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## Information sheet
## Intravenous tocilizumab for the treatment of patients with severe COVID-19 infection


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### Drug Description

Tocilizumab (RoActemra) is a monoclonal antibody **that blocks interleukin 6 receptor (IL-6),** a cytokine that plays a key role in activating inflammatory processes. Elevated tissue and serum levels of IL-6 are implicated in the pathogenesis of various inflammatory and autoimmune disorders (including many forms of rheumatic diseases) and also in cytokine release syndrome (CRS).

IL-6 is considered a potential therapeutic target for the treatment of patients with severe *coronavirus diseases 2019* (COVID-19). SARS-CoV-2 infection produces an amplified and aberrant host immune response associated with acute respiratory distress syndrome and, mostly in critical patients, a "cytokine storm" (increased plasma and tissue levels of various cytokines causing long-term damage and lung tissue fibrosis). It has been hypothesized that drugs targeting cytokines involved in this aberrant inflammatory response (including IL-6) may have an important therapeutic role to delay lung damage in patients with SARS-CoV2 infection [1, 2].

Tocilizumab has been approved for patients with moderate to severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis and for the management of CRS following CAR T-cell infusion (*chimeric antigen receptor T cell*) in adults and pediatric patients ≥ 2 years [3]. The known experience of long-term use in rheumatology setting has highlighted that tocilizumab can be considered a safe and well tolerated therapy [4,5]. Moreover, 50-70% of patients with CAR-T induced CRS are responsive to tocilizumab therapy [6]. The off-label use of intravenous tocilizumab in complex presentations of SARS-CoV-2 infection is based on the


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mechanism of blocking IL-6 receptor (IL-6R), thus preventing the effects of activation of the pro-inflammatory cascade.

**Scientific evidence on the use of tocilizumab in the treatment of patients with COVID-19**

The use of tocilizumab in patients with COVID-19 has been evaluated in observational studies and clinical trials. The main evidence currently available on the use of tocilizumab to treat patients with COVID-19 has been reported in some systematic reviews with metanalysis, summarized below.

A systematic metanalysis review of 7 observational studies, evaluating the effectiveness of tocilizumab in 592 patients with severe COVID-19, found that mortality for all causes in the tocilizumab group was 16,3%, lower than the control group (24,1%), although not statistically significant (RR= 0.62, CI 95% 0,31-1,22;12=68%) [7]. In addition, the risk of hospitalization in intensive care was similar between the two groups (35.1% vs. 15.8%; RR = 1.51, CI 95% 0.33-6.78; $I^2$ = 86%), as well as the use of mechanical ventilation (32.4% vs. 28.6%; RR = 0.82, CI 95% 0.14-4.94; $I^2$= 91%). Based on the results of the review, Lan and colleagues conclude that tocilizumab does not provide additional benefit in patients with severe COVID-19.

More encouraging results were reported in another systematic review with metanalysis of 16 observational studies investigating the efficacy of the drug in patients with severe COVID-19 [8]. The mortality rate was lower in the tocilizumab group than in the standard therapy group (22.4% vs. 26.2%). However, when steroids were administered to patients not treated with tocilizumab, no difference between the two groups in terms of mortality was observed.

Regarding to clinical trials, the results of a randomized clinical trial (RCT-TCZ-COVID-19) reported that early treatment with only tocilizumab of hospitalized patients and with severe clinical conditions did not provide any advantage over standard therapy alone [9]. The primary endpoint was clinical deterioration within 14 days of randomization, defined by one of the following events: admission to intensive care with invasive mechanical ventilation, death for all causes or clinical worsening documented by a PaO2/FIO2 ratio of less than 150 mmHg. **The study showed no statistically significant differences in terms of clinical worsening within 14 days from randomization, between the standard therapy group and the tocilizumab group** (RR 1.05, CI 95% 0.59-1.86; p = 0.87). In addition, mortality evaluated at 14 days and 30 days was similar between the two groups.

