אפריל, 2024

KEVZARA 200mg

Solution for Injection in prefilled syringe/pen

חומר פעיל: Sarilumab 200mg/1.14ml (175 mg/ml)

חברת סאנופי אוונטיס מבקשת לעדכן שאושרה תוספת התוויה לתכשיר קבזרה 200 מ"ג:

משטר המינון והעלונים התעדכנו בהתאם.

ההתוויה הנוכחית:

Rheumatoid Arthritis (RA)
Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs).
Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

ההתוויה הנוספת המאושרת:

Polymyalgia Rheumatica (PMR)
KEVZARA is indicated for treatment of adult patients with polymyalgia rheumatica who cannot tolerate corticosteroid taper.

להלן העדכונים העיקריים בעלוני התכשיר:

<u>בעלון לרופא:</u>

4.1 Therapeutic indications
[…]
<u>Polymyalgia Rheumatica (PMR)</u>
KEVZARA is indicated for treatment of adult patients with polymyalgia rheumatica who cannot tolerate corticosteroid taper.

4.2 Posology and method of administration

Treatment should be initiated and supervised by healthcare professionals experienced in the diagnosis and treatment of rheumatoid arthritis and polymyalgia rheumatica.

<u>Posology</u>
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<u>Polymyalgia Rheumatica</u>
Initiate treatment with Kevzara in patients who had at least one episode of unequivocal PMR flare while attempting to taper prednisone at a dose that is ≥7.5 mg/day or equivalent
The recommended dosage of KEVZARA is 200 mg once every two weeks given as a subcutaneous injection, in combination with a tapering course of systemic corticosteroids. KEVZARA can be used as monotherapy following discontinuation of corticosteroids.

Discontinue KEVZARA if the patient develops neutropenia (using ANC results obtained at the end of the dosing interval), thrombocytopenia, or liver enzyme abnormalities.

Dose modification:
Treatment with sarilumab should be withheld in patients who develop a serious infection or an opportunistic infection until the infection is controlled [see Special warnings and precautions for use (4.4)].

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~~Table 1: Recommended dose modifications in case of neutropenia, thrombocytopenia, or iver enzyme elevations~~ Table 1: Dosage Modifications due to Neutropenia, Thrombocytopenia, or Elevated Liver Enzymes in Patients with Rheumatoid Arthritis (see sections 4.4 and 4.8):

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Dosage Modifications for Patients with Polymyalgia Rheumatica

- Laboratory Abnormalities: Discontinue KEVZARA in patients with PMR who develop the following laboratory abnormalities [see Special warnings and precautions for use (4.4)]:
  - neutropenia (ANC below 1,000 per mm3 at the end of the dosing interval)
  - thrombocytopenia (platelet count below 100,000 per mm3)
  - ALT elevations 3 times above the ULN

Dosage modifications have not been studied in patients with PMR with these conditions. For treatment initiation criteria, refer to the dosage recommendations for PMR [see Posology and method of administration (4.2)].

4.8 Undesirable effects

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Polymyalgia Rheumatica

Safety has been studied in one Phase 3 study (SAPHYR) in 117 PMR patients of whom 59 received subcutaneous KEVZARA 200 mg [Pharmacodynamic properties (5.1)]. Of these, 45 patients received KEVZARA for at least 24 weeks, 44 patients for at least 40 weeks, and 10 patients for at least 52 weeks. The total patient years duration in the KEVZARA PMR population was 47.37 patient years during the 12-month double blind, placebo-controlled study .

The common adverse reactions occurring in ≥5% of patients treated with KEVZARA were neutropenia (15.3%), leukopenia (6.8%), constipation (6.8%), rash pruritic (5.1%), myalgia (6.8%), fatigue (5.1%), and injection site pruritus (5.1%)

Serious adverse reactions of neutropenia occurred in 2 patients (3.4%) in the KEVZARA group compared to none in the placebo group. In both cases of neutropenia, the participants had a neutrophil count less than 500 per mm3 without any infections and resolved following permanent discontinuation of study drug .

The most common adverse reactions that resulted in permanent discontinuation of therapy with KEVZARA were neutropenia in 3 patients (5.1%) and infection in 3 separate patients (5.1%), including COVID-19 (n=1), intervertebral discitis (n=1), and pneumonia (n=1).

Overall Infections

In SAPHYR, the proportion of patients with infections was lower in the KEVZARA group (37.3%) compared to the placebo group (50.0%). Two patients (3.2%) in the KEVZARA group and 1 patient (1.7%) in the placebo group had an event of herpes zoster .

