04.2021

KANUMA® (34903) **קנומה**

Active ingredient and strength: חומר פעיל וחוזק:
Sebelipase Alfa 2MG/1ML **סיביליבאס אלפא 2מ"ג /1 מ"ל**

CONCENTRATE FOR SOLUTION FOR INFUSION

רופא/ה, רוקח/ת נכבד/ה,
אלקסיון פארמה ישראל בע"מ שמחה להודיע על עדכון עלון לרופא של התכשיר Kanuma.

- עלון התכשיר עודכן באפריל 2021, בהודעה זו מתוארים שינויי הבטיחות העיקריים בעלון, בעלון קיימים שינויים נוספים.
- מידע חדש מופיע על רקע צהוב, טקסט שהוסר מסומן בקו חוצה.

להלן נוסח ההתוויה המאושר לתכשיר:

KANUMA is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency.

העדכונים העיקריים נעשו בסעיפים הבאים:

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In the sebelipase alfa clinical program, patients were routinely tested for anti-sebelipase alfa anti-drug antibodies (ADAs) to determine the immunogenicity potential of sebelipase alfa. Patients who tested positive for ADAs were also tested for inhibitory antibody activity. The presence of inhibitory activity has been detected at some postbaseline timepoints in clinical studies (see section 4.8). Overall, no conclusion on the relationship between development of ADAs/NAbs and associated hypersensitivity reactions or suboptimal clinical response can be made.

In clinical studies, 3 patients homozygous for a deletion affecting both alleles of genes Lipase A, lysosomal acid [LIPA] and Cholesterol 25-Hydroxylase developed inhibitory antibody activity associated with a suboptimal clinical response. These patients underwent either immunomodulatory therapy alone or in combination with haematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT), resulting in improved clinical response to sebelipase alfa.

4.5. Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of KANUMA in pregnant women. ~~There are no data from the use of KANUMA in pregnant women~~. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid use of sebelipase alfa during pregnancy.

4.7 Effects on ability to drive and use machines.

KANUMA ~~has~~ may have a minor ~~no or negligible~~ influence on the ability to drive and use machines.

Adverse events of dizziness have been reported with the use of KANUMA, which could affect the ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The data described below reflect the exposure to sebelipase alfa in 125 patients at doses ranging from 0.35 mg/kg once every other week to 7.5 mg/kg once weekly in clinical studies (see section 5.1), with a treatment duration range from 1 day to 60.5 months (5 years).

Of the 106 children and adults enrolled in clinical studies, 102 (96.2%) have received sebelipase alfa with a median duration of exposure of 33 months (6, 59 months). The median duration of exposure for the 19 infants enrolled in clinical studies was 35.5 months (1 day to 60 months).

The most serious adverse reactions experienced by 4% of patients in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival hyperaemia ~~injection~~, dyspnoea, ~~generalised and itchy rash~~ hyperaemia, ~~mild~~ eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia~~, tachypnoea~~ tachypnoea, irritability, flushing, pruritus, ~~and~~ urticaria, stridor, hypoxia, pallor and diarrhoea.

Tabulated list of adverse reactions

The data in Table 1 describe adverse reactions reported in infants who received KANUMA in clinical studies at doses up to 3 mg/kg weekly. The data in Table 2 describe adverse reactions reported in children and adults who received sebelipase alfa in clinical studies. at a dose of 1 mg/kg once every other week.

Table 1: Adverse reactions reported in infants receiving sebelipase alfa (N = 19 patients)

MedDRA System organ class	**MedDRA Preferred Term**	**Frequency**
Immune system disorders	Hypersensitivity[a] Anaphylactic reaction[b]	Very common
Eye Disorders	Eyelid oedema	Very common
Cardiac disorders	Tachycardia	Very common
Respiratory, thoracic and mediastinal disorders	Respiratory distress	Very common
Gastrointestinal disorders	Vomiting Diarrhoea	Very common
Skin and subcutaneous tissue disorders	Rash Rash maculo-papular	Very common
General disorders and administration site conditions	Pyrexia Hyperthermia	Very common
Investigations	Drug specific antibody present Body temperature increased Oxygen saturation decreased Blood pressure increased Heart rate increased Respiratory rate increased	Very common

[a] May include: irritability, agitation, vomiting, urticaria, eczema, pruritus, pallor, and drug hypersensitivity

[b] Occurred in 3 infant patients treated in clinical studies. Based on Preferred Term ‘anaphylactic reaction’ and application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis

Table 2: Adverse reactions reported in children and adults[d] receiving sebelipase alfa (N = 106 patients)

