TOCILIZUMAB SAFETY PROFILE

Date : 30-04-2020

Tocilizumab has the ATC code: L04AC07 : Immunosuppressants, Interleukin inhibitors.

RoActemra® (tocilizumab) received a marketing authorisation valid throughout the EU on 16 January 2009. The SmPC of Roactemra®[1] is available on the EMA's website in all European languages and on the AFMPS-FAGG's website.

Mechanism of action :

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling.

IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

RoActemra® is indicated for the treatment of different rheumatoid conditions (arthritis) and for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

The SmPC of RoActemra® recommends discontinuation of tocilizumab in case of laboratory abnormalities (liver enzyme abnormalities, low absolute neutrophil count (ANC), low platelet count) for the rheumatoid indications but not for CRS.

No dose adjustment is required in elderly patients or in patients with mild renal impairment.

RoActemra has not been studied in patients with moderate to severe renal impairment. Renal function should be monitored closely in these patients.

RoActemra has not been studied in patients with hepatic impairment and therefore no dose recommendations are made.

Contraindications :

- Hypersensitivity to the active substance or to any of the excipients.
- Active, severe infections.

Special warnings and precautions for use (summarized) :

[1] https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf

- *Infections* :
  Healthcare professionals should exercise caution when considering the use of RoActemra 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.
- *Tuberculosis*
- *Viral reactivation* :
  Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. In clinical studies with tocilizumab, patients who screened positive for hepatitis were excluded.
- *Hypersensitivity reactions*
- *Active hepatic disease and hepatic impairment*
- *Hepatotoxicity :*
  Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with RoActemra. Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of RoActemra. Cases of liver failure resulting in liver transplantation have been reported.
- *Haematological abnormalities*
  Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX. There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.
  In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l.
  Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ µL).
  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.
- *Lipid parameters*
- *Neurological disorders*
- *Malignancy*
- *Vaccinations*
- *Cardiovascular risk :*
  RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.
- *Combination with TNF antagonists*
- *Sodium :*
  This medicinal product contains 1.17 mmol (or 26.55 mg) sodium per maximum dose of 1200 mg. Doses below 1025 mg contain less than 1 mmol sodium (23 mg), i.e. essentially 'sodium free'.

  <u>Paediatric population</u> :
  Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS.

Interactions (summarized) :

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as tocilizumab, is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzyme expression. Tocilizumab normalises expression of these enzymes.

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of tocilizumab, to the level similar to, or slightly higher than, those observed in healthy subjects.

When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect.

Given its long elimination half-life (t1/2), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Fertility, pregnancy and lactation :

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Pregnancy

There are no adequate data from the use of tocilizumab in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown.

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether tocilizumab is excreted in human breast milk. The excretion of tocilizumab in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with RoActemra should be made taking into account the benefit of breast-feeding to the child and the benefit of RoActemra therapy to the woman.

Fertility

Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment.

Risk Management Plan[2] :

Note : During the last PSUSA reporting interval (procedure EMEA/H/C/PSUSA/00002980/201904), the important potential risk of 'liver enzyme and bilirubin elevations and potential risk of hepatotoxicity' was upgraded to an important identified risk and renamed to '**Hepatotoxicity'** during the reporting interval. This upgrade is already included in CDS version 18.0 and is being incorporated in EU Risk Management Plan (RMP) version 25.0 which is still under evaluation and

[2] https://www.ema.europa.eu/en/documents/rmp-summary/roactemra-epar-risk-management-plan-summary_en.pdf

approval from EMA. Some of safety concerns were reclassified in alignment with the current guidance in the GVP Module V (R2) regulation.

