דצמבר 2023

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

רופא/ה ורוקח/ת יקר/ה

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על רישום ההתוויה החדשה של אקטמרה לחולים עם COVID-19 וכיוצא בזאת 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.

Actemra is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 3 years of age and older.

Actemra is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

הסבר:
טקסט עם קו תחתי 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.

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אביטל ויסברוט
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עדכונים מהותיים בעלון לרופא

בסעיף 4.1 Therapeutic Indications עודכן המידע הבא:

Actemra is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

בסעיף 4.2 Posology and Method of administration עודכן המידע הבא:

COVID-19 Patients

The recommended posology for treatment of COVID-19 is a single 60-minute intravenous infusion of 8 mg/kg in patients who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation, see section 5.1. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of Actemra 8 mg/kg may be administered. The interval between the two infusions should be at least 8 hours.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see section 5.2).

Administration of Actemra is not recommended in patients with COVID-19 who have any of the following laboratory abnormalities:

Laboratory test type	Laboratory value	Action
Liver enzyme	>10x ULN	Administration of Actemra is not recommended
Absolute neutrophil count	< 1 x 10^9 /L	
Platelet count	< 50 x 10^3 /µL	

[…]

Method of administration
After dilution, Actemra for RA, sJIA, pJIA, CRS, and COVID-19 patients should be administered as an intravenous infusion over 1 hour.

RA, sJIA, pJIA, CRS and COVID-19 Patients ≥ 30 kg
Actemra should be diluted to a final volume of 100 mL with sterile, non-pyrogenic sodium chloride 9 mg/ mL (0.9%) solution for injection using aseptic technique .

For instructions on dilution of the medicinal product before administration, see section 6.6 .

sJIA, pJIA and CRS Patients < 30 kg
Actemra should be diluted to a final volume of 50 mL with sterile, non-pyrogenic sodium chloride 9 mg/ mL (0.9%) solution for injection using aseptic technique.

For instructions on dilution of the medicinal product before administration, see section 6.6.

If signs and symptoms of an infusion related reaction occur, slow or stop the infusion and administer appropriate medication/ supportive care immediately, see section 4.4.

בסעיף 4.3 Contraindications עודכן המידע הבא:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active, severe infections with the exception of COVID-19 (see section 4.4).

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

COVID-19 Patients

- The efficacy of Actemra has not been established in the treatment of COVID-19 patients who do not have elevated CRP levels, see section 5.1
- Actemra should not be administered to COVID-19 patients who are not receiving systemic corticosteroids as an increase in mortality cannot be excluded in this subgroup, see section 5.1.

Infections

In COVID-19 patients, Actemra should not be administered if they have any other concurrent severe active infection. Healthcare professionals should exercise caution when considering the use of Actemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes, and interstitial lung disease) which may predispose patients to infections.

Hepatotoxicity

Patients hospitalized with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COVID-19. The decision to administer tocilizumab should balance the potential benefit of treating COVID-19 against the potential risks of acute treatment with tocilizumab. In COVID-19 patients with elevated ALT or AST above 10 x ULN, administration of Actemra treatment is not recommended. In COVID-19 patients, ALT /AST should be monitored according to current standard clinical practices.

Haematological abnormalities

In COVID-19 patients who develop an ANC < 1 x 10^9 /L or a platelet count < 50 x 10^3 /µL, administration of treatment is not recommended. Neutrophil and platelet counts should be monitored according to current standard clinical practices, see section 4.2.

בסעיף 4.8 Undesirable Effects עודכן המידע הבא:

The most commonly reported ADRs (occurring in ≥ 5% of patients treated with tocilizumab for COVID-19) were hepatic transaminases increased, constipation, and urinary tract infection.

Patients with COVID-19

The safety evaluation of Actemra in COVID-19 was based on 3 randomized, double-blind, placebo controlled trials (studies ML42528, WA42380, and WA42511). A total of 974 patients were exposed to Actemra in these studies. Collection of safety data from RECOVERY was limited and is not presented here.