The COVACTA (Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia) and EMPACTA (Evaluating Minority Patients with


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Actemra) studies are phase III clinical trials sponsored by tocilizumab manufacturers. COVACTA is a randomized, double-blind, placebo-controlled study that evaluated the use of tocilizumab in hospitalized patients with severe pneumonia associated with COVID-19. There were no statistically significant differences in the clinical status of patients and no difference of mortality between the tocilizumab and placebo groups at day 28 (primary outcome) was observed [10]. Cron and colleagues (University of Alabama, USA) however recommends caution in the interpretation of COVACTA results, due to the wide selection criteria of patients recruited and other factors related to the study design. Particularly, timing of administration of tocilizumab and therefore the evaluation of the effect had to be considered: since COVACTA evaluated the outcomes of patients on a specific day, when different patients could have different duration and severity of disease as well as different previous treatments, clinically significant differences between patient groups might not be detected [11]. The results of the phase III EMPACTA study showed that tocilizumab treatment plus standard therapies in patients with COVID-19 pneumonia reduced the risk of mechanical ventilation or death within 28 days (primary endpoint), compared to the placebo-treated group in addition to standard care (HR 0.56, CI 95% 0.33-0.97; p= 0.04) [12].

Results from a randomized, placebo-controlled, double-blind clinical trial support **the lack of efficacy of tocilizumab in preventing mortality in hospitalized (non-intubated) patients with COVID-19** [13]. Specifically, the patients included in the trial had hyperinflammatory states and at least two of the following symptoms: fever > 38 °C, pulmonary infiltration or need for additional oxygen to maintain oxygen saturation > 92%. Patients were randomized to receive a single dose of tocilizumab plus standard care, or placebo. The primary endpoint was intubation or death. **Tocilizumab was ineffective in preventing intubation or death than placebo** (HR= 0.83, CI 95%, 0.38-1.81; p = 0.64) [13].

Data from available randomized studies show little benefits of tocilizumab on 28-30-day mortality in patients with COVID-19. However, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) COLLABORATIVE GROUP, in a large randomized, controlled and open study **(not still published in scientific journal and therefore not peer-reviewed**), which recruited patients hospitalized with COVID-19 in the United Kingdom, reported that in patients with hypoxia (levels of $0_2$< 92% or with oxygen therapy) and with evidence of systemic inflammation (PCR>75 mg/l), **co-administration of tocilizumab with standard care reduced mortality within 28 days** (primary endpoint) [14]. Patients eligible for randomization were divided into two arms: tocilizumab plus


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standard care (N=2,022) and standard care alone (N=2,094). In addition, 82% of randomized patients was treated with systemic corticosteroids. After 28 days of treatment, 596 deaths (29%) were recorded in the tocilizumab plus standard care group vs. 694 deaths (33%) in the control group (RR= 0.86, CI 95%, 0.77 to 0.96; p= 0.007) [14]. **A significant improvement for mortality outcome in patients receiving systemic corticosteroids (dexamethasone) was observed**. Patients treated with tocilizumab are more likely to be discharged alive from the hospital within 28 days than patients in the control group (54% vs. 47%; RR 1.22; 95% CI 1.12-48 1.34; p<0.0001). A **reduction of 13% of mortality evaluated at 28 days** (mortality rate 0.87; CI 95% 0.79-0.96; p = 0.005) for patients treated with tocilizumab plus standard care with corticosteroids was also showed [14].

A more recent clinical trial REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) [15] recruiting adult patients with COVID-19 within 24 hours of admission in the intensive care unit, randomized them to tocilizumab treatment (8 mg /kg) (N=353), sarilumab (400 mg) (N=48) or standard care (control group) (N=402). The primary outcome was the number of days without respiratory and cardiovascular support at day 21. The median number of days free from respiratory and cardiovascular support was 10 (Q1-Q3: -1-16) in the tocilizumab group, 11 (Q1-Q3: 0-16) in the sarilumab group and 0 (Q1-Q3: -1-15) in the control group [15]. A 90-day survival analysis also showed a better survival of patients in groups treated with IL-6 antagonists (pooled data) than placebo: HR 1.61 (CI 95%, 1.25-2.08) [15].

