08.2021

Soliris

Active ingredient:

ECULIZUMAB

Concentrate for solution for infusion
IV

סוליריס

חומר פעיל:
אקוליזומאב

תרכיז להכנת תמיסה לעירוי
תוך ורידי

רופא/ה, רוקח/ת נכבד/ה,
העלון לרופא של המוצר עודכן באוגוסט 2021 וזאת **לאחר קבלת אישור עבור התוויה חדשה:**
Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibodypositive with a relapsing course of the disease who have received prior therapy

העלון מכיל בתוכו עדכונים רבים בפרקים שונים.
מובאים להלן על רקע תכלת עדכונים בפרק התוויה ובנוסף עריכה שבוצעה בפרק משטר המינון. על רקע בצהוב עדכוני הבטיחות. טקסט שנמחק מופיע עם קו חוצה.
בעלון ניתן למצוא מידע קליני חדש אשר אינו מובא בהודעה זו.

נוסח ההתוויה המאושר לתכשיר כפי שמופיע ברישיון התכשיר:

Soliris is indicated for the treatment of patients with:
- Paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history. Eculizumab has not been studied in clinical trials in patients with PNH below 11 years of age.
- Atypical haemolytic uremic syndrome (aHUS).

Soliris is indicated in adults for the treatment of:
- Refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive.
- Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibodypositive with a relapsing course of the disease who have received prior therapy.

העדכונים בעלון לרופא הנוגעים להתוויה, משטר מינון ובטיחות:

4.1 Therapeutic indication

Soliris is indicated for the treatment of patients with:
- Paroxysmal nocturnal haemoglobinuria (PNH).
  Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1). Eculizumab has not been studied in clinical trials in patients with PNH below 11 years of age.
- Atypical haemolytic uremic syndrome (aHUS) (see section 5.1).

Soliris is indicated in adults for the treatment of:
- Refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive (see section 5.1).
- Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease who have received prior therapy (see section 5.1).

4.2 Posology and method of administration

Soliris must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological, renal, ~~or~~ neuromuscular or neuro-inflammatory disorders.

Posology

Adult Patients:

In Paroxysmal Nocturnal Haemoglobinuria (PNH):

The PNH dosing regimen for adult patients (≥18 years of age) consists of a 4-week initial phase followed by a maintenance phase:

- Initial phase: 600 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 900 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 900 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2 days (see section 5.1).

In atypical Haemolytic Uremic Syndrome (aHUS), ~~and~~ refractory generalized Myasthenia Gravis (gMG) and Neuromyelitis Optica Spectrum Disorder (NMOSD):

The aHUS, ~~and~~ refractory gMG and NMOSD dosing regimen for adult patients (≥18 years of age) consists of a 4 week initial phase followed by a maintenance phase:

- Initial phase: 900 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 1,200 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 1,200 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2 days (see section 5.1).

Paediatric patients in PNH and aHUS:

Paediatric PNH patients, above 11 years old, and aHUS patients with body weight ≥ 40 kg are treated with the adult dosing recommendations, respectively.

In paediatric PNH patients, above 11 years old, and aHUS patients with body weight below 40 kg, the Soliris dosing regimen consists of:

Patient Body Weight	**Initial Phase**	**Maintenance Phase**
30 to <40 kg	600 mg weekly x 2	900 mg at week 3; then 900 mg every 2 weeks
20 to <30 kg	600 mg weekly x 2	600 mg at week 3; then 600 mg every 2 weeks
10 to <20 kg	600 mg weekly x 1	300 mg at week 2; then 300 mg every 2 weeks
5 to <10 kg	300 mg weekly x 1	300 mg at week 2; then 300 mg every 3 weeks

Soliris has not been studied in patients with PNH who weigh less than 40 kg. The posology of Soliris for PNH patients less than 40 kg weight and who are above 11 years old is based on the posology used for patients with aHUS and who weigh less than 40 kg.

Soliris has not been studied in paediatric patients with refractory gMG or NMOSD.