The following adverse reactions, listed by MedDRA system organ class in Table 2, have been adjudicated from events which occurred in at least 3% of Actemra treated patients and more commonly than that in patients on placebo in the pooled safety-evaluable population from clinical studies ML42528, WA42380, and WA42511.

Table 2: List of Adverse Reactions1 Identified From the Pooled Safety-Evaluable Population From Actemra Clinical Studies in COVID-19 patients[2]

MedDRA System Organ Class	Very Common	Common
Infections and infestations		Urinary tract infection
Metabolism and nutrition disorders		Hypokalaemia
Psychiatric disorders		Anxiety, Insomnia
Vascular disorders		Hypertension
Gastrointestinal disorders		Constipation, Diarrhoea, Nausea
Hepatobiliary disorders		Hepatic transaminases increased

[1] Patients are counted once for each category regardless of the number of reactions
[2] Includes adjudicated reactions reported in studies WA42511, WA42380 and ML42528

Description of selected adverse drug reactions

Infections
In the pooled safety-evaluable population from studies ML42528, WA42380, and WA42511, the rates of infection/serious infection events were balanced between COVID-19 patients receiving tocilizumab (30.3%/18.6%, n=974) versus placebo (32.1%/22.8%, n=483).

The safety profile observed in the baseline systemic corticosteroids treatment group was consistent with the safety profile of tocilizumab from the overall population presented in Table 2. In this subgroup, infections and serious infections occurred in 27.8% and 18.1% of patients treated with IV tocilizumab and in 30.5% and 22.9% of patients treated with placebo, respectively.

Laboratory Abnormalities
The incidence of laboratory abnormalities was generally similar between patients with COVID-19 who received one or two doses of Actemra-IV compared with those who received placebo in the randomized, double-blind, placebo controlled trials with few exceptions. Decreases in platelets and neutrophils and elevations of ALT and AST were more frequent among patients receiving Actemra-IV versus placebo (see section 4.2 and 4.4).

בסעיף 5.1 Pharmacodynamic Properties עודכן המידע הבא:

In COVID-19 patients with one dose of tocilizumab 8 mg/kg administered intravenously, decreases in the levels of CRP to within normal ranges were seen as early as Day 7.

[…]

COVID-19

Clinical Efficacy

RECOVERY (Randomised Evaluation of COVID-19 Therapy) Collaborative Group Study in Hospitalized Adults Diagnosed with COVID-19

RECOVERY was a large, randomized, controlled, open-label, multi-center platform study conducted in the United Kingdom to evaluate the efficacy and safety of potential treatments in hospitalized adult patients with severe COVID-19. All eligible patients received usual care and underwent an initial (main) randomization. Eligible patients for the trial had clinically suspected

or laboratory-confirmed SARS-CoV-2 infection and no medical contraindications to any of the treatments. Patients with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) qualified for a second randomization to receive either intravenous tocilizumab or usual care alone.

Efficacy analyses were performed in the intent-to-treat (ITT) population comprising 4116 patients who were randomized with 2022 patients in the tocilizumab + usual care arm and 2094 patients in the usual care alone arm. The baseline demographic and disease characteristics of the ITT population were well balanced across treatment arms. The mean age of participants was 63.6 years (standard deviation [SD] 13.6 years). The majority of patients were male (67%) and White (76%). The median (range) level of CRP was 143 mg/L (75-982).

At baseline, 0.2% (n=9) of patients were not on supplemental oxygen, 45% of patients required low flow oxygen, 41% of patients required non-invasive ventilation or high-flow oxygen and 14% of patients required invasive mechanical ventilation; 82% were reported receiving systemic corticosteroids (defined as patients who initiated treatment with systemic corticosteroids either prior to or at the time of randomization). The most common comorbidities were diabetes (28.4%), heart disease (22.6%) and chronic lung disease (23.3%).