Currently 25 ongoing interventional clinical trials, testing tocilizumab in patients with COVID-19, are registered on the american website www.clinicaltrials.gov (update March 8, 2021).

In conclusion, results of a large number of clinical trial and observational studies on tocilizumab used in patients with COVID-19 are in contrast, due to methodological differences among studies and the heterogeneity of patients enrolled.

**Monitoring drug toxicity**

Data from RCT [10-15] did not reported new safety issues associated with the use of Tocilizumab in patients with COVID-19. In particular, the use of this drug in patients with COVID-19 in general was not associated with severe adverse effects compared to the placebo group. The RECOVERY study registered three severe adverse reactions, i.e. otitis externa, bacteremia from Staphylococcus aureus and lung abscess [13].


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*Tocilizumab therapy and its treatment scheme may be responsible for the following adverse reactions [3] to be managed as summarised in Table 2:*

**Table 1. Adverse drug reactions associated with tocilizumab treatment and management of toxicity**

| System Organ Class | Adverse reaction/ symptoms | Warnings and/or actions |
|---|---|---|
| Infections and infestations | **Serious, even fatal, infections**<br><br>(e.g hepatitis B virus reactivation) | - Patients should be screened for latent tuberculosis infection.<br>- Monitor to avoid serious infections.<br>- Administration of drug should be stopped immediately at the onset of infection. |
| Immune system disorders | **Serious hypersensitivity reactions** | Administration of drug should be stopped immediately and tocilizumab should be permanently discontinued. |
| Hepatic disorders | **Active hepatic disease and hepatic impairment** | - Liver function tests including bilirubin should be considered.<br>- In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended. |
| Blood and lymphatic system disorders | **Hematological abnormalities** (decreases in neutrophil and platelet counts) | In patients who develop an ANC < 0.5 x $10^9$/L or a platelet count < 50 x $10^3$/µL, continued treatment is not recommended. |

Abbreviations: ALT= alanine transaminase; ANC= Absolute neutrophil count; AST= aspartate transaminase; ULN= upper limit normal.

The Risk Management Plan of tocilizumab also reports as "identified potential risks" associated with use of this drug the risk of cardiovascular/cerebrovascular events, cancer and demyelinating diseases [16].

**Potential drug interactions with tocilizumab, stratified for type of recommendation (available at http://www.covid19-druginteractions.org/)**


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## Table 2. Drugs at risk of interaction with tocilizumab

| | Drug class | Active substance |
|---|---|---|
| **Drugs at risk of interaction that should NOT be co-administered with tocilizumab** | *Immunosuppressants* | Adalimumab<br>Basiliximab |
| | *Lipid-lowering agents* | Evolucumab |
| | | |
| | | |
| **Drugs with potential risk of tocilizumab interaction that require close monitoring or dosage adjustment or dosing times** | *Antibacterial* | Linezolid |
| | *Antipsycothics/ Neuroleptic* | Clozapine |
| | *Antibacterial* | Linezolid |
| | | |
| **Drugs with low risk of interaction with tocilizumab so dosing adjustment or other actions are probably not needed** | *Anesthetics and muscle relaxants* | Bupivacaine |
| | | Ethidocaine |
| | | Ketamine |
| | | Sufentanil |
| | *Opioid analgesics* | Alfentanil |
| | | Buprenorphine |
| | | Dextropropoxyphene |
| | | Fentanyl |


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| | | |
|---|---|---|
| | | Oxycodone |
| | *antiarrhythmic* | Amiodarone |
| | | Quinidine |
| | *Anticoagulants/ anti-aggregant fibrinolytic* | Acenocumarole |
| | | Apixaban |
| | | Clopidogrel |
| | | Fenprocumone |
| | | Plasugrel |
| | | Rivaroxaban |
| | | Ticagrelor |
| | | Warfarin |
| | *Anticonvulsant* | Carbamazepine |
| | | Phenobarbital |
| | | Phenytoin |
| | | Primidone |
| | *Bronchodilators* | Theophylline |
| | *Immunosuppressants* | Cyclosporin |
| | | Sirolimus |
| | | Tacrolimus |


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