Serious infections

In SAPHYR, the proportion of patients with serious infections was similar in the KEVZARA group (5.1%) compared to the placebo group (5.2%)

Injection Site Reactions

In SAPHYR, three patients (5.1%) in the KEVZARA group experienced injection site reactions of pruritus which were mild in severity. No patient in the placebo group experienced injection site reactions.

Laboratory Abnormalities

Decreased neutrophil count

In SAPHYR, decreases in neutrophil counts less than 1,000 per mm3 occurred in 12% of the KEVZARA treated group and no patient in the placebo treated group. Decreases in neutrophil counts less than 500 per mm3 occurred in 3.4% of patients in KEVZARA treated group compared to no patient in the placebo treated group.

Decreased platelet count
In SAPHYR, decreases in platelet counts between 75,000 to 100,000 per mm3 occurred in two patients (3.4%) in the KEVZARA group, compared to no patient in the placebo treated group. These platelet count decreases were transient and not associated with bleeding events.

Elevated liver enzymes
In SAPHYR, no KEVZARA treated patients had an ALT or AST greater than 3 times the upper limit of normal (ULN). In the placebo treated group, 2 patients had ALT elevations greater than 3 times the ULN.

Lipid Abnormalities
In SAPHYR, cholesterol levels ≥299.27 mg/dL were observed in 8/58 (13.8%) patients in the KEVZARA group compared to 4/58 (6.9%) patients in the placebo group. Triglycerides ≥407.4 mg/dL were observed in 3/58 (5.2%) patients in the KEVZARA group compared to 1/58 (1.7%) in the placebo group .
No significant differences in mean HDL between KEVZARA group and placebo group were observed. At Week 52, mean increase from baseline for LDL and triglycerides levels were observed in the KEVZARA group though both remained within the normal range.
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Immunogenicity
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In the PMR population, 1 patient (1.8%) in the KEVZARA 200 mg + 14-week corticosteroid taper group exhibited an ADA response. None of the patients in the placebo +52-week corticosteroid taper group exhibited an ADA response. Neutralizing antibodies were detected in the PMR patient with ADA response on KEVZARA 200 mg; the patient did not demonstrate a clinical response. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the safety, and/or effectiveness of sarilumab is unknown.

5.1 Pharmacodynamic properties
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Polymyalgia Rheumatica
The efficacy and safety of KEVZARA in PMR were assessed in a randomized, double-blind, placebo-controlled, 52-week, multicenter study (SAPHYR) (NCT03600818) in adults with PMR diagnosed according to American College of Rheumatology/European Union League against Rheumatism (ACR/EULAR) classification criteria. Patients had at least one episode of unequivocal PMR flare while attempting to taper corticosteroids .
In SAPHYR, patients with active PMR were randomized to receive KEVZARA 200 mg every two weeks with a pre-defined 14-week taper of prednisone (n= 60) or placebo every two weeks with a pre-defined 52-week taper of prednisone (n=58). One participant was randomized but not treated in the KEVZARA 200 mg arm. Patients experiencing a disease flare or unable to adhere to the assigned prednisone tapering schedule could receive corticosteroids as rescue therapy .
The primary endpoint was the proportion of patients with sustained remission at Week 52. Sustained remission was defined as achievement of disease remission no later than Week 12, absence of disease flare from Week 12 through Week 52, sustained reduction of CRP (to <10 mg/L) from Week 12 through Week 52, and successful adherence to prednisone taper from Week 12 through Week 52. An additional endpoint was total cumulative corticosteroid dose over 52 weeks.

Clinical Response
The proportion of participants achieving sustained remission at Week 52 was higher in the KEVZARA arm compared to the placebo arm; this difference was statistically significant. At 52 weeks, a higher proportion of patients in the KEVZARA arm achieved each component of the sustained remission endpoint compared to the placebo An analysis was conducted that removed all acute phase reactants (CRP and ESR) criteria from the definition of the sustained remission, given sarilumab's direct impact on acute phase reactants. The results of this analysis were consistent with the primary analysis (see Table 8).

