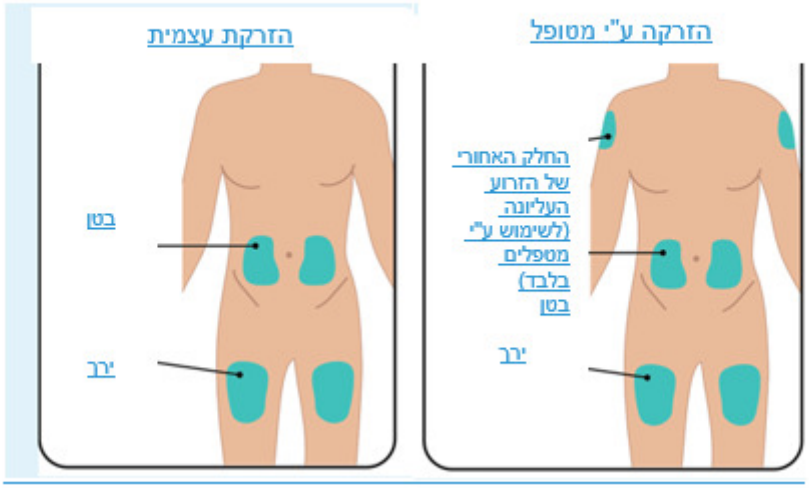
איור ~~ה~~ז': אזרי הזרקה



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