הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: 01/07/2012

שם תכשיר באנגלית: Soliris

מספר רישום : 144 09 32985 00

שם בעל הרישום : Alexion Pharma Israel Ltd

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פרטים על השינוי/ים המבוקש/ים

פרק בעלון	טקסט נוכחי Current	טקסט חדש Proposed
4.4 Special warnings and precautions for use	Meningococcal Infection … To reduce the risk of infection, all patients must be vaccinated at least 2 weeks prior to receiving Soliris..Patients less than 2 years of age and those who are treated with Soliris less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients must be re-vaccinated according to current medical guidelines for vaccination use. Tetravalent vaccines against serotypes A, C, Y and W135 are strongly recommended, preferably conjugated ones. …. Patients should be informed of these signs and symptoms and steps taken to seek medical care immediately. (see Package Leaflet for a description). Other Systemic Infections: Due to its mechanism of action, Soliris therapy should be administered with caution to patients with active systemic infections. The overall severity and frequency of infections in Soliris-treated patients was similar to placebo treated patients in clinical studies, although an increase in the	Meningococcal Infection … To reduce the risk of infection, all patients must be vaccinated at least 2 weeks prior to receiving Soliris. PNH patients must be vaccinated 2 weeks prior to Soliris initiation. aHUS patients who are treated with Soliris less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients must be re-vaccinated according to current medical guidelines for vaccination use. Tetravalent vaccines against serotypes A, C, Y and W135 are strongly recommended, preferably conjugated ones. … Patients should be informed of these signs and symptoms and steps taken to seek medical care immediately. Physicians must discuss the benefits and risks of Soliris therapy with patients and provide them with a patient information brochure and a patient safety card. (see Package Leaflet for a description). Other Systemic Infections: Due to its mechanism of action, Soliris therapy should be

administered with caution to patients with active systemic infections. Patients should be provided with information from the Package Leaflet to increase their awareness of potential serious infections and the signs and symptoms of them. 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 and other studies conducted with Soliris. ... Immunogenicity .... Immunization ... Additionally, all patients must be vaccinated against meningococcus at least 2 weeks prior to receiving Soliris. Patients who are treated with Soliris less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. ...	number and severity of infections, particularly due to encapsulated bacteria, cannot be excluded. Patients should be provided with information from the Package Leaflet to increase their awareness of potential serious infections and the signs and symptoms of them. Infusion Reactions As with all therapeutic proteins, 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 and other studies conducted with Soliris. … Immunogenicity … Immunization … Additionally, all patients must be vaccinated against meningococcus at least 2 weeks prior to receiving Soliris. Patients less than 2 years of age and those who are treated with Soliris less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. ...	
Woman of childbearing potential Woman of childbearing potential have to use effective contraception during treatment and up to 5 months after treatment. Pregnancy: ... Human IgG are known to cross human placental barrier, and thus	Pregnancy: ... Human IgG are known to cross human placental barrier, and thus eculizumab may potentially cause terminal complement inhibition in the foetal circulation. Therefore, Soliris should be given to a pregnant woman only if clearly needed. Woman of childbearing	**4.6 Fertility, pregnancy and lactation**

eculizumab may potentially cause terminal complement inhibition in the foetal circulation. Therefore, Soliris should be given to a pregnant woman only if clearly needed. Breast-feeding: … and because of the potential for serious adverse reactions in nursing infants, breast-feeding should be discontinued during treatment and up to 5 months after treatment. Fertility: No specific study on fertility has been conducted.	potential have to use effective contraception during treatment and up to 5 months after treatment. Breast-feeding: … and because of the potential for serious adverse reactions in nursing infants, breast-feeding should be discontinued during treatment and up to 5 months after treatment.	
Soliris has no or negligible influence on the ability to drive and use machines.	No studies on the effects on the ability to drive and use machines have been performed.	**4.7 Effects on ability to drive and use machines**
Summary of the safety profile The most common or serious adverse reactions were headache (occurred mostly in the initial phase), leukopenia and meningococcal infection. *Tabulated* list *of adverse reactions* Table 1 gives the adverse reactions observed from spontaneous reporting and in clinical trials in PNH and aHUS. Adverse reactions reported at a very common (≥1/10) common (≥1/100 to <1/10) or uncommon (≥1/1,000 to <1/100) 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. See attached table 1 Description of selected adverse reactions	*Summary of the safety profile* Eculizumab for the treatment of PNH was studied in three clinical studies that included 195 eculizumab-treated patients and most of these patients have been enrolled in the E05-001 extension study. There was one pivotal trial comparing the eculizumab-treatment arm to a placebo-treatment arm. Eculizumab for the treatment of aHUS was studied in 37 patients enrolled in two prospective controlled clinical studies (C08-002A/B and C08-003A/B). Additional safety data were collected in 30 patients in a retrospective study (C09-001r).The most frequent adverse reactions were:Headache, dizziness, nausea and pyrexia each occurring in 5% or more in PNH clinical trials. Most headaches did not persist after the initial administration phase of Soliris. .Leukopenia occurring in 10% or more in aHUS clinical trials	**4.8 Undesirable effects**

In all PNH clinical studies the most serious adverse reaction was meningococcal septicaemia in two vaccinated PNH patients (see section 4.4). There were no meningococcal infections or deaths in the aHUS clinical studies. ... Paediatric population The safety profile in adolescents (patients aged 12 years to less than 18 years) is similar to that observed in adults. In infants and children aHUS patients (aged 2 months to less than 12 years) included in the retrospective study C09-001 r, the safety profile (appeared similar to that observed in adult/adolescent aHUS patients. The most common (>10%) adverse reactions reported in paediatric patients were diarrhoea, vomiting, pyrexia, upper respiratory tract infection and headache. Patients with other diseases *Safety Data From Other Clinical Studies* ...	*b. Tabulated summary of adverse reactions* Table 1 gives the adverse reactions observed from spontaneous reporting and in clinical trials in PNH and aHUS. Adverse reactions reported at a very common (≥1/10) common (≥1/100 to <1/10) or uncommon (≥1/1,000 to <1/100) frequency with eculizumab are listed by system organ class and preferred term. See attached table 1 Description of selected adverse reactions There was no evidence of an increased incidence of infection across PNH studies with eculizumab as compared to placebo, including serious infections, severe infections or multiple infections. In all PNH clinical studies the most serious adverse reaction was meningococcal septicaemia in two vaccinated PNH patients (see section 4.4). There were no meningococcal infections or deaths in the aHUS clinical studies. There did not appear to be evidence for an increased risk of other serious infections with eculizumab treatment in the aHUS studies. ... Paediatric population The safety profile in paediatric aHUS patients in the retrospective study C09-001 r, (N=15, patients ages 2 months to less than 12 years) treated with Soliris appeared similar to that observed in adult/adolescent aHUS patients. The most common (>10%) adverse events reported in paediatric patients were diarrhoea, vomiting, pyrexia, upper respiratory tract infection and headache.	

	Safety Data From Other Clinical Studies …	

העלון, שבו מסומנים השינויים המבוקשים על רקע צהוב הועבר בדואר אלקטרוני בתאריך.....03/07/12.....

√ קיים עלון לרופא והוא מעודכן בהתאם.

√ אסמכתא לבקשה: SPC

√ השינוי הנ"ל הוגש לרשויות הבריאות - EMA approval 20 June 2012

√ אני, הרוקח הממונה של חברת Alexion Pharma Israel Ltd. מצהיר בזה כי אין שינויים נוספים בעלון.

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חתימת הרוקח הממונה

Current

Table 1: Adverse Reactions Reported in 232 patients included in PNH and aHUS clinical trials and in postmarketing reports

MedDRA System Organ Class	Very Common (≥1/10);	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infection and infestations		Bronchitis, Pneumonia, Gastrointestinal infection, Nasopharyngitis, Oral Herpes, Sepsis, Septic shock, Upper respiratory tract infection, Urinary tract infection, Cystitis, Viral infection, Meningococcal sepsis, Meningococcal meningitis, Arthritis bacterial	Abscess, Cellulitis, Fungal infection, Gingival infection, Haemophilus infection, Infection, Influenza, Lower respiratory tract infection, Neisseria infection, Sinusitis, Tooth infection, Impetigo
Neoplasms benign, malignant and unspecified			Malignant melanoma, Myelodysplastic syndrome
		…	
Psychiatric disorders			Abnormal dreams, Anxiety, Depression Insomnia, Mood swings, Sleep disorder
Nervous system disorders	Headache	Dizziness, Dysgeusia, Paraesthesia	Syncope, Tremor
Eye disorders			Conjunctival irritation, Vision blurred
Ear and labyrinth		Vertigo	Tinnitus,

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

Proposed

Table 1: Adverse Reactions Reported in 232 patients included in PNH and aHUS clinical trials and in postmarketing reports

MedDRA System Organ Class	Very Common (≥1/10);	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infection and infestations		Meningococcal sepsis, Meningococcal meningitis, Sepsis, Septic shock, Pneumonia, Arthritis bacterial Upper respiratory tract infection, , Nasopharyngitis, Bronchitis, Oral Herpes Gastrointestinal infection, , Urinary tract infection, Cystitis, Viral infectionl	Neisseria infection, Lower respiratory tract infection, Fungal infection, Haemophilus infection, Abscess, Cellulitis, Influenza, Gingival infection, Infection, Sinusitis, Tooth infection, Impetigo
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Malignant melanoma, Myelodysplastic syndrome
		...	
Psychiatric disorders			Depression, Anxiety, Insomnia, Sleep disorder Abnormal dreams, Mood swings
Nervous system disorders	Headache	Dizziness, Paraesthesia, Dysgeusia	Syncope, Tremor
Eye disorders			Vision blurred, Conjunctival irritation,
Ear and labyrinth disorders		Vertigo	Tinnitus,
Cardiac disorders			Palpitation
Vascular disorders		Accelerated hypertension	Hypertension, Hypotension, Haematoma, Hot flush, Vein disorder
Respiratory, thoracic and mediastinal disorders		Cough, Nasal congestion, Pharyngolaryngeal pain, Throat irritation	Epistaxis, Rhinorrhoea,
Gastrointestinal disorders		Diarrhoea, Vomiting, Nausea,Abdominal pain, Constipation, Dyspepsia,	Peritonitis, Gastrooesophagal reflux disease, Abdominal distension, Gingival pain,
Hepatobiliary disorders			Jaundice
Skin and subcutaneous tissue disorders		Rash, Alopecia, Dry skin, Pruritus,	Urticaria, Dermatitis, Erythema, Petechiae, Skin depigmentation,

			Hyperhidrosis, ,
Musculoskeletal and connective tissue disorders		Arthralgia, Myalgia, Back pain, , Neck pain, Pain in extremity	Trismus, Joint swelling, Muscle spasms, Bone pain,
Renal and urinary disorders		Dysuria	Renal impairment, Haematuria
Reproductive system and breast disorders		Spontaneous penile erection	Menstrual disorder
General disorders and administration site condition		Oedema, Infusion related reaction, Chest discomfort, Pyrexia, Chills, Fatigue, Asthenia,	Chest pain, , Infusion site paraesthesia, Infusion site pain, Extravasation, Influenza like illness Feeling hot
Investigations		Coombs test positive*	Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Haematocrit decreased, Haemoglobin decreased