Safety concerns :

List of important risks and missing information	
Important identified risks	• Serious infection • Complications of diverticulitis • Serious hypersensitivity reactions • Neutropenia
Important potential risks	• Thrombocytopenia and the potential risk of bleeding • Liver enzyme and bilirubin elevations and the potential risk of hepatotoxicity • Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Demyelinating disorders • Immunogenicity
Missing information	None

Summary of important risks :

Important Identified Risk: Serious infections	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Patients with **diabetes** reported a higher rate of serious infections compared to patients without diabetes. Patients treated with TCZ and taking background **corticosteroids** reported a higher rate of serious infections compared to patients not taking background corticosteroids. The rate of serious infections appears to increase by **body weight**. Healthcare professionals should exercise caution when considering the use of TCZ 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.
Risk minimization measures	**Routine risk measure:** SmPC (and PIL) Section 4.3 Contraindications, severe infections (see section

	4.4) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (...) **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	Epidemiology data : EU registries (ARTIS, RABBIT, WA29358)
Important Identified Risk: Complications of Diverticulitis	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	TCZ should be used with caution in patients with previous history of intestinal ulceration or diverticulitis.
Risk minimization measures	**Routine risk minimization measure:** SmPC (and PIL) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (...) **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	Epidemiology data : EU registries (ARTIS, RABBIT, WA29358)
Important identified Risk : Serious Hypersensitivity Reactions	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** SmPC (and PIL) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (...) **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure Rheumatoid Arthritis Dosing Guide pJIA and sJIA Dosing Guide

Additional pharmacovigilance activities	Epidemiology data : EU registries (ARTIS, RABBIT, WA29358)
Important Identified Risk: Neutropenia	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	None identified
Risk minimization measures	**Routine risk communication:** SmPC (and PIL) Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects/Laboratory evaluations **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (...) **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	Epidemiology data • EU registries (ARTIS, RABBIT) • WA28029 (ARTHUR)
Important Potential Risk : Thrombocytopenia and the potential risk of bleeding	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 4.2 Posology and method of administration (IV formulation) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (...) **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	Epidemiology data • EU registries (ARTIS, RABBIT) • WA28029 (ARTHUR)
Important Potential Risk: Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Treatment with other hepatotoxic drugs (e.g., MTX).

Risk minimization measures	**Routine risk communication:** SmPC (and PIL) Section 4.2 Posology and method of administration (IV formulation) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (...) **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	Epidemiology data • EU registries (ARTIS, RABBIT) • WA28029 (ARTHUR)
Important Potential Risk : Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** SmPC (and PIL) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (...) **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	Epidemiology data : EU registries (ARTIS, RABBIT, WA29358)
Important Potential Risk: Malignancies	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	None identified
Risk minimization measures	**Routine risk minimization measures:** SmPC (and PIL) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (...) **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional	Epidemiology data :

pharmacovigilance activities	EU registries (ARTIS, RABBIT, WA29358)
Important Potential Risk: Demyelinating Disorders	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Treatment with other hepatotoxic drugs (e.g., MTX).
Risk minimization measures	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (…) **Additional risk minimization measures:** Healthcare Provider Brochure
Additional pharmacovigilance activities	Epidemiology data : EU registries (ARTIS, RABBIT)
Important Potential Risk : Immunogenicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None (…) **No Additional Risk Minimization Measure**
Additional pharmacovigilance activities	None

Studies in post-authorization development plan

Study short name: WA22480 (ARTIS) registry study
Purpose of the study: To provide long term safety data from the use of TCZ in Sweden for RA patients.

Study short name: ML28664 (formerly tracked as GA28719) (RABBIT)
Purpose of the study: The long-term observation of treatment with biologics in RA (RABBIT) in German biologics registry

Study sort name: WA28029 (ARTHUR)
Purpose of the study: To investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients.

Study sort name: WA29358
Purpose of the study: To provide long term safety and efficacy data from the use of TCZ in pJIA patients.

