ינואר 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,

בת אל מלכה כהן
רוקחת ממונה

אביטל ויסברוט
מחלקת רישום

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עדכונים מהותיים בעלון לרופא

בסעיף 4.8 Undesirable effects עודכן המידע הבא:

[…]

pJIA Patients
The safety profile of ~~tocilizumab~~ intravenous Actemra in pJIA has been studied in 188 patients from 2 to 17 years of age. The total patient exposure was 184.4 patient years.

[…]

Lipid parameters
During routine laboratory monitoring in the ~~tocilizumab all exposure population, elevation in total cholesterol >1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL >1.5-2 x ULN in one patient (0.5%).~~intravenous Actemra study WA19977 3.4% and 10.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during the study treatment, respectively.

[…]

sJIA Patients
The safety profile of ~~tocilizumab~~ intravenous Actemra in sJIA has been studied in 112 patients from 2 to 17 years of age. In the 12 week double-blind, controlled phase, 75 patients received treatment with tocilizumab (8 mg/kg or 12 mg/kg based upon body weight). After 12 weeks or at the time of switching to tocilizumab, due to disease worsening, patients were treated in the ~~ongoing~~ open label extension phase.

[…]

Infections
In the 12 week controlled phase, the rate of all infections in the ~~tocilizumab~~ intravenous Actemra group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the ~~ongoing~~ open label extension phase (Part II), the overall rate of infections remained similar at 306.6 per 100 patient years.

In the 12 week controlled phase, the rate of serious infections in the ~~tocilizumab~~ intravenous Actemra group was 11.5 per 100 patient years. At one year in the ~~ongoing~~ open label extension phase the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

[…]

Lipid parameters
During routine laboratory monitoring in the 12 week controlled phase~~, elevation in total cholesterol > 1.5 x ULN to 2 x ULN occurred in 1.5% of the tocilizumab group and none in the placebo group. Elevation in LDL > 1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the tocilizumab group, and in 0% of the placebo group~~ (study WA18221), 13.4% and 33.3% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

In the ~~ongoing~~ open label extension phase, ~~the pattern~~ (study WA18221), 13.2% and ~~incidence~~ 27.7% of ~~elevations~~ patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively .
~~in lipid parameters remained consistent with the 12 week controlled phase data.~~

בסעיף 5.2 Pharmacokinetic properties עודכן המידע הבא:

sJIA Patients :
The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of ~~75~~140 sJIA patients treated with 8 mg/kg IV every 2 weeks (patients with a body weight ≥ 30 kg) ~~or~~ 12 mg/kg IV every 2 weeks (patients with a body weight < 30 kg), ~~given every 2 weeks. The predicted mean (± SD) AUC_{2weeks}, C_{max} and C_{min} of tocilizumab were 32200 ± 9960 µg•h/mL, 245 ± 57.2 µg/ml and 57.5 ± 23.3 µg/mL, respectively. The accumulation ratio for C_{min} (~~162 mg SC every week ~~12 / week~~ (patients weighing ≥ 30 kg), 162 mg SC every 10 days or every 2 ~~was 3.2 ± 1.3. The tocilizumab C_{min} was stabilized after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.~~ weeks (patients weighing below 30 kg).

Table 10. Predicted mean ± SD PK parameters at steady-state after IV dosing in sJIA

RoActemra PK Parameter	**8 mg/kg Q2W ≥ 30 kg**	**12 mg/kg Q2W below 30 kg**
C_{max} (µg/mL)	256 ± 60.8	274 ± 63.8
C_{trough} (µg/mL)	69.7 ± 29.1	68.4 ± 30.0
C_{mean} (µg/mL)	119 ± 36.0	123 ± 36.0
Accumulation C_{max}	1.42	1.37
Accumulation C_{trough}	3.20	3.41
Accumulation C_{mean} or AUC_{τ}*	2.01	1.95

*τ = 2 weeks for IV regimens

After IV dosing, approximately 90% of the steady-state was reached by week 8 for both the 12 mg/kg (BW < 30 kg) and 8 mg/kg Q2W (BW ≥ 30 kg) regimens.

In sJIA patients, the central volume of distribution was ~~35 ml/kg~~ 1.87 L and the peripheral volume of distribution was ~~60 ml/kg~~ 2.14 L resulting in a volume of distribution at a steady state of ~~95 ml/kg~~ 4.01 L. The linear clearance estimated as a parameter in the population pharmacokinetic analysis, was ~~0.142 ml/hr/kg~~ 5.7 mL/h.

The half life of tocilizumab in sJIA patients is up to ~~23~~ 16 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

pJIA Patients :
The pharmacokinetics of tocilizumab in pJIA patients was characterized by a population pharmacokinetic analysis which included 237 patients who were treated with 8 mg/kg IV every 4 weeks (patients weighing ≥ 30 kg), 10 mg/kg IV every 4 weeks (patients weighing below 30 kg), 162 mg SC every 2 weeks (patients weighing ≥ 30 kg), or 162 mg SC every 3 weeks (patients weighing below 30 kg).

~~The pharmacokinetics of tocilizumab was determined using a population pharmacokinetic analysis on a database composed of 188 patients with pJIA.~~
~~The following parameters are valid for a dose of 8 mg/kg tocilizumab (patients with a body weight ≥ 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 29500 ± 8660 µg·hr/mL, 182 ± 37 µg/mL and 7.49 ± 8.20 µg/mL, respectively.~~
~~The following parameters are valid for a dose of 10 mg/kg tocilizumab (patients with a body weight < 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 23200 ± 6100 µg·hr/mL, 175 ± 32 µg/mL and 2.35 ± 3.59 µg/mL, respectively.~~

~~The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{min} for 10 mg/kg (body weight < 30 kg) and 8 mg/kg (body weight ≥ 30 kg) doses, respectively. No accumulation for C_{max} was observed.~~

~~In pJIA patients, the central volume of distribution was 50 ml/kg, the peripheral volume of distribution was 53 ml/kg, resulting in a volume of distribution at steady state of 103 ml/kg. The linear clearance estimated as a parameter in the population pharmacokinetic analysis was 0.146 ml/hr/kg.~~

Table 11. Predicted mean ± SD PK parameters at steady-state after IV dosing in pJIA

RoActemra PK Parameter	**8 mg/kg Q4W ≥ 30 kg**	**10 mg/kg Q4W below 30 kg**
C_{max} (µg/mL)	183 ± 42.3	168 ± 24.8
C_{trough} (µg/mL)	6.55 ± 7.93	1.47 ± 2.44
C_{mean} (µg/mL)	42.2 ± 13.4	31.6 ± 7.84
Accumulation C_{max}	1.04	1.01
Accumulation C_{trough}	2.22	1.43
Accumulation C_{mean} or AUC_{τ}*	1.16	1.05

*τ = 4 weeks for IV regimens

After IV dosing, approximately 90% of the steady-state was reached by week 12 for the 10 mg/kg (BW < 30 kg), and by week 16 for the 8 mg/kg (BW ≥ 30 kg) dose.

בסעיף 6.3 Shelf life עודכן המידע הבא:

The expiry date of the product is indicated on the packaging materials.