For adult aHUS, ~~and~~ refractory gMG and NMOSD patients and paediatric aHUS patients supplemental dosing of Soliris is required in the setting of concomitant PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion):

Type of Plasma Intervention	**Most Recent Soliris Dose**	**Supplemental Soliris Dose With Each PE/PI Intervention**	**Timing of Supplemental Soliris Dose**
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Treatment monitoring
aHUS patients should be monitored for signs and symptoms of thrombotic microangiopathy (TMA) (see section 4.4 aHUS laboratory monitoring).
Soliris treatment is recommended to continue for the patient's lifetime, unless the discontinuation of Soliris is clinically indicated (see section 4.4).

Elderly
Soliris may be administered to patients aged 65 years and over. There is no evidence to suggest that any special precautions are needed when older people are treated – although experience with Soliris in this patient population is still limited.

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.1).

Hepatic impairment
The safety and efficacy of Soliris have not been studied in patients with hepatic impairment.

Method of administration
Do not administer as an intravenous push or bolus injection. Soliris should only be administered via intravenous infusion as described below.

For instructions on dilution of the medicinal product before administration, see section 6.6. The diluted solution of Soliris should be administered by intravenous infusion over 25 – 45 minutes (35 minutes ± 10 minutes) in adults and 1-4 hours in paediatric patients under 18 years of age via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of Soliris from light during administration to the patient.
Patients should be monitored for one hour following infusion. If an adverse event occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time may not exceed two hours in adults ~~and adolescents (aged 12 years to under 18 years)~~ and four hours in ~~children aged less than 12 years~~ yearspaediatric patients under 18 years of age.

Refractory gMG
Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment. Discontinuation of the therapy should be considered in a patient who shows no evidence of therapeutic benefit by 12 weeks.

4.3 Contraindications
(…)

4.4 Special warnings and precautions for use
(…)

Meningococcal Infection
(…)

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH, aHUS, ~~and~~ refractory gMG and NMOSD, may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH), TMA (aHUS) ~~or~~, MG exacerbation (refractory gMG) or relapse (NMOSD). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.
(…)

Infusion Reactions

Administration of Soliris may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis), though immune system disorders within 48 hours of Soliris administration did not differ from placebo treatment in PNH, aHUS, refractory gMG, and other studies conducted with Soliris. In clinical trials, 1 (0.9%) gMG patient experienced an infusion reaction which required discontinuation of Soliris. no No PNH, aHUS, or refractory gMGor NMOSD patients experienced an infusion reaction which required discontinuation of Soliris. Soliris administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy administered.

Immunogenicity

Infrequent antibody responses have been detected in Soliris-treated patients across all clinical studies. In PNH placebo controlled studies low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%).

In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 3/100 (3%) by the ECL bridging format assay. 1/100 (1%) aHUS patients had low positive values for neutralizing antibodies.

In a refractory gMG placebo controlled study, none (0/62) of the Soliris treated patients showed antidrug antibody response during the 26 week active treatment, whereas in a refractory gMG extension study, a total of 2.6% overall were positive for ADAs at any post-baseline visit. Positive ADA results appeared to be transient, as positive titers were not observed at subsequent visits, and there were no clinical findings in these patients suggestive of an effect of positive ADA titers.

In a NMOSD placebo controlled study, 2/95 (2.1%) of the Soliris treated patients showed antidrug antibody response post-baseline. Both patients were negative for neutralizing antibodies. Positive ADA samples were low titer and transient. There has been no observed correlation of antibody development to clinical response or adverse events.

Immunization

Prior to initiating Soliris therapy, it is recommended that PNH, aHUS, and refractory gMG and NMOSD patients initiate immunizations according to current immunization guidelines. Additionally, all patients must be vaccinated against meningococcal infections at least 2 weeks prior to receiving Soliris unless the risk of delaying Soliris therapy outweighs the risks of developing a meningococcal infection. Patients who initiate Soliris treatment less than 2 weeks after receiving tetravalent a tetravalent meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W 135 and B where available are recommended in preventing the commonly pathogenic meningococcal serogroups. (see Meningococcal Infection).

