דצמבר 2022

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון : **Kymriah, dispersion for infusion [162-91-35711]**

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלון לרופא ובעלון לצרכן של התכשיר קימריה.

התוויות התכשיר:

Kymriah is indicated for the treatment of:
Paediatric and young adult patients up to and including 25 years of age with CD19+ B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary or secondary central nervous system lymphoma.
Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

חומר פעיל:

Tisagenlecleucel (1.2×10^6 to 6×10^8 CAR- positive viable T cells)

בעמודים העוקבים מצויינים סעיפים בהם נעשה שינוי אשר מהווה החמרה או שינוי משמעותי. למידע נוסף, יש לעיין בעלונים לצרכן ולרופא כפי שאושרו על ידי משרד הבריאות.
העלונים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום: נוברטיס ישראל בע"מ. תוצרת הארץ 6, ת"ד 7126, תל אביב.

בברכה,

שירן חן גולדשטיין
רוקחת ממונה
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להלן פירוט השינויים העיקריים (טקסט באדום עם קו תחתי מציין טקסט שהוסף לעלון ואילו טקסט שהושמט מסומן באדום עם קו חוצה. החמרה במידע בטיחותי מודגשת בצהוב)

בעלון לרופא:

4.4 Special warnings and precautions for use

Prior treatment with anti-CD19 therapy

There is limited experience with Kymriah in patients exposed to prior CD19-directed therapy. While activity of tisagenlecleucel has been observed, data are currently too limited to make an adequate assessment of the benefit-risk profile in these patients. Kymriah is not recommended if the patient has relapsed with CD19-negative leukaemia after prior anti-CD19 therapy.

4.8 Undesirable effects

Summary of the safety profile

Safety assessment was based on a total of ~~291~~ 424 patients (with paediatric and young adult B-cell ALL, DLBCL and FL) who received Kymriah in three multicentre pivotal clinical studies.

B-cell ALL

The adverse reactions described in this section were characterised in 212 ~~79~~ patients infused with Kymriah in the ~~multicentre,~~ pivotal clinical study CCTL019B2202 and in the supportive studies CCTL019B2205J and CCTL019B2001X.

The most common non-haematological adverse reactions were cytokine release syndrome (~~77~~75%), infections (~~72~~70%), hypogammaglobulinaemia (~~53~~49%), pyrexia (~~42~~43%) and decreased appetite (~~38~~28%).

The most common haematological laboratory abnormalities were decreased white blood cells (100%), decreased haemoglobin (~~100~~99%), decreased neutrophils (~~100~~98%), decreased lymphocytes (~~100~~98%) and decreased platelets (~~97~~95%).

Grade 3 and 4 adverse reactions were reported in ~~89~~86% of patients. The most common Grade 3 and 4 non-haematological adverse reaction was cytokine release syndrome (~~48~~37%).

The most common Grade 3 and 4 haematological laboratory abnormalities were white blood cells decreased (97%), lymphocytes decreased (~~96~~94%), neutrophils decreased (~~95~~96%), platelets decreased (~~77~~70%) and haemoglobin decreased (~~48~~46%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (~~82~~78% of patients) compared to after 8 weeks post-infusion (~~51~~49% of patients).

...

Tabulated list of adverse drug reactions

The adverse reactions described in this section were identified in 79, 115 and 97 patients in the ongoing multicentre pivotal clinical studies (CCTL019B2202, CCTL019C2201 and CCTL019E2202), as well as 64 and 69 patients in the supportive studies (CCTL019B2205J and CCTL019B2001X). Adverse drug reactions from these clinical studies (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions observed in clinical studies

