ינואר 2025

Kevzara 150mg
Kevzara 200mg

SOLUTION FOR INJECTION

חומר פעיל:

Kevzara 150mg - SARILUMAB 131.6 MG / 1 ML
Kevzara 200mg - SARILUMAB 175 MG / 1 ML

ההתוויה המאושרת:

Kevzara 150mg & 200mg:
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.

Kevzara 200mg:
KEVZARA is indicated for treatment of adult patients with polymyalgia rheumatica who cannot tolerate corticosteroid taper.

חברת סאנופי ישראל בע"מ מבקשת להודיע על עדכון העלונים לרופא ולצרכן.

העדכונים העיקריים הינם:

בעלון לרופא:

בסעיף משטר מינון חלו עדכוני נוסח:

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~~the condition for which this medicinal product is intended.

Posology
Rheumatoid ~~Arthritis~~ arthritis
The recommended dose of sarilumab is 200 mg once every 2 weeks administered as a subcutaneous injection.

Greenwork Park, Yakum, Building E, 6097600, Israel
Tel.: +972-9-8633081 - Fax: +972-9-8851444 - www.sanofi.co.il

~~Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations.~~

Polymyalgia rheumatica
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 dos~~ag~~e of ~~KEVZARA~~ sarilumab is 200 mg once every ~~two~~ 2 weeks ~~given~~ administered as a subcutaneous injection, in combination with a tapering course of systemic corticosteroids~~. KEVZARA can be used~~, after which sarilumab can be continued ~~-~~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:
Rheumatoid arthritis
Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations.

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)].

Initiating treatment with sarilumab is not recommended in patients with a low neutrophil count, i.e. absolute neutrophil count (ANC) less than 2 x 10^9/L.

Initiating treatment with sarilumab is not recommended in patients with a platelet count below 150 x 10^3/µL.

Table 1: ~~Dosage Modifications due to N~~Recommended dose modifications in case of neutropenia, ~~Thrombocytopenia~~thrombocytopenia, or ~~Elevated L~~liver ~~Enzymes~~ enzyme elevations ~~in Patients with~~ for ~~Rheumatoid~~ rheumatoid ~~Arthritis~~ arthritis (see sections 4.4 and 4.8):

Low Absolute Neutrophil Count (see section 5.1)	
Lab Value (cells x 10^9/L)	**Recommendation**
ANC greater than 1	Current dose of sarilumab should be maintained.
ANC 0.5-1	Treatment with sarilumab should be withheld until >1 x 10^9/L. ~~sarilumab~~ Sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ANC less than 0.5	Treatment with sarilumab should be discontinued.

Low Platelet Count	
Lab Value (cells x 10^3/µL)	**Recommendation**
50 to 100	Treatment with sarilumab should be withheld until >100 x 10^3/µL. ~~sarilumab~~ Sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
Less than 50	If confirmed by repeat testing, treatment with sarilumab should be discontinued.

Liver Enzyme Abnormalities	
Lab Value	**Recommendation**
ALT > 1 to 3 x Upper Limit of Normal (ULN)	Clinically appropriate dose modification of concomitant DMARDs should be considered.
ALT > 3 to 5 x ULN	Treatment with ~~sarilumab~~ Sarilumab should be withheld until < 3 x ULN. sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ALT > 5 x ULN	Treatment with sarilumab should be discontinued.

~~**Dosage Modifications for Patients with** ***Polymyalgia Rheumaticarheumatica (PMR)***~~

- Laboratory Abnormalities: Discontinue ~~KEVZARA~~ sarilumab in patients with PMR who develop the following laboratory abnormalities ~~[~~(see ~~Special warnings and precautions for use (~~section 4.4~~)]:~~ and 5.1):
  - neutropenia (ANC below 1 x 10^9/L~~1,000 per mm^3~~ at the end of the dosing interval)
  - thrombocytopenia (platelet count below 100 x 10^3/µL~~100,000 per mm^3~~)
  - 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)]~~ posology for PMR.

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4.4 Special warnings and precautions for use

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Serious infections

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Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents ~~including sarilumab~~. The most frequently observed serious infections with sarilumab included pneumonia and cellulitis (see section 4.8). Among opportunistic infections, tuberculosis, candidiasis, and pneumocystis were reported with sarilumab in RA. In ~~isolated cases,~~ some patients with RA with concomitant tuberculosis, disseminated rather than localised infections were observed, most of whom were ~~in patients often~~ taking concomitant immunosuppressants such as MTX or corticosteroids, which may increase the risk of infection.

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Polysorbate 20 (E432)

This medicine contains 2.28 ~~-~~mg of polysorbate 20 in each 1.14 ~~-~~mL of solution for injection which is equivalent to 2 ~~-~~mg/mL. Polysorbates may cause allergic reactions.