(…)

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH, aHUS and, refractory gMG and NMOSD may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH), TMA (aHUS) or, MG exacerbation (refractory gMG) or relapse (NMOSD). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Anticoagulant therapy

Treatment with Soliris should not alter anticoagulant management.

Immunosuppressant and anticholinesterase therapies

Refractory gMG

Patients in refractory gMG clinical trials continued treatment with immunosuppressant and anticholinesterase therapies while on Soliris treatment. Withdrawal of immunosuppressant and anticholinesterase therapies during Soliris treatment for refractory gMG was not assessed in the placebo-controlled studies.

~~In the open-label extension trial (Study ECU-MG-302), physicians had the option to adjust background immunosuppressant therapies. In this setting, a decrease of the daily dose of at least 1 immunosuppressant was observed in 47% of patients. The most common reason for change in immunosuppressant therapy was improvement in MG symptoms while on eculizumab treatment.~~ When immunosuppressant and anticholinesterase therapies are decreased or discontinued, patients should be monitored closely for signs of disease exacerbation.

Neuromyelitis Optica Spectrum Disorder
When immunosuppressant therapy is decreased or discontinued, patients should be monitored closely for signs and symptoms of potential NMOSD relapse.
(…)

Treatment discontinuation for refractory gMG:
Use of Soliris in refractory gMG treatment has been studied only in the setting of chronic administration. Patients ~~that~~who discontinue Soliris treatment should be carefully monitored for signs and symptoms of ~~deterioration of~~ disease exacerbation.

Treatment discontinuation for NMOSD:
Use of Soliris in NMOSD treatment has been studied only in the setting of chronic administration and the effect of Soliris discontinuation has not been characterized. Patients who discontinue Soliris treatment should be carefully monitored for signs and symptoms of potential NMOSD relapse.
(…)

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed. Based on the potential inhibitory effect of eculizumab on complement-dependent cytotoxicity of rituximab, eculizumab may reduce the expected pharmacodynamic effects of rituximab.

Chronic intravenous human immunoglobulin (IVIg) treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as eculizumab and thereby decrease serum eculizumab concentrations. ~~Drug interaction studies have not been conducted with eculizumab in patients treated with IVIg.~~

4.6 Fertility, pregnancy and lactation
(…)

4.7 Effects on ability to drive and use machines
(…)

4.8 Undesirable effects

Summary of the safety profile
Supportive safety data were obtained from ~~29~~31 completed ~~and one ongoing~~ clinical studies that included 1,~~407~~503 patients exposed to eculizumab in ~~ten~~ complement-mediated disease populations, including PNH, aHUS, ~~and~~ refractory gMG and NMOSD. The most common adverse reaction was headache, (occurred mostly in the initial phase of dosing), and the most serious adverse reaction was meningococcal sepsis.

Tabulated list of adverse reactions
Table 1 gives the adverse reactions observed from spontaneous reporting and in eculizumab completed clinical trials, including PNH, aHUS, ~~and~~ refractory gMG and NMOSD studies. Adverse reactions reported at a very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) or rare (≥1/10,000 to <1/1,000) frequency with eculizumab, are listed by system organ class and preferred term. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse Reactions reported in ~~1,407 patients included in overall~~ eculizumab clinical trials, including patients with PNH, aHUS, ~~and~~ refractory gMG and NMOSD as well as from postmarketing experience