Infections and infestations[1)]	
Very common:	Infections - pathogen unspecified, viral infections, bacterial infections
Common:	Fungal infections
Blood and lymphatic system disorders	
Very common:	Anaemia, ~~haemorrhage~~[2)]~~,~~ febrile neutropenia, neutropenia, thrombocytopenia
Common:	~~Haemophagocytic lymphohistiocytosis, l~~Leukopenia, pancytopenia, coagulopathy, lymphopenia
Uncommon:	B-cell aplasia
Immune system disorders	
Very common:	Cytokine release syndrome, hypogammaglobulinaemia[32)]
Common:	Infusion-related reaction, graft-versus-host disease[43)], haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders	
Very common:	Decreased appetite, hypokalaemia, hypophosphataemia~~, hypomagnesaemia~~
Common:	Hypomagnesaemia, Hypoalbuminaemia[54)], hyperglycaemia, hyponatraemia, hyperuricaemia[5)], hypercalcaemia, tumour lysis syndrome, hyperkalaemia, hyperphosphataemia[6)], hypernatraemia, ~~hypermagnesaemia,~~ hyperferritinaemia[67)], hypocalcaemia
Uncommon:	Hypermagnesaemia
Psychiatric disorders	
Common:	Anxiety, delirium[78)], sleep disorder[89)]
Nervous system disorders	
Very common:	Headache[910)], encephalopathy[1110)]
Common:	Dizziness[121)], peripheral neuropathy[132)], tremor[143)], motor dysfunction[154)], seizure[165)], speech disorders[176)], neuralgia[187)]~~, immune effector cell-associated neurotoxicity syndrome**~~
Uncommon:	Ischaemic cerebral infarction, ataxia[198)], immune effector cell-associated neurotoxicity syndrome**
Eye disorders	
Common:	Visual impairment[~~19~~20)]
Cardiac disorders	
Very common:	Tachycardia[210)]
Common:	Cardiac failure[221)], cardiac arrest, atrial fibrillation
Uncommon:	Ventricular extrasystoles
Vascular disorders	
Very common:	Haemorrhage[23)], Hypotension[242)], hypertension
Common:	Thrombosis[253)], capillary leak syndrome~~, hypertension~~
Uncommon:	Flushing
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough[264)], dyspnoea[275)], hypoxia
Common:	Oropharyngeal pain[286)], pulmonary oedema[297)], nasal congestion, pleural effusion, tachypnoea~~, acute respiratory distress syndrome~~
Uncommon:	Acute respiratory distress syndrome, ~~l~~Lung infiltration
Gastrointestinal disorders	
Very common:	Diarrhoea, nausea, vomiting, constipation, abdominal pain[2830)]
Common:	Stomatitis, abdominal distension, dry mouth, ascites
Hepatobiliary disorders	
~~Very common:~~	~~Hepatic enzyme increased~~[29)]
Common:	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Very common:	Rash[310)]
Common:	Pruritus, erythema, hyperhidrosis, night sweats

Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, musculoskeletal pain[3~~2~~1)]
Common:	Myalgia
Renal and urinary disorders	
Very common:	Acute kidney injury[3~~3~~2)]
General disorders and administration site conditions	
Very common:	Pyrexia, fatigue[3~~4~~3)], oedema[3~~5~~4)], pain[3~~6~~5)]
Common:	Influenza-like illness, asthenia, multiple organ dysfunction syndrome, chills
Investigations	
Very common:	Lymphocyte count decreased*, white blood cell count decreased*, haemoglobin decreased*, neutrophil count decreased*, platelet count decreased*, hepatic enzyme increased[37)]
Common:	Blood bilirubin increased, weight decreased, blood fibrinogen decreased, international normalised ratio increased, fibrin D dimer increased, activated partial thromboplastin time prolonged, prothrombin time prolonged

1) Infections and infestations presented reflect high-level group terms.

~~2)~~ ~~Haemorrhage includes anal haemorrhage, blood blister, blood urine present, catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, cystitis haemorrhagic, duodenal ulcer haemorrhage, disseminated intravascular coagulation, epistaxis, eye contusion, gastrointestinal haemorrhage, gingival bleeding, haematochezia, haemarthrosis, haematemesis, haematoma, haematuria, haemoptysis, heavy menstrual bleeding, large intestinal haemorrhage, melaena, mouth haemorrhage, mucosal haemorrhage, oral blood blister, peritoneal haematoma, petechiae, pharyngeal haemorrhage, post-procedural haemorrhage, pulmonary haemorrhage, purpura, retinal haemorrhage, subdural haematoma, traumatic haematoma, tumour haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.~~

~~3~~2) Hypogammaglobulinaemia includes ~~immunoglobulins decreased,~~ blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinaemia, immunodeficiency, immunodeficiency common variable and immunoglobulins decreased~~hypogammaglobulinaemia~~.