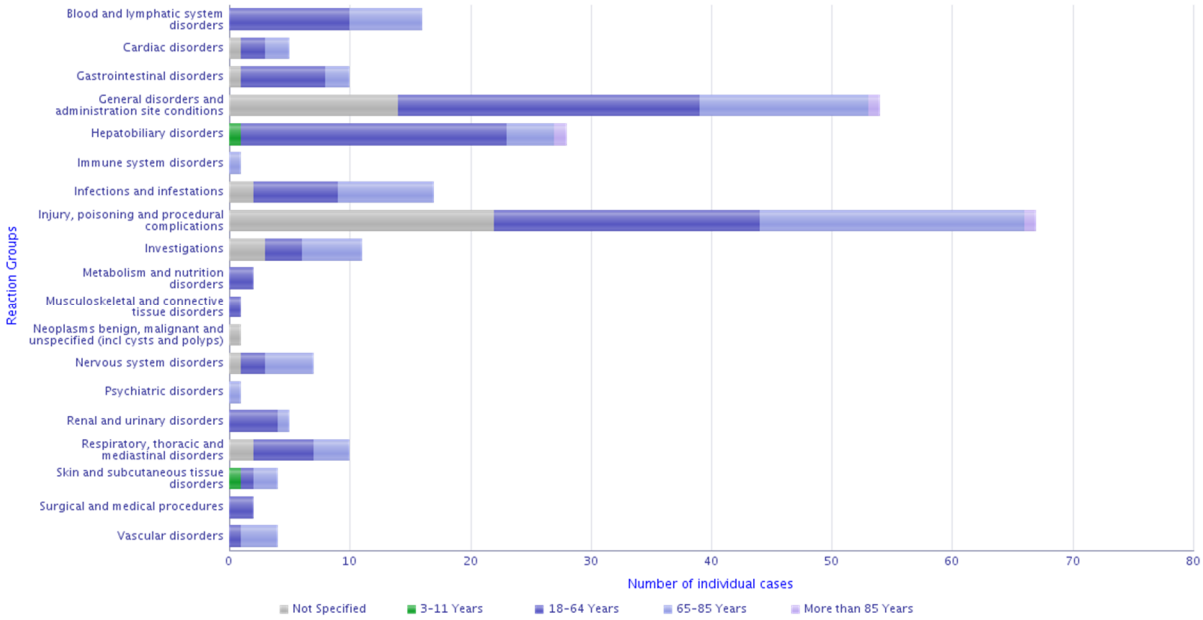
Analysis of data from the EudraVigilance database

Reports of adverse drug reactions (ADRs) with tocilizumab mentioned as suspect or interacting drugs, with the indication coded as 'corona virus infection' have been retrieved on 30-04-2020 :

123 reports (14 reports from studies + 109 spontaneous reports)

Seriousness : 113 serious (including 51 cases with fatal outcome)

Number of Individual Cases by Patient Age Group and by SOC :



Number of ADRs by PT and by SOC :

SOC Blood and lymphatic system disorders	
Blood loss anaemia	1
Coagulopathy	1
Haemolytic anaemia	2
Hypocoagulable state	1
Hypofibrinogenaemia	6
Leukopenia	1
Lymphopenia	2
Neutropenia	5
Thrombocytopenia	1
SOC Cardiac disorders	
Atrial flutter	2

Bundle branch block right	1
Cardiac arrest	1
Cardiac failure	1
Cardio-respiratory arrest	1
Cor pulmonale	1
Ventricular tachycardia	1
SOC Gastrointestinal disorders	
Abdominal pain	1
Gastrointestinal haemorrhage	1
Intestinal perforation	3
Melaena	1
Nausea	1
Pancreatitis acute	2
Rectal haemorrhage	2
SOC General disorders and administration site disorders	
Chills	2
Condition aggravated	11
Death	32
Disease progression	1
Fatigue	1
General physical health deterioration	3
Injection site extravasation	1
No adverse event	3
SOC Hepatobiliary disorders	
Cholestasis	1
Hepatitis	21
Hepatitis acute	4
Hepatocellular injury	3
Hyperbilirubinaemia	2
SOC Immune system disorders	
Anaphylactic shock	1
SOC Infections and infestations	
Corona virus infection	4
Dural abscess	1
Fungaemia	1
Pneumonia	5
Pneumonia bacterial	1
Pneumonia escherichia	2
Sepsis	1
Septic shock	1