Table 8 Clinical Response in Placebo-Controlled SAPHYR in Adults with Active PMR

	Placebo (N=58)	KEVZARA (N=60)
Sustained remission at Week 52		
Number of patients with sustained remission, n (%)	6 (10.3)	17 (28.3)
Proportion difference (95% CI) vs. placebo		18.0 (4.2, 31.8; p=0.0193)
Components of sustained remission at Week 52		
Absence of signs and symptoms and CRP < 10 mg/L (disease remission*) no later than Week 12, n (%)	22 (37.9)	28 (46.7)
Absence of disease flare‡ from Week 12 through Week 52, n (%)	19 (32.8)	33 (55.0)
Sustained reduction of CRP (<10 mg/L) from Week 12 through Week 52, n (%)	26 (44.8)	40 (66.7)
Successful adherence to prednisone taper from Week 12 through Week 52, n (%)	14 (24.1)	30 (50.0)
Sensitivity analysis removing acute phase reactants (CRP and ESR) from sustained remission at Week 52		
Number of patients with sustained remission, n (%)	8 (13.8)	19 (31.7)
Proportion difference (95% CI) for sarilumab vs. placebo		17.9 (3.1, 32.6)

*Disease remission is defined as the resolution of signs and symptoms of PMR, and normalization of CRP (<10 mg/L).
‡Flare is defined as recurrence of signs and symptoms attributable to active PMR requiring an increase in corticosteroid dose, or elevation of ESR attributable to active PMR plus an increase in corticosteroid dose.

Effect on Concomitant Corticosteroid Use
The total actual cumulative corticosteroid dose included all corticosteroids taken during the study (i.e., prednisone taper regimen per protocol, add-on prednisone prior to Week 12, corticosteroid use due to rescue, or corticosteroid use during the treatment period to manage an adverse reaction not related to PMR). The total actual cumulative prednisone equivalent corticosteroid dose was lower in the KEVZARA arm (mean [SD] 1039.5 [612.2] mg and median 777 mg) relative to the placebo arm (mean [SD] 2235.8 [839.4] mg and median 2044 mg).

5.2 Pharmacokinetic properties
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Polymyalgia Rheumatica
The pharmacokinetic profile of subcutaneous sarilumab in PMR patients was determined using a population pharmacokinetic analysis on a data set including 58 PMR patients treated with repeated subcutaneous administration of sarilumab 200 mg every two weeks. In general, pharmacokinetic exposures were higher in patients with PMR when compared to patients with RA. For this dose regimen, the estimated mean (± SD) steady-state AUC, Cmin and Cmax of sarilumab were 551 ± 321 mg.day/L, 27.0 ± 21.5 mg/L, and 46.5 ± 23.0 mg/L, respectively. The median time to steady state in PMR patients was estimated to be 28 weeks. There was accumulation following subcutaneous administration of sarilumab 200 mg, with an accumulation ratio of approximately 6-fold based on the mean trough concentrations.

<u>בעלון לצרכן:</u>

1. למה מיועדת קבזרה ?
קבזרה משמשת לטיפול:
- במבוגרים עם דלקת פרקים שגרונית פעילה בדרגה בינונית עד חמורה במידה וטיפול קודם לא סייע מספיק או שלא היה סביל. ניתן להשתמש בקבזרה לבד או בשילוב עם תרופה בשם מטוטרקסט.
- במבוגרים עם פולימאלגיה ראומטיקה עבורם הפחתת מינון הדרגתית (taper) מקורטיקוסטרואידים לא הייתה סבילה.

2. לפני השימוש בתרופה

תרופות אחרות וקבזרה
[…]
-תרופות ביולוגיות אחרות המשמשות לטיפול בדלקת פרקים שגרונית או בפולימיאלגיה ראומטיקה.
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3. כיצד תשתמש בתרופה?

הטיפול בקבזרה הוא בהמלצת רופא המנוסה באבחון וטיפול בדלקת פרקים שגרונית ובפולימאלגיה ראומטיקה.
[…]
המינון ואופן הטיפול יקבעו על ידי הרופא בלבד. המינון המקובל בדרך כלל הוא זריקה אחת של 200 מ"ג, כל שבועיים.
אין לעבור על המנה המומלצת. הרופא עשוי להנחות אותך להפסיק את הטיפול או להתאים את מינון התרופה, בהתאם לתוצאות בדיקות הדם שלך. יש להתמיד בטיפול כפי שהומלץ על ידי הרופא.
[…]

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום - סאנופי ישראל בע"מ, Greenwork Park, מתחם העסקים בקיבוץ יקום, בניין E, 6097600, יקום או בטלפון: 09-8633081.

להלן הקישור לאתר משרד הבריאות: https://www.gov.il/he/service/israeli-drug-index

בברכה,
חברת סאנופי ישראל בע"מ