~~4~~3) Graft-versus-host ~~D~~disease (GvHD) includes GvHD, GvHD in gastrointestinal tract, GvHD in skin

~~5~~4) Hypoalbuminaemia includes blood albumin decreased, hypoalbuminaemia

5) Hyperuricaemia includes blood uric acid increased, hyperuricaemia

6) Hyperphosphataemia includes blood phosphorus increased, hyperphosphataemia

~~6~~7) Hyperferritinaemia includes hyperferritinaemia, serum ferritin increased

~~7~~8) Delirium includes agitation, delirium, hallucination, hallucination visual, irritability and restlessness.

~~8~~9) Sleep disorder includes ~~sleep disorder,~~ insomnia~~, and~~ nightmare and sleep disorder.

~~9~~10) Headache includes headache and migraine.

1~~0~~0) Encephalopathy includes automatism, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, memory impairment, mental status changes, ~~automatism, cognitive disorder, confusional state, disturbance in attention, encephalopathy, somnolence, lethargy, memory impairment,~~ metabolic encephalopathy, somnolence and thinking abnormal. Encephalopathy is a dominant feature of immune effector cell-associated neurotoxicity syndrome (ICANS), along with other symptoms.

1~~1~~1) Dizziness includes dizziness, presyncope and syncope.

1~~2~~2) Peripheral neuropathy includes dysaesthesia, hyperaesthesia, hypoaesthesia, neuropathy peripheral, paraesthesia~~,~~ and peripheral sensory neuropathy~~, neuropathy peripheral, hyperaesthesia and hypoaesthesia~~.

1~~3~~3) Tremor includes dyskinesia and tremor.

1~~4~~4) Motor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy.

1~~5~~5) Seizure includes ~~seizure,~~ generalised tonic-clonic seizures, seizure and status epilepticus.

1~~6~~6) Speech disorders includes aphasia, dysarthria and speech disorders~~, dysarthria and aphasia~~.

1~~7~~7) Neuralgia includes neuralgia and sciatica.

1~~8~~8) Ataxia includes ataxia and dysmetria.

2019)	Visual impairment includes vision blurred and visual impairment.
210)	Tachycardia includes sinus tachycardia, supraventricular tachycardia, tachycardia
221)	Cardiac failure includes cardiac failure, ~~left ventricular dysfunction,~~ cardiac failure congestive, left ventricular dysfunction and right ventricular dysfunction.
23)	Haemorrhage includes anal haemorrhage, blood blister, blood urine present, catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, cystitis haemorrhagic, disseminated intravascular coagulation, duodenal ulcer haemorrhage, ecchymosis, epistaxis, eye contusion, gastrointestinal haemorrhage, gingival bleeding, haemarthrosis, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, heavy menstrual bleeding, injection site haematoma, intermenstrual bleeding, large intestinal haemorrhage, lip haemorrhage, melaena, mouth haemorrhage, mucosal haemorrhage, oral blood blister, periorbital haematoma, peritoneal haematoma, petechiae, pharyngeal haemorrhage, postprocedural haemorrhage, pulmonary haemorrhage, purpura, rectal haemorrhage, retinal haemorrhage, stoma site haemorrhage, subcutaneous haematoma, subdural haematoma, subdural haemorrhage, tooth socket haemorrhage, tracheal haemorrhage, traumatic haematoma, tumour haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.
242)	Hypotension includes hypotension and orthostatic hypotension.
253)	Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis.
264)	Cough includes cough, productive cough and upper-airway cough syndrome.
275)	Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory distress and respiratory failure.
286)	Oropharyngeal pain includes oral pain and oropharyngeal pain.
297)	Pulmonary oedema includes acute pulmonary oedema and pulmonary oedema.
3028)	Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain~~abdominal discomfort~~.
~~29)~~	~~Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hepatic enzyme increased, transaminases increased.~~
310)	Rash includes dermatitis, dermatitis acneiform, dermatitis contact, rash, rash maculo-papular, rash papular and rash pruritic.
321)	Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, neck pain, non-cardiac chest pain.
332)	Acute kidney injury includes acute kidney injury, anuria, azotaemia, blood creatinine abnormal, blood creatinine increased, blood urea increased, renal failure, renal tubular dysfunction and renal tubular necrosis.
343)	Fatigue includes fatigue and malaise.
354)	Oedema includes face oedema, fluid retention, generalised oedema, hypervolaemia, localised oedema, ~~fluid overload,~~ oedema peripheral, periorbital oedema~~generalised oedema, localised oedema, face oedema~~ and peripheral swelling.
365)	Pain includes pain and pain in extremity.
37)	Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hepatic enzyme increased, transaminases increased.
*	Frequency is based on laboratory values. Patients are counted only for the worst grade observed post baseline.
**	Abbreviated as ICANS. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.