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4.5 Interaction with other medicinal products and other forms of interaction

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Various *in vitro* and limited *in vivo* human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) and therefore have the potential to alter the pharmacokinetics of concomitantly administered medicinal products that are substrates of these enzymes. Elevated levels of interleukin-6 (IL-6) may down-regulate CYP activity such as in patients with RA or PMR and hence increase drug levels compared to subjects without RA or PMR. Blockade of IL-6 signalling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered medicinal products concentrations.

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4.8 Undesirable effects

~~**Rheumatoid Arthritis**~~

Summary of the safety profile

The most frequent adverse reactions in RA (n=661) and PMR (n=59) patients are neutropenia (14.~~2~~3%), upper respiratory infections (~~7.1~~6.8%), increased ALT (6.~~8~~3%), urinary tract infections (5.~~7~~3%), and injection site erythema (5.~~3~~0%). The most common serious adverse reactions are infections (~~2.9~~3.1%) (see section 4.4).

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Table 2: Adverse reactions in patients with RA and PMR

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection
		Urinary tract infection
		~~Nasopharyngitis~~
		Oral herpes
		Cellulitis
		Pneumonia

	Uncommon	~~Pneumonia~~
		~~Cellulitis~~
		Nasopharyngitis
		Diverticulitis
Blood and lymphatic system disorders	Very common	Neutropenia*
	Common	~~Thrombocytopenia~~
		Leukopenia*
		Thrombocytopenia
Metabolism and nutrition disorders	Common	~~Hypercholesterolemia~~
		Hypertriglyceridemia
		Hypercholesterolemia
Gastrointestinal disorders	Rare	Gastrointestinal perforation
Hepatobiliary disorders	Common	Transaminases increased
General disorders and administration site conditions	Common	Injection site erythema
		Injection site pruritus*

*In the SAPHYR study, the reported ADRs in PMR patients are neutropenia, leukopenia and injection site pruritus.

Description of selected adverse reactions

Rheumatoid arthritis

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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 mm^3 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 mm^3 occurred in 12% of the KEVZARA treated group and no patient in the placebo treated group. Decreases in neutrophil counts less than 500 per mm^3 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 mm^3 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.

Rheumatoid Arthritis and Polymyalgia Rheumatica

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with sarilumab. In the placebo-controlled population, 4.0%, 5.6%, and 2.0% of ~~RA~~ patients treated with sarilumab 200 mg + DMARDs, sarilumab 150 mg + DMARDs and placebo + DMARDs respectively, exhibited a positive response in the anti-drug antibody (ADA) assay. Positive responses in the neutralising antibody (NAb) assay were detected in 1.0%, 1.6%, and 0.2% of patients on sarilumab 200 mg, sarilumab 150 mg, and placebo respectively.

In the ~~RA~~ sarilumab monotherapy population, observations were consistent with the sarilumab + DMARDs population.

Anti-Drug Antibody (ADA) formation may affect pharmacokinetics of sarilumab. No correlation was observed between ADA development and either loss of efficacy or adverse reactions. ~~The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used and testing conditions. For these reasons, comparison of the incidence of antibodies to sarilumab with the incidence of antibodies to other products may be misleading.~~

Polymyalgia Rheumatica

The safety of sarilumab was studied in one Phase 3 study (SAPHYR) in 117 PMR patients of whom 59 received subcutaneous sarilumab 200 mg (see section 5.1). The total patient years duration in the sarilumab PMR population was 47.37 patient years during the 12-month double blind, placebo-controlled study. Safety data are available for up to 1 year.

Infections

In the SAPHYR study, the proportion of patients with infections was lower in the sarilumab 200 mg with 14-week prednisone taper group (37.3%) compared to the placebo with 52-week prednisone taper group (50.0%). Serious infections were reported in 3 (5.1%) patients in the sarilumab 200 mg with 14-week prednisone taper group (all of which were cases of bacterial infections) and 3 (5.2%) patients in the placebo with 52-week prednisone taper group (all of which were cases of COVID-19 infection).

Laboratory abnormalities

Neutrophil count

In the SAPHYR study, decreases in neutrophil counts below 1 x 10^9/L occurred in 7 (12%) patients in the sarilumab group of which 2 (3.4%) were serious (decreases in neutrophil counts below 0.5 -x -10^9/L).

Liver enzymes

In the SAPHYR study, no sarilumab treated patients had an ALT or AST greater than 3 times the upper limit of normal (ULN). In the placebo group, 2 patients had ALT elevations greater than 3x -ULN.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with sarilumab.
In the PMR population, 1 ~~patient~~ (1.8%) patient treated with sarilumab ~~in the KEVZARA 200 mg + 14-week corticosteroid taper group~~ exhibited a~~n~~ persistent anti-drug antibody (ADA) response~~.~~ and ~~None~~ none of the patients in the placebo ~~+52-week corticosteroid taper~~ group exhibited an ADA response. Positive response in the ~~Neutralizing~~ neutralizing ~~antibodies~~ antibody assay ~~were~~

was detected in the PMR patient with ADA response on ~~KEVZARA~~ sarilumab 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~~ efficacy of sarilumab is unknown.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Pharmacodynamic effects

….. Sarilumab treatment for PMR patients taking 200 mg once every 2 weeks has a similar effect compared to RA patients on the PD biomarker profiles (CRP and ANC) over time.