Staphylococcal bacteraemia	1
Staphylococcal infection	1
Urinary tract infection	1
SOC Injury, poisoning and procedural complications	
Intentional product use issue	46
Off label use	67
Product use in unapproved indication	12
SOC Investigations	
Blood creatinine increased	1
Blood gases abnormal	1
Chest X-ray abnormal	1
Fibrin D dimer increased	3
Hepatic enzyme increased	2
Interleukin level increased	2
Oxygen saturation decreased	2
Platelet count decreased	1
White blood cell count decreased	2
White blood cell count increased	1
SOC Metabolism and nutrition disorders	
Hyperamylasaemia	1
Hypertriglyceridaemia	1
SOC Musculoskeletal and connective tissue disorders	
Musculoskeletal pain	1
Neck pain	1
SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Malignant melanoma	1
SOC Nervous system disorders	
Cerebral haemorrhage	3
Dizziness	1
Lethargy	1
Motor dysfunction	1
Tremor	1
SOC Psychiatric disorders	
Confusional state	1
SOC Renal and urinary disorders	
Acute kidney injury	1
Proteinuria	1
Renal colic	1
Renal failure	2
Renal impairment	1

SOC Respiratory, thoracic and mediastinal disorders	
Acute respiratory failure	1
Dyspnoea	1
Lung disorder	1
Pneumonitis	1
Pulmonary embolism	4
Respiratory distress	2
SOC Skin and subcutaneous tissue disorders	
Angioedema	1
Pruritus	1
Rash	3
SOC Surgical and medical procedures	
Endotracheal intubation	1
Mechanical ventilation	1
Product used for unknown indication	1
SOC Vascular disorders	
Deep vein thrombosis	1
Hypertension	2
Thrombosis	1

Analysis of fatal cases :

Reported cause of death :

Cases of death + other reaction (other than 'off label use' or 'product use in unapproved indication' or 'intentional product use issue') :

- EU-EC-10005830291 : a 67 year old male patient died due to worsening respiratory distress whilst being treated with tocilizumab (one day after administration). The patient's concurrent conditions included parkinson's disease and hypertension.

- EU-EC-10005835834 : a 65 year old male patient who died due to condition worsened and pneumonia aggravated whilst being treated with tocilizumab. Concurrent conditions included cardiomyopathy (heart valve disease and arrhythmia), paroxysmal atrial fibrillation, hyperthyroidism. Concomitant medications included bisoprolol fumarate (Concor), rivaroxaban (Xarelto), thiamazole (Tapazole), flecainide acetate (Tambocor). The patient was hospitalized. Treatment : oxygen therapy, co-amoxiclav 1200 mg 3x/day and antipyretic therapy (Paracetamol Fresenius 1 g 2x/day, metamizole sodium (Novalgin) 1 g 1x/day) on 19/Mar/2020; he was also put on prophylactic anticoagulant therapy subcutaneous enoxaparin sodium (Clexane) 70 mg 2x/day), intravenous hydration and continued his regular betablocker treatment of Concor 2.5 mg/day.
  Over the first few days in hospital, he remained stable with good saturations on high flow oxygen therapy (Venturi 60%), initially dyspnoeic but improvement was observed from 19/Mar/2020, febrile temperatures. On 20/Mar/2020, his condition was slightly worse, rising CRP (C-reactive protein) and procalcitonin, well-controlled dyspnoea and acceptable saturations but still on high flow oxygen therapy.

On 20/Mar/2020, the first dose of tocilizumab was administered at 8 mg/kg body weight, equivalent to 600 mg, and the second dose of 600 mg was administered on 21/Mar/2020, for a total of 1200 mg.
On 21/Mar/2020, he presented a significant desaturation despite the continuation of high flow oxygen therapy, as well as severe dyspnoea and tachypnoea. Given the clinical picture of rapidly progressing ARDS (Acute respiratory distress syndrome), he was transferred to intensive care for orotracheal intubation. Following the intubation, he went into atrial fibrillation and was tachycardic with haemodynamic instability, responsive to fluid resuscitation, treatment with amiodarone and vasoactive drugs. In the hours following the intubation, despite increasing administration of catecholamine (noradrenaline up to 100 mcg/min), initiating antibiotic therapy with meropenem and vancomycin due to suspected septic shock (SOFA score of 6) and protective controlled ventilation, a rapid deterioration of all vital signs was observed. He was pronounced dead on 22/Mar/2020. He died due to acute respiratory distress syndrome, condition worsened and pneumonia aggravated. It was not reported if an autopsy was performed or not.

