Annex 1: Model Information Letter for the **Office-Based Rheumatologist**

Evidence Based Medicine | Official recommendations | Expert opinion

....., ...

Dear Colleague,

Thank you for referring your patient,

M. (Ms) .....

born on ..... for treatment with tocilizumab (RoActemra®).

You are following this patient for rheumatoid arthritis with unresponsiveness, contraindications, or intolerance to conventional maintenance drugs or to TNF antagonists.

The following data were evaluated before starting tocilizumab therapy.

❑ Evaluation of the patient before the first tocilizumab injection:

- DAS 28 *(Disease Activity Score)*: ❑ obtained on.....
- HAQ *(Health Assessment Questionnary)*: ❑ obtained on..... ❑ not obtained
- ESR/CRP: ❑ obtained on..... ❑ not obtained
- ASAT/ALAT : ❑ obtained on..... ❑ not obtained
- Blood cell counts: ❑ obtained on..... ❑ not obtained
- Total cholesterol/LDL-Ch/Triglycerides: ❑ obtained on..... ❑ not obtained
- Intradermal tuberculin test: ❑ obtained on..... ❑ not obtained
- Chest radiograph: ❑ obtained on..... ❑ not obtained
- Radiographs of the hands and feet: ❑ obtained on..... ❑ not obtained
- Erosions: ❑ obtained on..... ❑ not obtained
- Chondrolysis: ❑ obtained on..... ❑ not obtained

❑ The patient stopped any prior TNF antagonist therapy or other biotherapies (with or without a wash-out period) for the following reason:

.....
.....
.....
.....
.....
.....

❑ The patient has no contraindications to tocilizumab therapy (allergy, active infection, premalignant or malignant lesions diagnosed within the past 5 years).

❑ We checked whether the patient was taking drugs having potential interactions with tocilizumab and possibly requiring dosage adjustment at tocilizumab initiation or discontinuation.

- The patient is not receiving any drug likely to interact with tocilizumab.

- The patient is taking the following drug(s) (.....) and we have

- no dosage adjustment yes ❑ no ❑
- dosage adjustment yes ❑ no ❑

If yes, new dosage(s): .....

❑ We have checked the immunisation status of the patient (particularly vaccines against tetanus, polio, influenza, and pneumococcal infections).

Inactivated or component vaccines, particularly those against seasonal infections, can be given safely after the tocilizumab infusion. Although perhaps less effective in this situation, yearly influenza immunisation is recommended.

Live attenuated vaccines (yellow fever, varicella-zoster, oral poliomyelitis, MMR, and BCG) are contraindicated in tocilizumab-treated patients. If a live attenuated vaccine must be administered, the tocilizumab treatment must be stopped at least 70 days before the immunisation. The recommended interval from vaccine administration to tocilizumab re-treatment is 2 weeks at least and 4 weeks ideally.

❑ We performed the following:

❑ No immunisations

❑ The following immunisations: ..... ❑on ...../...../.....
..... ❑on ...../...../.....
.....❑on ...../...../.....

❑ We checked that the patient was screened for latent tuberculosis (history, chest radiograph, and Tubertest©).

In your patient, the pre-treatment status was as follows:

– Contact with a TB case	❑yes, on	❑no	❑ not assessed
– Chest radiograph abnormality	❑yes, on	❑no	❑ not assessed
– Tubertest®	❑yes, on	❑no	❑ not assessed
– QuantiFERON Gold® or T-Spot-TB®	❑yes, on	❑no	❑ not assessed
– Prior anti-TB prophylaxis	❑yes, on	❑no	❑ not assessed

Date on D1 : .....

1) If the screen done before TNF antagonist therapy was positive, the patient received prophylactic treatment against tuberculosis.

If the patient adhered to this treatment, and in the absence of contact with a tuberculous patient since then, tocilizumab therapy can be started with no other specific precautions.

2) If the screen done before TNF antagonist therapy was negative and dates back more than 1 year, a new screen in recommended. These precautions are recommended although there is no proof that tocilizumab therapy increases the risk of tuberculosis. This risk cannot be evaluated accurately, because the patients who participated in the early studies underwent screening and, based on the results, were either excluded or received prophylactic anti-tuberculous therapy. Should the screen be positive, the patient should receive the anti-tuberculous regimen recommended for TNF antagonist therapy (AFSSAPS 2005). The first tocilizumab infusion can be given after 3 weeks of anti-tuberculous therapy, which should be continued for 3 months in all (if it consists of isoniazid (Rimifon®) + rifampin).

❑ We evaluated the factors listed below.

1) The risk of infection, based on classic factors (age, diabetes, glucocorticoid therapy, co-morbidities...) and iatrogenic factors related to prior biological therapy. In patients previously treated with rituximab, the serum immunoglobulin level and the circulating B-cell count will be taken into account when evaluating the risk of infection.

2) The risk of malignancy, which depends on pre-existing premalignant or malignant lesions, personal risk factors, and familial risk factors.