Description of selected adverse drug reactions

Cytokine release syndrome

In the ~~ongoing~~ clinical studies~~y~~ in paediatric and young adult B-cell ALL (N=~~79~~212), cytokine release syndrome was reported in 75~~7~~% of patients (~~48~~37% with Grade 3 or 4; 0.5% [1 patient] with fatal

outcome). ~~Two deaths occurred within 30 days of tisagenlecleucel infusion, including one patient, who died from progressive leukaemia in the setting of possible cytokine release syndrome and one patient who experienced fatal intracranial haemorrhage that developed during the course of resolved cytokine release syndrome, abdominal compartment syndrome, coagulopathy and renal failure.~~

In the ongoing clinical study in DLBCL (N=115), cytokine release syndrome was reported in 57% of patients (23% with Grade 3 or 4).
In the ongoing clinical study in FL (N=97), cytokine release syndrome was reported in 50% of patients. No Grade 3 or 4 events were reported.

Cytokine release syndrome was graded per Penn criteria in the paediatric and young adult B-cell ALL and DLBCL studies as follows: Grade 1: mild reactions, reactions requiring supportive care;
Grade 2: moderate reactions, reactions requiring intravenous therapies; Grade 3: severe reactions, reactions requiring low-dose vasopressors or supplemental oxygen; Grade 4: life-threatening reactions, those requiring high-dose vasopressors or intubation; Grade 5: death.

Cytokine release syndrome was graded per the Lee criteria in the FL study as follows: Grade 1: mild general symptoms requiring symptomatic treatment; Grade 2: symptoms requiring moderate intervention such as low-flow oxygen supplementation or low-dose vasopressor; Grade 3: symptoms requiring aggressive intervention, such as high-flow oxygen supplementation and high-dose vasopressor; Grade 4: life-threatening symptoms requiring intubation; Grade 5: death.

For clinical management of cytokine release syndrome, see section 4.4 and Table 1.

Infections and febrile neutropenia
In B-cell ALL patients severe infections (Grade 3 and higher), which can be life-threatening or fatal, occurred in ~~48~~36% of patients after Kymriah infusion. The overall incidence (all grades) was ~~72~~70% (unspecified ~~57~~55%, viral ~~38~~31%, bacterial ~~27~~24% and fungal ~~15~~12%) (see section 4.4). ~~43~~41% of the patients experienced an infection of any type within 8 weeks after Kymriah infusion.

In DLBCL patients severe infections (Grade 3 and higher), which can be life-threatening or fatal, occurred in 34% of patients. The overall incidence (all grades) was 58% (unspecified 48%, bacterial 15%, fungal 11% and viral 11%) (see section 4.4). 37% of the patients experienced an infection of any type within 8 weeks.