- EU-EC-10005839489 : patient report with limited information : the patient was admitted to hospital after testing covid-19 positive. He started therapy with tocilizumab (dosage regimen not reported) for covid-19 (off label use). It was administrated late to him. The patient died as a result of cardiac arrest.

- EU-EC-10005848568 : patient report : a 67 year old male patient experienced worsening of arterial blood gases while being treated with tocilizumab. It was reported that on 13/Mar/2020, the patient arrived to hospital emergency room reporting cough and fever since 10 days, fever 38.2 C and 97% of oxygen saturation were observed and he went back home. On 22/Mar/2020, he came back in emergency room in serious but not in critical conditions. In the following days the situation worsened. A lung HRCT showed COVID-19 infection. Chloroquine, azithromycin, lopinavir/rtv and 3 doses of tocilizumab were administered. His arterial blood gases worsened and the oxygen therapy was necessary (C-PAP first and intubation later was given). On an unknown date, he died.

- EU-EC-10005853636 : a 78 years old male patient experienced fatal cerebral haemorrhage one day after tocilizumab initiation (560 mg). Concomitant drugs : acetylsalicylic acid (admin dates not reported), bisoprolol (admin dates not reported), dexamethasone (20 mg ; 18-22/03/2020), enoxaparin (admin dates not reported), hydroxychloroquine (200 mg ; 13-21/03/2020), omeprazole (admin dates not reported), Ramipril (admin dates not reported), Rezolsta (800 mg/150 mg ; 13-21/03/2020).

- EU-EC-10005858286 : concerns a 87 years old female patient started therapy with tocilizumab for severe pneumonia due to COVID-19. The patient had a very elevated IL-6 concentration. The patient was in a very bad condition, even though her IL-6 level has dropped, her platelet level has decreased, her lungs are still in very bad condition (lung disorders). She had very high, undetectable level IL-6, procalcitonin was on low level. The patient died as she was in very poor general condition. It was unknown if an autopsy was performed or not.

- EU-EC-10005871539 : On 20/Mar/2020, a 67 year old male patient presented to hospital and was admitted due to shortness of breath and dry cough. On day of admission he also received a chest x-ray and CT scan. He also had a PCR test done by the public health department prior, which came back positive. Upon admission he was placed in the ICU and was placed on a ventilator. He did not receive dialysis but received nor-epinephrine. There

was no other co-infection along with his COVID-19. On 26/Mar/2020, the patient started therapy with intravenous tocilizumab (lot number: not reported) infusion, solution 800 mg single dose. Following these treatments he did not improve and oxygenation continued to worsen (captured as oxygen saturation decreased). On 29/Mar/2020, he had an IL-6 count and the count was >400 pg/mL. There was no IL-6 count taken prior to this. Did not clarify if this is within normal range. On 06/Apr/2020, he died. On an unspecified date, therapy with tocilizumab was stopped. It was not reported if an autopsy was performed or not. The patient concurrent conditions included hypothyroidism, glaucoma and hyperlipidemia. His concomitant medications included hydroxychloroquine, azithromycin and methylprednisolone.

- EU-EC-10005873605 : (narrative in Spanish) A 59 years old male patient experienced Cor pulmonale, Acute massive pulmonary embolism, Hypofibrinogenemia, Coagulopathy 3 days after administration of 600 mg tocilizumab (single admin). Tratamiento SARS-CoV2 (fecha inicio, días): HCQ +7 (inicio en domicilio el 25/03) (tocilizumab 31/3) Dexamet(31/3) Azitro (inicio 28/03), ceftriaxona (+5, inicio 28/03-2/4).Meropenem 2/4
  Note : lab values available in the CIOMS

- EU-EC-10005875057 : condition aggravated. 62 yo female patient. Paziente con obesità patologica, OSAS, Cardiopatia ipertensiva, linfedemi da stasi. GB: 12190/mmc, d-dimero 11408, cr 1,53 ALT 37, AST 225

