דצמבר 2019

**Actemra® 20 mg/ml I.V.**
**אקטמרה 20 מ"ג/מ"ל I.V.**
**tocilizumab**
**Concentrate for solution for infusion**

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על מספר עדכונים שבוצעו בעלון לרופא של התכשיר.

בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

**ההתוויות הרשומות לתכשיר בישראל:**

Actemra (tocilizumab) is indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs (Disease Modifying Anti-Rheumatic Drugs) or TNF antagonists or in whom DMARDs cannot be used. Actemra can be used alone or in combination with methotrexate or other DMARDs.

Actemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

Actemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Actemra in combination with methotrexate (MTX) in indicated for the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.

**הסבר:**

<u>טקסט עם קו תחתי</u> מציין טקסט שהוסף לעלון.
~~טקסט עם קו חוצה~~ מציין טקסט שהוסר מן העלון.

למידע נוסף יש לעיין בעלון לרופא כפי שנשלח למשרד הבריאות.

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפסים ע"י פנייה לבעל הרישום: רוש פרמצבטיקה (ישראל) בע"מ, ת.ד 6391 , הוד השרון 4524079
טלפון 09-9737777. כתובתנו באינטרנט: www.roche.co.il.

ב ב ר כ ה,


לביא עמי-עד
רוקח ממונה

אביטל ויסברוט
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# עדכונים מהותיים בעלון לרופא

**בסעיף 4.4 Special warnings and precautions for use עודכן המידע הבא:**

~~Hepatic transaminase elevations~~

Hepatotoxicity

Transient ~~In clinical trials, transient~~ or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment, ~~without progression to hepatic injury~~ (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with Actemra (see section 4.8). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of Actemra. Cases of liver failure resulting in liver transplantation have been reported. Patients should be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

Caution should be exercised when considering initiation of Actemra treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

In RA, pJIA and sJIA patients, ALT ~~and~~ /AST ~~levels~~ should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications, including Actemra discontinuation, based on transaminases levels see section 4.2. For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, Actemra treatment should be interrupted .

~~In sJIA and pJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice, see section 4.2.~~

**בסעיף 4.8 Undesirable Effects עודכן המידע הבא:**

*Table 1. List of ADRs occurring in patients with RA receiving tocilizumab as monotherapy or in combination with MTX or other DMARDs in the double-blind controlled period or during postmarketing experience*

| MedDRA System Organ Class | Frequency categories with preferred terms | | | |
|---|---|---|---|---|
| | Very Common | Common | Uncommon | Rare |
| Skin and subcutaneous tissue disorders | | Rash, Pruritus, Urticaria | | Stevens-Johnson-Syndrome[3] |
| Immune system disorders | | | | Anaphylaxis (fatal)[1, 2 ,3] |
| Hepatobiliary disorders | | | | Drug-induced liver injury, Hepatitis, Jaundice, Very rare: Hepatic failure |

* Includes elevations collected as part of routine laboratory monitoring (see text below)

[1] See section 4.3

[2] See section 4.4

[3] This adverse reaction was identified through post marketing surveillance but not observed in controlled clinical trials. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to TCZ in clinical trials.

[…]

Hepatic transaminase elevations

During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg tocilizumab plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. ~~These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment~~. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg tocilizumab + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 2 x ULN.

[…]

Skin Reactions

~~Very rare~~ Rare reports of Stevens-Johnson Syndrome have occurred in the post marketing setting.

[…]

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form : /https://sideeffects.health.gov.il
~~http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il~~