In FL patients severe infections (Grade 3 or 4), occurred in 16% of patients. The overall incidence (all grades) was 50% (unspecified 36%, viral 17%, bacterial 6%, and fungal 2%) (see section 4.4). 19% of the patients experienced an infection of any type within 8 weeks.

Severe febrile neutropenia (Grade 3 or 4) was observed in ~~34~~26% of paediatric and young adult B-cell ALL patients, 17% of DLBCL patients and 12% of FL patients. See section 4.4 for the management of febrile neutropenia before and after Kymriah infusion.

Prolonged cytopenias
Cytopenias are very common based on prior chemotherapies and Kymriah therapy.

All paediatric and young adult B-cell ALL patients had a Grade 3 or 4 cytopenia at some time after Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 after Kymriah infusion based on laboratory findings included decreased count of white blood cells (50~~7~~%), neutrophils (~~54~~56%), lymphocytes (~~44~~43%), and thrombocytes (~~42~~32%) and decreased haemoglobin (~~13~~11%).

All adult DLBCL patients had Grade 3 and 4 cytopenias at some time after Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 based on laboratory findings included decreased count of thrombocytes (39%), lymphocytes (29%), neutrophils (25%), and white blood cells (21%) and decreased haemoglobin (14%).
In adult patients with FL, 99% had Grade 3 and 4 cytopenias at any time post Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 after Kymriah infusion based on laboratory findings

included a decreased count of lymphocytes (23%), thrombocytes (17%), neutrophils (16%), white blood cells (13%) and decreased haemoglobin (3%).

Neurological adverse reactions
The majority of neurotoxic events occurred within 8 weeks following infusion and were transient.

In paediatric and young adult B-cell ALL patients, serious neurological adverse reactions including manifestations of encephalopathy and/or delirium occurred in ~~39~~32% of patients (~~13~~10% were Grade 3 or 4) within 8 weeks after Kymriah infusion. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 20% of patients (11% were Grade 3 or 4) within 8 weeks after Kymriah infusion. In FL patients, these occurred in 9% of patients (1% Grade 3 or 4) within 8 weeks after Kymriah infusion. Among the neurotoxic events in FL patients, immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 4% of patients (1% Grade 3 or 4), all within 8 weeks of Kymriah infusion.

Hypogammaglobulinaemia
Hypogammaglobulinaemia was reported in ~~53~~49% of patients treated with Kymriah for r/r ALL,17% of patients with r/r DLBCL and 17% of patients with r/r FL.

Pregnant women who have received Kymriah may have hypogammaglobulinaemia. Immunoglobulin levels should be assessed in newborns of mothers treated with Kymriah.

Immunogenicity

In clinical studies, humoral immunogenicity of tisagenlecleucel was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients tested positive for pre-dose anti-mCAR19 antibodies in paediatric and young adult ALL (B2202, ~~91.1~~ B2205J, B2001X, 84.0%), adult DLBCL (C2201, 93.9%) and adult FL (E2202, 66.0%) patients.

Treatment-induced anti-mCAR19 antibodies were found in 40.5% of paediatric and young adult ALL (B2202), 8.7% of adult DLBCL and 28.7% of adult FL patients. Pre-existing and treatment-induced antibodies were not associated with an impact on clinical response nor did they have an impact on the expansion and persistence of tisagenlecleucel. There is no evidence that the presence of pre-existing and treatment-induced anti-mCAR19 antibodies impacts the safety or effectiveness of Kymriah.

T-cell immunogenicity responses were not observed in paediatric and young adult B-cell ALL, adult r/r DLBCL and adult FL patients.