- EU-EC-10005878183 : concerns a male patient (age not reported) developed desaturation of ventilatory mechanics that merited endotracheal intubation (captured as endotracheal intubation), patient is under assisted mechanical ventilation, acute respiratory failure secondary due to covid-19 pneumonia, on the same day of tocilizumab (Actemra) initiation. Concurrent conditions included chronic smoker. The physician decided to use tocilizumab because he was not responding to hydroxychloroquine, azithromycin, piperacillin nor clexane. A colleague recommended him to use tocilizumab. He received the first dose of tocilizumab on 31/Mar/2020 and the second dose 01/Apr/2020. He was evaluated after infusion: three hours of infusion improved his respiratory parameters, but in the following two hours he presented desaturation that merited endotracheal intubation. He was under assisted mechanical ventilation, very poor prognosis. He started to evolve in a satisfactory way, with improvement in his respiratory parameters and lab tests. He continues intubated in ITU, but with a favourable prognosis. The IL-6 test was not performed. The physician refers he was improved his inflammatory laboratory parameters (ferritin, D-dimer), but he had no significant clinical improvement. He died due to acute respiratory failure secondary to COVID-19 pneumonia.

- EU-EC-10005880628 : A 70 years old male patient received azithromycin and hydroxychloroquine on 26-03 and tocilizumab on 27-03. He experienced hypofibrinognaemia on 01-04, Pneumonia Escherichia on 02-04, hypertension on 03-04, atrial flutter, bundle branch block right on 06-04 and ventricular tachycardia on 07-04.

- EU-EC-10005881911: A 76 years old male patient experienced cerebral haemorrhage and thrombocytopenia on 06-04. He was on enoxaparin since 19-03 and had received tocilizumab on 23 and 24-03.

- EU-EC-10005890230 : anaphylactic shock (Belgian case)

- EU-EC-10005891640 : A 78 years old male patient received tocilizumab on 31-03, 02-04 and 03-04. He experienced condition aggravated, coronavirus infection on 03-04.

- EU-EC-10005892488 : a 75 year old male patient experienced disease progression whilst being treated with tocilizumab. Concurrent conditions included deep vein thrombosis, pneumonia, oxygen therapy, hemofiltration. Concomitant medications included rivaroxaban, norepinephrine hydrochloride, epinephrine.

- EU-EC-10005895961 : a 35 year old male patient who received off-label use of Actemra for Severe pneumonia with ventilator support (COVID-19) and died due to heart failure whilst being treated with tocilizumab. He received tocilizumab on 9-Apr-2020 at 10.30am then status was stable. On 9 Apr 2020 at 8.30 PM, patient experienced death from heart failure. No past medical history or past drugs or concurrent conditions or concomitant medications were reported.

- EU-EC-10005907543 : a 44 year old male patient who developed increased serum creatinine, proteinuria, infiltrate worsen after second dose of Tocilizumab, renal failure and cerebral hemorrhage whilst being treated with tocilizumab, hydroxychloroquine, lopinavir, ritonavir, favipiravir, darunavir, azithromycin, piperacillin, tazobactam, vancomycin and enoxaparin.
  The patient developed shortness of breath on day 2 of admission. On 25-28/Mar/2020: He had been transferred to hospital B as diagnosed with COVID-19. On 25/Mar/2020, the patient started therapy with hydroxychloroquine for covid-19, lopinavir for covid-19, ritonavir) for covid-19. His condition deteriorated. Favipiravir was started on 26/Mar/2020. (Lab values available in CIOMS) Pulse methylprednisolone was given. On 28/Mar/2020: He was transferred to Bamras Institute. Lopinavir was switched to Darunavir. IV Azithromycin was started. On 29/Mar/2020: Intravenous Tocilizumab 640 (8 mg/kg/day) mg was given. Piperacillin/ tazobactam and vancomycin were initiated. On 30/Mar/2020: His chest X-ray improved and FiO2 at 1.0 was decreased to 0.4. Serum creatinine increased from 1.1 to 4.0 mg/dL. On the same day, he developed proteinuria. On 31/Mar/2020, CBC (complete blood count) showed hct (hematocrit) was 40%, WBC (white blood cell count) was 19,600, platelets was 170,000 (N88%,L6%,M2%, Atyp L 4%). The 2nd dose of tocilizumab (8mg/kg/day) mg was given and infilrate worsen. On the same day, sputum culture yieled no growth. vancomycin was discontinued. It was reported that he had renal failure. He did not had IL-6 tests. The treatment duration of tocilizumab was for 2 days (details unspecified). On an unknown date, he started therapy with enoxaparin (lot number and dosage regimen not reported) for a continuous renal replacement therapy. It was reported that he repeated the dose of tocilizumab and underwent treatment duration of 2 days (details unspecified). He had COVID-19 infection on 22/Mar/2020. His death is from cerebral haemorrhage on an unknown date.