The primary outcome was time to death through Day 28. The hazard ratio comparing the tocilizumab +usual care arm to the usual care alone arm was 0.85 (95% CI: 0.76 to 0.94), a statistically significant result (p=0.0028). The probabilities of dying by Day 28 were estimated to be 30.7% and 34.9% in the tocilizumab and usual care arms, respectively. The risk difference was estimated to be -4.1% (95% CI: -7.0% to -1.3%), consistent with the primary analysis. The hazard ratio among the pre-specified subgroup of patients receiving systemic corticosteroids at baseline was 0.79 (95% CI: 0.70 to 0.89), and for the pre-specified subgroup not receiving systemic corticosteroids at baseline was 1.16 (95% CI: 0.91 to 1.48).

The median time to hospital discharge was 19 days in the tocilizumab+ usual care arm and >28 days in the usual care arm (hazard ratio [95% CI] = 1.22 [1.12 to 1.33]).

Among patients not requiring invasive mechanical ventilation at baseline, the proportion of patients who required mechanical ventilation or died by Day 28 was 35% (619/1754) in the tocilizumab + usual care arm and 42% (754/1800) in the usual care alone arm (risk ratio [95% CI] = 0.84, [0.77 to 0.92] p<0.0001).

בסעיף 5.2 Pharmacokinetic Properties עודכן המידע הבא:

COVID-19 Patients
The pharmacokinetics of tocilizumab was characterized using a population pharmacokinetic analysis of a database composed of 380 adult COVID-19 patients in Study WA42380 (COVACTA) and Study CA42481 (MARIPOSA) that treated with a single infusion of 8 mg/kg tocilizumab or two infusions separated by at least 8 hours. The following parameters (predicted mean+SD) were estimated for a dose of 8 mg/kg tocilizumab: area under curve over 28 days (AUC_{0-28}) = 18312 (5184) hour•µg/mL, concentration at Day 28 (Cday28) = 0.934 (1.93) µg/mL and maximum concentration (C_{max}) = 154 (34.9) µg/mL. The AUC_{0-28}, C_{day28} and C_{max}, following two doses of 8 mg/kg tocilizumab separated by 8 hours, were also estimated (predicted mean +SD): 42240 (11520) hour•µg/mL and 8.94 (8.5) µg/mL, and 296 (64.7) µg/mL respectively.

Distribution
In RA patients the central volume of distribution was 3.72 L, the peripheral volume of distribution was 3.35 L resulting in a volume of distribution at steady state of 7.07 L.

In COVID-19 adult patients, the central volume of distribution was 4.52 L, the peripheral volume of distribution was 4.23 L, resulting in a volume of distribution of 8.75 L.

Elimination
Following intravenous administration, tocilizumab undergoes a dual elimination from the circulation, one following a linear clearance and one following a concentration-dependent non-linear clearance. In RA patients, the linear clearance was 9.5 mL/h.
In COVID-19 adult patients, the linear clearance was 17.6 mL/h in patients with baseline ordinal scale category 3 (OS 3, patients requiring supplemental oxygen), 22.5 mL/h in patients with baseline OS 4 (patients requiring high-flow oxygen or non-invasive ventilation), 29 mL/h in patients with baseline OS 5 (patients requiring mechanical ventilation), and 35.4 mL/h in patients with baseline OS 6 (patients requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support). The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

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In COVID-19 patients, serum concentrations were below the limit of quantification after 35 days on average following one infusion of tocilizumab IV 8 mg/kg.

[…]

Age, gender and ethnicity: Population pharmacokinetic analyses in RA and COVID-19 patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

Results of the population PK analysis for COVID-19 patients confirmed that body weight and disease severity are both covariates which have an appreciable impact on the linear clearance of tocilizumab.

בסעיף 6.6 Special precautions for disposal and other handling עודכן המידע הבא:

RA, CRS Patients (≥ 30 kg) and COVID-19
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of Actemra concentrate required for the patients dose, under aseptic conditions. The required amount of Actemra concentrate (0.4 mL/kg) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.