בעלון לצרכן

4. תופעות לוואי
תופעות לוואי שכיחות מאוד (תופעות שמופיעות ביותר ממשתמש אחד מעשרה)
- עור חיוור, חולשה, קוצר נשימה בגלל מספר נמוך של כדוריות דם אדומות או המוגלובין נמוך
- דימום מוגבר או מתמשך או חבורות בגלל מספר נמוך של טסיות הדם
- חום עם ספירה נמוכה של תאי דם לבנים ברמה מסוכנת
- סיכון מוגבר לזיהום בגלל מספר נמוך באופן חריג של תאי דם לבנים
- זיהומים תכופים ומתמשכים בגלל ירידה בנוגדנים בדם שלך
- חולשה, קצב לב לא תקין בגלל רמה נמוכה לא תקינה של מלחים בדם כולל זרחן, אשלגן~~, מגנזיום~~
- רמות גבוהות של אנזימי כבד או קריאטינין בדם המראים כי הכבד או הכליות שלך אינם פועלים כרגיל
- דופק מהיר או לא סדיר
- לחץ דם גבוה
- קוצר נשימה, נשימה מאומצת, נשימה מהירה, נוזל בריאות
- שיעול
- כאב בטן, עצירות

- כאב בעצם ובגב
- פריחה בעור
- נפיחות בקרסוליים, בגפיים ובפנים

תופעות לוואי שכיחות (תופעות שמופיעות ב- 1-10 משתמשים מתוך 100)

- חום, הרגשת חולי, כבד מוגדל, צבע צהוב בעור ובעיניים שלך, ספירה נמוכה של תאי דם כתוצאה מהפעלה חיסונית חמורה
- סחרחורת או עילפון, הסמקה, פריחה, גירוד, חום, קוצר נשימה או הקאה, כאב בטן, שלשול כתוצאה מתגובה הקשורה לעירוי
- פריחה, בחילה, הקאה, שלשול כולל צואה דמית (תסמינים אפשריים של מחלת השתל נגד המאכסן, כאשר תאים מושתלים תוקפים את התאים שלך)
- כאבי פרקים בגלל רמה גבוהה של חומצת שתן
- תוצאות לא תקינות של בדיקות דם (רמה גבוהה של: זרחן, אשלגן, סידן, ~~מגנזיום~~ ונתרן, אנזים הנקרא אלקליין פוספטאז המסייע לגלות מחלת כבד, פיברין די-דימר, פריטין בסרום; רמה נמוכה של: חלבון בדם הנקרא אלבומין, נתרן, מגנזיום)
- פרכוסים, עוויתות
- התכווציות שרירים/עוויתות בגלל רמה נמוכה לא תקינה של מלחים בדם כולל סידן
- תנועות לא רצוניות או לא נשלטות
- רעד בלתי רצוני של הגוף, קושי בכתיבה, קושי להביע מחשבות באופן מילולי, הפרעות קשב, ישנוניות
- עקצוץ או חוסר תחושה, קושי לנוע בגלל נזק עצבי
- ירידה בראייה
- צמא
- ירידה במשקל
- כאב עצבי
- חרדה, עצבנות
- מצב חמור של בלבול
- קשיי שינה
- חוסר נשימה, קושי לנשום בשכיבה, נפיחות בכפות הרגליים או ברגליים (תסמינים אפשריים של אי ספיקת לב), הפסקת פעימות הלב
- נפיחות וכאב בגלל קרישי דם
- נפיחות כתוצאה מנוזלים שדולפים מכלי הדם לתוך הרקמה שמסביב
- ~~לחץ דם גבוה~~
- נפיחות ואי נוחות (נפיחות בבטן), בגלל הצטברות נוזל בבטן
- יובש בפה, כאב בפה, דימום בפה, דלקת חניכיים
- עור ועיניים צהובים כתוצאה מרמות גבוהות חריגות של בילירובין בדם
- גרד
- הזעת יתר, הזעות לילה
- מחלה דמוית שפעת
- אי ספיקה של איברים רבים

תופעות לוואי שאינן שכיחות (תופעות שמופיעות ב- 1-10 משתמשים מתוך 1,000)

- תוצאות לא תקינות של בדיקות דם (רמה גבוהה של מגנזיום)
- חולשה או שיתוק בגפיים או בפנים, קושי בדיבור (תסמינים אפשריים לשבץ מוחי כתוצאה מהפחתת אספקת הדם)
- עור חם או מאדים במהירות
- שיעול המייצר ליחה או לפעמים דם, חום, קוצר נשימה או קושי לנשום
- קושי בשליטה בתנועה