MedDRA System organ class	MedDRA preferred term	Frequency[a]
Immune system disorders	Hypersensitivity[b]	Very Common
	Anaphylactic reaction[a]	Common
Nervous system disorders	Dizziness	Very common
Cardiac disorders	Tachycardia	Common
Vascular disorders	Hyperaemia Hypotension	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
Gastrointestinal disorders	Abdominal pain Diarrhoea	Very common
	Abdominal distension	Common
Skin and subcutaneous tissue disorders	Rash Rash papular	Common
General disorders and administration site conditions	Fatigue Pyrexia	Very common
	Chest discomfort Infusion site reaction[c]	Common
Investigations	Body temperature increased	Common

[a] Occurred in 2 patients treated in clinical studies. Based on Preferred Term 'anaphylactic reaction' and application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis
[b] May include: chills, eczema, laryngeal oedema, nausea, pruritus, urticaria
[c] Includes: infusion site extravasation, infusion site pain and infusion site urticaria

Description of selected adverse reactions

Hypersensitivity
~~Three patients~~ Five of ~~106~~ 125 (~~3~~ 4%) patients treated with KANUMA, including ~~1~~ 3 of ~~14~~ 19 (~~7~~ 16%) infants and 2 of ~~92~~ 106 (2%) children and adults, in clinical studies experienced serious signs and symptoms consistent with anaphylaxis to KANUMA. Anaphylaxis occurred during the infusion as late as 1 year after treatment initiation.

In clinical studies,~~21~~ 59 of ~~106~~ 125 (~~20~~ 47%) KANUMA-treated patients, including ~~9~~ 13 of ~~14~~ 19 (~~64~~ 68%) infants and 46 of 106 (43%) children and adults, experienced at least 1 hypersensitivity reaction (selected using a validated, pre-determined set of terms grouped together to identify potential hypersensitivity reactions). Signs and symptoms either consistent with or that may be related to a hypersensitivity reaction ~~These reported signs and symptoms~~ occurring in two or more patients included but were not limited to abdominal pain, agitation, bronchospasm, chills, diarrhoea, eyelid oedema, eczema, face oedema, hypertension, irritability, laryngeal oedema, lip swelling, nausea, oedema, pallor, pruritus, pyrexia/body temperature increased, rash, tachycardia, urticaria, and vomiting. The majority of reactions occurred during or within 4 hours of the completion of the infusion.

(…)

Immunogenicity

There is potential for immunogenicity (see section 4.4). ~~Patients have developed anti-drug antibodies (ADA) to sebelipase alfa.~~ Patients have developed anti-drug antibodies (ADA) to sebelipase alfa. Compared to children and adults, an increased occurrence of ADA positivity was observed within the infant population (10/19 patients). ~~Based on the limited data currently available the development of ADA seems to occur more frequently in infants.~~

~~In LAL-CL03, 4 of 7 evaluable infants (57%) developed ADA during treatment with KANUMA. At the time of initial ADA positivity, 3 patients were receiving a dose of 1 mg/kg once weekly and 1 patient was receiving a dose of 3 mg/kg once weekly. Most patients who developed ADA did so within the first 2 months of exposure. ADA titres decreased to undetectable levels during continued treatment in 3 of the 4 patients. Two patients were determined to be positive for antibodies that inhibit *in vitro* enzyme activity and cellular uptake of the enzyme. In a separate study in infants, one of five evaluable patients developed antibodies that inhibit *in vitro* enzyme activity and cellular uptake of the enzyme~~.

~~In LAL-CL02, 5 of 35 evaluable children and adults (14%) who were administered KANUMA during the 20-week double-blind period of the study developed ADA. All patients were receiving 1 mg/kg once every other week. Those patients who developed ADA did so within the first 3 months of exposure. ADA titres decreased to undetectable levels during continued treatment in all patients. Two patients were positive at only a single time point. No patients developed antibodies that inhibited *in vitro* enzyme activity and one patient developed antibodies that inhibited cellular uptake of the enzyme *in vitro*.~~

~~The association between the development of ADA to sebelipase alfa and reductions in treatment effect or the occurrence of adverse reactions has not been determined.~~

Among 125 patients with LAL Deficiency enrolled in the clinical studies, 19/125 (15.0%) patients tested positive for anti-drug antibodies (ADAs) at some timepoint after starting treatment with sebelipase alfa (9 children and adult patients and 10 infants). For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported. Persistence of ADA positivity was observed for all 10 infants and persistence of high titer ADAs was observed for 3 of the 10 infants. Among those 19 patients, 11 (58%) also showed the presence of inhibitory antibody activity (NAbs) at some postbaseline timepoint.

- העלון לרופא מצורף להודעתנו להלן
- העלון נשלח למשרד הבריאות לצורך העלאתו למאגר התרופות שבאתר משרד הבריאות.
- ניתן לקבל עלון זה מודפס על ידי פניה ישירה לבעל *הרישום*: אלקסיון פארמה ישראל בע"מ, רח' השילוח 6, ת.ד. 7063 , פתח תקווה 4917001 , טלפון: 03-9373753.

בברכה,
עוז וולך,
רוקח ממונה של בעל הרישום