MedDRA System Organ Class	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)
Infection and infestations		Pneumonia, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Urinary tract infection, Oral Herpes	Meningococcal ~~infection~~[a]infection[b], Sepsis, Septic shock, Peritonitis, Lower respiratory tract infection, Fungal infection, Viral infection~~, Bronchitis~~, Abscess[a], Cellulitis, Influenza, Gastrointestinal infection, Cystitis, Infection, Sinusitis, ~~Tooth infection~~	Aspergillus ~~infection~~[b]infection[c], Arthritis ~~bacterial~~[b]bacterial[c], Genitourinary tract gonococcal infection, Haemophilus influenzae infection, Impetigo, Gingivitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Malignant melanoma, Myelodysplastic syndrome
Blood and lymphatic system disorders		Leukopenia, Anaemia	Thrombocytopenia, Lymphopenia	Haemolysis*, Abnormal clotting factor, Red blood cell agglutination, Coagulopathy
Immune system disorders			Anaphylactic reaction, Hypersensitivity	
Endocrine disorders				Basedow's disease
Metabolism and nutrition disorders			Decreased appetite	
Psychiatric disorders		Insomnia	Depression, Anxiety, Mood swings	Abnormal dreams, Sleep disorder
Nervous system disorders	Headache	Dizziness, Dysgeusia~~,~~ ~~Tremor~~	Paraesthesia, Tremor	Syncope
Eye disorders			Vision blurred	Conjunctival irritation
Ear and labyrinth disorders			Tinnitus,Vertigo	
Cardiac disorders			Palpitation	

Vascular disorders		Hypertension	Accelerated hypertension, Hypotension, Hot flush, Vein disorder	Haematoma
Respiratory, thoracic and mediastinal disorders		Cough, Oropharyngeal pain	Dyspnoea, Epistaxis, Throat irritation, Nasal congestion, Rhinorrhoea	
Gastrointestinal disorders		Diarrhoea, Vomiting, Nausea, Abdominal pain	Constipation, Dyspepsia, Abdominal distension	Gastroesophageal reflux disease, Gingival pain
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders		Rash, Pruritus, Alopecia	Urticaria, Erythema, Petechiae, Hyperhidrosis, Dry skin	Dermatitis, Skin depigmentation
Musculoskeletal and connective tissue disorders		Arthralgia, Myalgia, ~~Pain in extremity~~	Muscle spasms, Bone pain, Back pain, Neck pain, Joint swelling, Pain in extremity	Trismus
Renal and urinary disorders			Renal impairment, Dysuria, Haematuria	~~Haematuria~~
Reproductive system and breast disorders			Spontaneous penile erection, ~~Menstrual disorder~~	Menstrual disorder
General disorders and administration site conditions		Pyrexia, ~~Chills~~, Fatigue, Influenza like illness	~~Oedema~~E~~e~~dema, Chest discomfort, Asthenia, Chest pain, Infusion site pain, Chills	Extravasation, Infusion site paraesthesia, Feeling hot
Investigations			Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Haematocrit decreased, Haemoglobin decreased	Coombs test ~~positive~~[b] positive[c]
Injury, poisoning and procedural complication			Infusion related reaction	

~~*See paragraph Description of selected adverse reactions~~

~~[a]=Meningococcal infection includes the following group of PTs: Meningococcal sepsis, Meningococcal meningitis, Neisseria infection; [b]= Adverse reactions identified in postmarketing reports;~~

Included Studies: Asthma (C07-002), aHUS(C08-002, C08-003, C10-003, C10-004), Dermatomyositis (C99-006), gMG (C08-001, ECU-MG-301, ECU-MG-302), Neuromyelitis Optica Spectrum Disorder (ECU-NMO-301), IMG (C99-004, E99-004), PNH (C02-001, C04-001, C04-002, C06-002, C07-001, E02-001, E05-001, E07-001, M07-005, X03-001, X03-001A), Psoriasis (C99-007), RA (C01-004, C97-001, C99-001, E01-004, E99-001), STEC-HUS (C11-001), SLE (C97-002). MedDRA version 21.0.

*See paragraph Description of selected adverse reactions.
[a] Abscess includes the following group of PTs: Abscess limb, Colonic abscess, Renal abscess, Subcutaneous abscess, Tooth abscess, Hepatosplenic abscess, Perirectal abscess, Rectal abscess.
[b] Meningococcal infection includes the following group of PTs: Meningococcal infection, Meningococcal sepsis, Meningitis meningococcal, Neisseria infection.
[c] ADRs identified in postmarketing reports
(…)

- העלון לרופא 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, ת.ד. 7063, פתח תקווה 4917001.
טלפון: 03-9373753, פקס: 03-9373774

בברכה,
עוז וולך - רוקח ממונה
אלקסיון פארמה ישראל בע"מ