- EU-EC-10005907715 : On an unknown date, a 82 year old male patient received therapy with intravenous tocilizumab (lot number, dose and frequency not reported) for an COVID-19 (off label use). It was reported that two weeks (details unspecified) after taking the tocilizumab he died due to the fungemia on an unknown date.

- EU-EC-10005909042 : On 16/Mar/2020, a 69 year old male patient was diagnosed with COVID-19. IL-6 test was not performed. He received supplemental oxygen therapy and was treated in an ICU with ventilator support (intubation on 24/3). He needed adrenalin infusion and noradrenaline infusion. On 26/Mar/2020, he started therapy with intravenous tocilizumab, 600 mg, 1 dose used for covid-19 (worsening chest x-ray, rapid deterioration

of respiratory function, deteriorating renal function). He was clinically improved 1 day after administration of tocilizumab, improving metabolic & respiratory acidosis, renal profile and transaminase improving. LFT showed improving trend, they were slightly deranged at baseline. FBC no changes. Tocilizumab did not work as well as the patient who was already very ill by the time treatment was given. On 01/Apr/2020, he had temperature spiking, worsening chest x-ray and confirmed pulmonary embolism (PE). On 04/Apr/2020, his WCB and inflammatory marker were much elevated. On 15/Apr/2020, he died due to pulmonary embolism (PE), hospital acquired pneumonia.

- EU-EC-10005910698 (no narrative) : 74 yo male patient. Suspected drugs : azithromycin + HCQ, started on 26-03 ; Kaletra, started on 29-03 ; and tocilizumab, administered on 31-03. ADR : atrial flutter on 31-03 ; cardio-respiratory arrest on 06-04.

- EU-EC-10005919262 : condition aggravated in a 54 yo patient, 3 days after initiation of tocizilizumab.

- EU-EC-10005923797 : On 23/Mar/2020, a 76 year old male patient started therapy with intravenous tocilizumab (dosing regimen and lot number: not reported) for covid-19. After three weeks, he performed blood test and diagnosed with fungemia and he was treated with steroids too, his CRP (C-reactive protein) was elevated. Two days after diagnosis, he was died. The cause of death was not reported.

- EU-EC-10005925844 : A 62 years old male patient with medical history of arterial hypertension, type 2 diabetes mellitus, dyslipidemia had been treated with tocilizumab 800 mg IV on 15-Apr-2020 and 400 mg IV on 17-Apr-2020. Concomitant drug: not reported.
  On 23-Apr-2020, the patient experienced pulmonary embolism and pulmonary necrosis : a bi-basal parenchymatous necrosis and a right lower lobar segment pulmonary embolism in the main necrosis area. First symptom occurred on 23-Apr-2020: worsening of the hematosis.
  Symptomatic measures taken: on 23-Apr-2020: anticoagulant treatment. Surgical opinion: no indication for surgery. Patient put in a prone position. Pleural puncture.
  According to hospitalization report from 26-Apr-2020: poor respiratory evolution on purulent pleuropneumopathy with necrosis with C. freundi, wild E. cloacae, flora found in bronchoalveolar lavage on 21-Apr-2020 and C. freundi wild and KP BLSE found in the pleural drainage on 23-Apr-2020.