~~Rheumatoid Arthritis~~

Clinical efficacy

Rheumatoid Arthritis

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Sarilumab 200 mg was superior to adalimumab 40 mg in reducing disease activity and improving physical function, with more patients achieving clinical remission over 24 weeks (see Table 7).

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Polymyalgia ~~Rheumatica~~rheumatica (PMR)

The efficacy and safety of ~~KEVZARA~~ sarilumab ~~in PMR~~ were assessed in a ~~randomized~~randomised, double-blind, placebo-controlled, ~~52-week,~~ multicenter study (SAPHYR) ~~(NCT03600818) in adults~~ in patients 50 years and older 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 the SAPHYR study, patients with active PMR were ~~randomized~~ randomised to receive ~~KEVZARA~~ sarilumab 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~~ patient was randomized but not treated in the ~~KEVZARA~~ sarilumab 200 mg arm. The number of patients who completed the study treatment period was 42 (70%) and 36 (62.1%) in the sarilumab group and placebo group, respectively. Patients experiencing a disease flare or unable to adhere to the assigned prednisone tapering schedule could receive corticosteroids as rescue therapy.

By design, the prednisone tapers in the treatment arms differed. The total actual cumulative prednisone equivalent corticosteroid dose in the sarilumab arm (median 777 mg) was lower compared to placebo (median 2044 mg).

The primary end~~-~~point 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~~ Other endpoints included total cumulative corticosteroid dose over 52 weeks, time to first PMR flare, and patient reported outcomes.

Clinical Response

~~The~~ A greater proportion of patients in the sarilumab arm achieved ~~participants achieving~~ sustained remission at Week 52 ~~was higher in the KEVZARA arm~~ compared to the placebo arm~~;~~ (p=0.0193). ~~this difference was statistically significant.~~ At 52 weeks, a higher proportion of patients in the ~~KEVZARA~~ sarilumab arm achieved each component of the sustained remission endpoint compared to ~~the~~ placebo. The cumulative corticosteroid dose during the 52-week treatment period was lower in~~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~~sarilumab arm compared to placebo (see Table 8).

Table 8: Clinical Response in ~~Placebo-Controlled SAPHYR in~~ Adults with Active PMR (SAPHYR study)

			Placebo (N=58)	Sarilumab ~~Kevzara~~ (N=60)	p value vs placebo
Sustained remission at Week 52					
	Number of patients with sustained remission ~~, n (%)~~	n (%)	6 (10.3)	17 (28.3)	
	Proportion difference (95% CI) vs. placebo			18.0 (4.15, 31.82)	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 (%)~~	n (%)	22 (37.9)	28 (46.7)	NC[†]
	Absence of disease flare[‡] from Week 12 through Week 52 ~~, n (%)~~	n (%)	19 (32.8)	33 (55.0)	NC
	Sustained reduction of CRP (<10 mg/L) from Week 12 through Week 52 ~~, n (%)~~	n (%)	26 (44.8)	40 (66.7)	NC
	Successful adherence to prednisone taper from Week 12 through Week 52 ~~, n (%)~~	n (%)	14(24.1)	30 (50.0)	NC
~~**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).
†NC: Not calculated
‡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 Rheumaticarheumatica

The pharmacokinetic profile characteristics of subcutaneous sarilumab in PMR patients was determined using a population pharmacokinetic analysis on a data set including sparse C_{trough} observations collected from 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. PK data analyses suggest the median time to steady state The median time to steady state in PMR patients to be approximately 24was estimated to be 28 weeks. There was accumulation following subcutaneous administration of sarilumab 200 mg, with an accumulation ratio of approximately of5-6-fold based on the mean trough concentrations.

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בעלונים לצרכן:

2. לפני השימוש בתרופה

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קבזרה מכילה פוליסורבאט 20

תרופה זו מכילה 2.28 מ"ג פוליסורבאט 20 בכל 1.14 מ"ל של תמיסה להזרקה. כמות זו שווה ערך ל- 2 מ"ג / מ"ל. פוליסורבאטים עשויים לגרום לתגובה אלרגית. ספר לרופא שלך אם יש לך אלרגיות כלשהן.

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4. תופעות לוואי

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תופעות לוואי שכיחות (תופעות שמופיעות בעד 1 מ 10 משתמשים)

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- דלקת ברקמת העור העמוקה
- זיהום בריאות

תופעות לוואי שאינן שכיחות (תופעות שמופיעות בעד 1 מ 100 משתמשים)

- ~~זיהום בריאות~~
- ~~דלקת ברקמת העור העמוקה~~
- .....

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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 (קומה 1), 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