The findings that are important in your patient are listed below.

❑ Risk factors for infection ❑yes ❑no

If yes, specify which ones .....

❑ Risk factors for malignancy ❑yes ❑no

If yes, specify which ones .....

❑ No risk factors for infection or malignancy

How was the treatment conducted?

❑ Tocilizumab treatment was started in a dosage of ..... mg/kg with no premedication

❑ was given with methotrexate or, in the event of a contraindication, in combination with the following treatment .....

❑ or was given as monotherapy.

The tocilizumab infusion

❏ was uneventful, with no infusion-related reaction

❏ was complicated by the following event: .....

Intolerance (reaction to the molecule) may develop during or after the infusion. This event is rare and, more importantly, very rarely severe (0.3%).

Although infusion-related reactions are not serious, they warrant symptomatic treatment. The patient should be admitted on an emergency basis if any of the following develops: constitutional symptoms, respiratory manifestations, cardiovascular manifestations, or diffuse skin lesions.

The tocilizumab infusions will be given once a month, in the same dosage, except in the event of transaminase elevation or neutropenia.

Evaluating the clinical and biological response to tocilizumab

The monthly infusion provides an opportunity for regular monitoring, with an evaluation before each infusion. However, as his/her usual rheumatologist, you will evaluate the patient. Your objective is to evaluate the treatment response and to monitor the patient in conjunction with the primary-care physician.

The therapeutic objectives are as follows:

➤ response by week 12, with an at least 0.6-point decrease in the DAS 28

➤ and response by week 24, with an at least 1.2-point decrease in the DAS 28 and ideally a DAS 28 ≤ 3.2.

To monitor the response to tocilizumab, the following should be evaluated at least every 3 months: clinical disease activity (DAS 28 or SDAI), quality of life, and laboratory tests for inflammation (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]). The effect of tocilizumab on structural disease progression will be assessed by obtaining radiographs of the hands and feet about 1 year after the first infusion.

Evaluating the safety of tocilizumab

During tocilizumab therapy, the only laboratory tests required are as follows:

➤ blood cell counts (risk of neutropenia, which is uncommon and usually transient)

➤ liver function tests (transaminases, of which elevations are uncommon and usually moderate)

➤ and serum lipid levels (total cholesterol, LDL cholesterol, and triglycerides, as the LDL-cholesterol level may increase, which infrequently requires the introduction of a lipid-lowering medication), every 3 months initially.

When selecting laboratory tests for treatment monitoring, it is important to consider concomitant drugs, most notably methotrexate. There are no routinely available immunological tests for monitoring and assessing the effectiveness of tocilizumab therapy.

Risks associated with tocilizumab therapy

Infections may occur in tocilizumab-treated patients. Pneumonia and bronchitis are the most common forms, although cellulitis, pyelonephritis, and diverticulitis have also been reported. These infections require prompt management with appropriate antimicrobials.

In tocilizumab-treated patients, infections may fail to elevate the levels of CRP, other inflammation markers, or neutrophils. Elevations in other biological markers (e.g., overexpression of the membrane marker CD64 by neutrophils detected by flow cytometry) may suggest a diagnosis of infection in a tocilizumab-treated patient.

Therefore, infections should be looked for by obtaining specimens for microbiological studies and by performing appropriate imaging studies. In patients with a strong clinical suspicion of infection, promptly initiate treatment with appropriate antibiotics or, if warranted, antiviral, antifungal, or antiparasitic agents.

Other adverse events have been reported such as blood pressure changes (hypertension, hypotension), hepatic cytolysis (without severe hepatitis), neutropenia (reversible), hypercholesterolemia, and headaches.

There is no evidence that tocilizumab can induce the development of autoimmune disease. However, there have been reports of demyelination, for which no causal link with tocilizumab therapy has been demonstrated.

Available data do not suggest an increased risk of malignancy in association with tocilizumab therapy for RA. However, close monitoring is warranted.

Further tocilizumab treatment

If after 12 weeks there is no treatment response (less than 0.6-point improvement in the DAS 28), further tocilizumab therapy is not recommended.

If there is a partial response by week 12, with a DAS 28 improvement of at least 0.6 (but of less than 1.2), the treatment can be continued until week 24.

If the DAS 28 improvement is less than 1.2 by week 24, the treatment strategy should be reappraised.

In patients who have a response (DAS 28 improvement >1.2 by week 24) with residual disease activity (DAS 28 >3.2), the treatment strategy should be reappraised in the light of available alternative treatments.

Modalities of follow-up in everyday practice

Several situations such as vaccinations, surgery, travel, pregnancy, and lactation are discussed in fact sheets available from us on request or from the CRI site (www.cri.net.com). We have given the patient a written document that describes tocilizumab and the treatment modalities.

We will be happy to provide you with any additional information you may need.

Sincerely,

Physician in charge:

Dr.....

Telephone:.....

Stamp: