הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 05.2013)

תאריך:25.10.2016

שם תכשיר באנגלית: **ILARIS 150mg/mL**

מספר הרישום:[1446032964]

שם בעל הרישום: נוברטיס ישראל, בע"מ

טופס זה מיועד לפירוט ההחמרות בלבד!

טקסט שחור שאינו צבוע בצהוב– טקסט מאושר כיום ומוחלף
~~טקסט עם קו חוצה~~ – מחיקת טקסט מהעלון המאושר
טקסט המסומן בצהוב– תוספת והחמרה

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
		Indication
		Contraindications
Addition: **To** *TRAPS, HIDS/MKD and FMF: Adults, adolescents and children aged 2 years and older…….* Continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating physician. **Addition:** **To** *SJIA* Continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating physician.		**Posology& method of administration**
4.4 Special warnings and precautions for use Infections Ilaris is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with Ilaris. Physicians should exercise caution when administering Ilaris to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections.	**4.4 Special warnings and precautions for use** Infections Ilaris is associated with an increased incidence of serious infections. Physicians should exercise caution when administering Ilaris to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections.	**Special Warnings and precautions for use**

Neutropenia and leukopenia Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including Ilaris. . Treatment with Ilaris should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment. If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.	**Neutropenia** Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10⁹/L) has been observed commonly with another medicinal product that inhibits IL-1 used in a patient population (rheumatoid arthritis) other than CAPS. Neutropenia was observed commonly in patients with rheumatoid arthritis (not Page 6 ILA API SEP14 CL V4 COR CPO CL REF CDS 31102012 + USPI 05.2013 an approved use) who were administered ILARIS subcutaneously in clinical studies. Treatment with ILARIS should not be initiated in patients with neutropenia. It is recommended that neutrophil counts be assessed prior to initiating treatment, after 1 to 2 months, and periodically thereafter while receiving ILARIS. If a patient becomes neutropenic, the ANC should be monitored closely and treatment discontinuation should be considered.	
Macrophage activation syndrome in SJIA patients Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular SJIA. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of SJIA, as these are known triggers for MAS. Based on clinical trial experience, Ilaris does not appear to increase the incidence of MAS in SJIA patients, but no definitive conclusion can be made.	**Macrophage activation syndrome (in SJIA patients)** Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular SJIA, and should be aggressively treated. Physicians should be attentive to symptoms of infection or worsening of SJIA, as these are known triggers for MAS. Based on clinical trial experience, ILARIS does not appear to increase the incidence of MAS in SJIA patients, but no definitive conclusion can be made.	

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of Ilaris treatment, the recommendation is to wait for at least 3 months after the last Ilaris injection and before the next one (see section 4.4).	No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving ILARIS. Therefore, live vaccines should not be given concurrently with ILARIS. It is recommended that, if possible, pediatric and adult patients should complete all immunisations in accordance with current immunisation guidelines prior to initiating ILARIS therapy.	**Interactions**
Pregnancy There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The risk for the fetus/mother is unknown. Women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit-risk evaluation. Animal studies indicate that canakinumab crosses the placenta and is detectable in the foetus. No human data are available, but as canakinumab is an immunoglobulin of the G class (IgG1), human transplacental transfer is expected. The clinical impact of this is unknown. However, administration of live vaccines to newborn infants exposed to canakinumab *in utero* is not recommended for 16 weeks following the mother's last dose of Ilaris before childbirth. Women who received canakinumab during pregnancy should be instructed to inform the baby's healthcare professional before any vaccinations are given to their newborn infant. Breast-feeding It is unknown whether canakinumab is excreted in human milk. The decision whether to breast-feed during Ilaris therapy should therefore only be taken after a thorough benefit-risk evaluation. Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see section 5.3).	**Pregnancy** There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 13 Non-clinical safety data). The risk for the fetus/mother is unknown. Women should use effective contraceptives during treatment with ILARIS and for up to 3 months after the last dose. Because animal reproduction studies are not always predictive of the human response, canakinumab should be given to a pregnant woman only if clearly needed. **Breast-feeding** It is not known whether canakinumab is excreted in human milk. Animal studies have shown that a murine anti-murine IL-1beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see section 13 Non-clinical safety data). Breast-feeding is not recommended during ILARIS therapy.	**Fertility, Pregnancy and lactation**

4.8 Undesirable effects Summary of the safety profile Over 2,600 subjects including approximately 480 children (aged 2 to 17 years) have been treated with Ilaris in interventional studies in patients with CAPS, TRAPS, HIDS/MKD, FMF, SJIA, gouty arthritis, or other IL-1beta mediated diseases, and healthy volunteers. Serious infections have been observed. The most frequent adverse drug reactions were infections predominantly of the upper respiratory tract. The majority of the events were mild to moderate. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment. Hypersensitivity reactions have been reported in patients treated with Ilaris (see sections 4.3 and 4.4). Addition to table 1: **Infections and infestations** Common- Vulvovaginal candidiasis **Musculoskeletal and connective tissue disorders** Very common- Arthralgia [1] Common- Musculoskeletal pain [1] **Investigations** Very common- Creatinine renal clearance decreased [1,3] Proteinuria [1,4] Leukopenia [1,5] Common- Neutropenia [5] Unknown- Platelet count decreased [5] [1] In SJIA [2] In GA [3] Based on estimated creatinine clearance, most were transient [4] Most represented transient trace to 1+ positive urinary protein by dipstick [5] See further information below *Laboratory abnormalities in SJIA patients* *Haematology* In the overall SJIA programme, transient decreased white blood cell (WBC) counts ≤ 0.8× lower limit of normal (LLN) were	**Adverse drug reactions** **Summary of the safety profile** Over 2300 subjects including approximately 250 children (aged 2 to 17) have been treated with ILARIS in interventional studies in CAPS, SJIA, gouty arthritis, or other IL-1beta mediated diseases, and healthy volunteers. The most frequently reported adverse drug reactions were infections (e.g nasopharyngitis and upper respiratory tract infections). The majority of the events were mild to moderate although serious infections were observed. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment. Hypersensitivity reactions have been reported in patients treated with ILARIS (see section 5 Contraindications and 6 Warnings and precautions). **Laboratory abnormalities (SJIA)** ***Hematology*** In the randomized, placebo-controlled portion of SJIA	**Adverse drug reactions**

reported in ~~5~~33 patients (~~10.4 %~~16. 5%). In the overall SJIA programme, transient decreases in absolute neutrophil count (ANC) to less than 1x10^{9}/L were reported in ~~3~~ 12 patients (6.0%). In the overall SJIA programme, transient decreases in platelet counts (<LLN) were observed in ~~3~~ 19 patients (~~6.3%~~9.5%). *ALT/AST* In the overall SJIA program, high ALT and/or AST > 3 x upper limit of normal (ULN) were reported in ~~2~~ 19 patients (~~4.1%~~9.5%).	Study 2 decreased white blood cell counts (WBC) less than or equal to 0.8 × lower limit of normal (LLN) were reported in 5 patients (10.4%) in the ILARIS group compared to 2 (4.0%) in the placebo group. Transient decreases in absolute neutrophil counts (ANC) to less than 1x10^{9}/L were reported in 3 patients (6.0%) in the ILARIS group compared to 1 patient (2.0%) in the placebo group. One case of ANC counts less than 0.5x10^{9}/L was observed in the ILARIS group and none in the placebo group (see section 6 Warnings and precautions). Mild (less than LLN and greater than 75x10^{9}/L) and transient decreases in platelet counts were observed in 3 (6.3%) ILARIS-treated patients versus 1 (2.0%) placebo-treated patient. ***Hepatic transaminases*** Elevations of transaminases have been observed in patients treated with ILARIS. In the randomized, placebo-controlled portion of SJIA Study 2, high ALT and/or AST greater than or equal to 3 × upper limit of normal (ULN) were reported in 2 (4.1%) ILARIS-treated patients and 1 (2.0%) placebo-patient. All patients had normal values at the next visit.	
4.9 Overdose Reported experience with overdose is limited. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg administered intravenously or subcutaneously without evidence of acute toxicity. In case of overdose, it is recommended for the patient to be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.	**Overdosage** There is limited experience with overdosage. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg administered intravenously or subcutaneously without evidence of acute toxicity. In case of overdosage, it is recommended for the patient to be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted as necessary.	**Overdose**

מצ"ב העלון שבו מסומנות ההחמרות המבוקשות על רקע צהוב.
שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך 26 באוקטובר 2016