Note : a search for reports with tocilizumab as suspected or interacting drug and with a patient medical history mentioning 'corona virus infection' has been also performed on 30-04-2020. After exclusion of the cases already included in the above results, only 2 extra cases were identified.

Analysis of cases with hepatobiliary disorders : (35 reports)

Only 3 reports mention tolicizumab as the sole suspected drug :

- EU-EC-10005834447 : A 69 yo male patient received 560 mg iv tocilizumab on 19/03. Reported ADRs : Staphylococcal bacteraemia, Urinary tract infection on 02-04 ; rectal haemorrhage on 03-04 ; hepatitis on 04-04.

- EU-EC-10005888957 : Patient de 92 ans. 21/03/2020 : hospitalisation pour prise en charge d'un AVC ischémique temporo-occipital postérieur gauche d'origine cardio-embolique. Syndrome infectieux biologique et toux à l'admission motivant la réalisation d'un test covid qui revient négatif. 22/03/2020 : sérologies VHB et VHC négatives. 01/04/2020 : test covid positif. 16/04/2020 : instauration d'un traitement par ROACTEMRA (tocilizumab) 8 mg/kg soit 600 mg dans le cadre de l'essai DISCOVERY. ASAT 36 UI/L, ALAT 64 UI/L.
17/04/2020 : survenue d'une cytolyse hépatique modérée avec ASAT 80 UI/L et ALAT 106 UI/L. 20/04/2020 : régression de l'atteinte hépatique avec ASAT 34 UI/L et ALAT 77 UI/L. Évolution : rétabli. Conclusion : cytolyse hépatique suite à une perfusion de ROACTEMRA (tocilizumab), d'évolution spontanément favorable. Autres traitements : lansoprazole 30 mg 0 0-0-1, LOVENOX 7000 UI 1-0-1, CORDARONE 200 mg 1-0-0, amlodipine 5 mg 0-0-1, ramipril 2,5 mg 0-0-1, tamsulosine 0,4 mg 0-0-1, méthylprednisolone 20 mg 1-0-0, pipéracilline / tazobactam 4 g/ 500 mg 3x/j, paracétamol si besoin, néfopam si besoin, prégabaline 25 mg 1-0-1, ULTIBRO 2-0-0

- EU-EC-10005911942 : Enfant 4 ans, né en juin 2015, 20 kg, 110 cm. ANTECEDENT: Acute lymphocytic leukaemia-B en rechute précoce. (…) Cytolyse hépatique et cholestase anictérique le lendemain de la première administration de Roactemra chez un patient de 4 ans hospitalisé pour un SDRA sur COVID-19 dans un contexte d'aplasie post-chimiothérapie. (défaillance multi-viscérale et décès le 19/04, 15 jours après la 1ère administration de tocilizumab).

  Times to onset between first administration of tocilizumab and reported date for hepatic disorder :

  1 day : 4 reports
  2 days : 3 reports
  3 days : 5 reports
  4 days : 8 reports
  5 days : 3 reports
  6 days : 1 reports
  7 days : 5 reports
  8 days : 2 reports
  15 days : 1 reports

  (in one report, the hepatic disorder appeared 3 days before administration of tocilizumab)

Conclusions :

The safety profile of tocilizumab used in the context of COVID-19 seems to be in line with its known safety profile.

Hepatic disorders and **infections** are the main safety concerns.

Hypofibrinogenaemia is a listed ADR. Considering the information from the RMP and cases of fatal cerebral haemorrhage retrieved in EudraVigilance, **disorders of the coagulation** (thrombocytopenia) and **risk of bleeding** should be considered, in particular when an anticoagulant therapy is co-administered.

Drug-drug interactions to be considered :

As per RoActemra's SmPC, when starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect.

Given its long elimination half-life (t1/2), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Reporting adverse reactions to AFMPS-FAGG :

Reports are registered in international pharmacovigilance databases. This helps for the monitoring of the safety profile of drugs.

Healthcare professionals and patients in Belgium can report suspected adverse drug reactions to AFMPS-FAGG using the webform available on :

www.notifieruneffetindesirable.be

www.eenbijwerkingmelden.be