HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE
Opinion
4 December 2013

ROACTEMRA 20 mg/ml, concentrate for solution for infusion

B/1 vial of 4 ml (CIP: 340 095 574 643.1)
B/1 vial of 10 ml (CIP: 340 095 574 644.8)
B/1 vial of 20 ml (CIP: 340 095 574 645.4)

Applicant: ROCHE

INN	Tocilizumab
ATC code (2013)	L04AC07 (Biologics)
Reason for the review	**Re-assessment of Improvement in Actual Benefit at the company's request, in accordance with article R 163-12 of the French Social Security Code.**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**Treatment in combination with methotrexate (MTX) or as monotherapy of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.**

Actual Benefit	**The actual benefit of ROACTEMRA as monotherapy is substantial in the treatment of rheumatoid arthritis in patients requiring treatment with a biologic.**
Improvement in Actual Benefit	**In patients requiring a biologic as monotherapy, taking into account the superiority of ROACTEMRA (tocilizumab) to adalimumab as monotherapy (ADACTA study), the Transparency Committee considers that ROACTEMRA as monotherapy provides a minor improvement in actual benefit (level IV) in comparison with adalimumab in terms of efficacy.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	16 January 2009 (centralised procedure)
Prescribing and dispensing conditions / special status	Medicinal product reserved for hospital use Prescription restricted to specialists in rheumatology or internal medicine Medicine requiring special monitoring during treatment This proprietary medicinal product has a risk management plan[1]

ATC Classification	2012	
	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AC	Interleukin inhibitors
	L04AC07	tocilizumab

02 BACKGROUND

The proprietary medicinal product ROACTEMRA has been included on the list of medicines approved for hospital use since 2009. In its RA indication, its AB had been considered substantial and its IAB had been assessed in two subpopulations:

- In patients in whom previous therapy with one or more conventional disease-modifying drugs including MTX had failed, its IAB had been considered non-existent (level V) in comparison with TNF inhibitors.
- In patients in whom previous therapy with one or more TNF inhibitors had failed, the Committee had considered that ROACTEMRA shared substantial IAB (level II) with ORENCIA in the therapeutic strategy.

No distinction was made between the two regimens possible with ROACTEMRA: dual therapy (with MTX) and monotherapy.

In 2012, having been made aware that the pharmaceutical company ROCHE had conducted the first superiority study to compare two biologics for RA, the Transparency Committee office requested access to the results of this study. These data were submitted as part of the present application and led the company to request re-assessment of the IAB of ROACTEMRA in the subpopulation treated with monotherapy.

[1] The following risks are subject to surveillance:
- Severe infections
- Severe hypersensitivity reactions
- Complications of diverticulitis, including gastrointestinal perforation
- Potential risk of elevated liver transaminases and potential risk of hepatotoxicity
- Potential risk of elevated lipid parameters
- Potential risk of haematological abnormalities: neutropenia and thrombocytopenia
- Potential risk of acute central demyelinating disorders
- Potential risk of malignancy
- Potential risks associated with restoration of CYP450 activity
- Potential risk of immunogenicity
- Potential risk on skeletal development in children

03 THERAPEUTIC INDICATIONS

“ROACTEMRA, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, ROACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
ROACTEMRA 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.”

This assessment does not concern ROACTEMRA’s indication in systemic juvenile idiopathic arthritis.

04 DOSAGE

“The recommended posology is 8 mg/kg body weight, given once every four weeks. For patients whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. Doses above 1.2 g have not been evaluated in clinical studies.”

05 THERAPEUTIC NEED

The aims of treatment in rheumatoid arthritis are to initiate and maintain clinical remission and to limit the progression of joint damage and thus subsequent disability. The disease management has changed considerably in recent years because of the use of new disease-modifying anti-rheumatic drugs, particularly biologics in combination with methotrexate. The standard conventional disease-modifying drug remains methotrexate. Different disease-modifying drugs need to be available because of the phenomena of treatment failure and intolerance.

The following categories of biologic are available:

- TNF inhibitors such as etanercept (ENBREL), adalimumab (HUMIRA), infliximab (REMICADE), certolizumab (CIMZIA) and golimumab (SIMPONI), which are offered in cases of inadequate response or intolerance to conventional disease-modifying anti-rheumatic drugs including methotrexate. They may also be used as first-line therapy (in patients naive to MTX) in some active and severe forms of rheumatoid arthritis.
- Biologics with targets other than TNF, namely abatacept (ORENCIA), rituximab (MABTHERA) and tocilizumab (ROACTEMRA). These medicines are offered in cases where TNF inhibitors fail. Abatacept and tocilizumab also have marketing authorisation in patients for whom conventional disease-modifying anti-rheumatic drugs, including MTX, have failed.
- Anakinra, an interleukin-1 inhibitor which has limited therapeutic use because it appears to be less effective than the other biologics.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

RA with inadequate response to conventional disease-modifying anti-rheumatic drugs including MTX

- **In combination with MTX:**
  - interleukin-1 receptor antagonist, KINERET (anakinra)
  - TNF inhibitors (CIMZIA - certolizumab pegol, ENBREL - etanercept, REMICADE - infliximab, HUMIRA - adalimumab, SIMPONI - golimumab)
  - T-cell co-stimulation modulator, ORENCIA (abatacept)

- **As monotherapy:**
  - three TNF inhibitors (CIMZIA - certolizumab pegol, ENBREL - etanercept, HUMIRA - adalimumab)

RA with inadequate response to at least one TNF inhibitor

- **In combination with MTX:** MABTHERA (rituximab), ORENCIA (abatacept)
- **As monotherapy:** none

Conclusion

The comparators listed are all clinically relevant.
See Tables 1 and 2 below for a reminder of indications, AB and IAB.

Table 1. Reminder of Marketing Authorisation indications, actual benefit and improvement in actual benefit for TNF inhibitors in RA

INN	Company	Indication	Date of relevant opinion	AB	IAB (wording)	Reimbursed Yes/No
ENBREL (etanercept) *Soluble tumour necrosis factor (TNF) receptor*	PFIZER	ENBREL in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drugs, including methotrexate (unless contraindicated), has been inadequate. **ENBREL can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.** ENBREL is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. ENBREL, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.	2 March 2005	Substantial	Substantial IAB (level II) in terms of clinical efficacy but also in terms of slowing the progression of structural joint damage, in comparison with conventional treatments including treatment with MTX alone.	Yes
REMICADE (infliximab) *Monoclonal antibody targeting TNF*	MSD	REMICADE, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in: - patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate; - patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated.	26/04/2006	Substantial	Shares substantial IAB (level II) with other TNF inhibitors in terms of clinical efficacy and slowing the progression of structural joint damage, in comparison with conventional treatments including treatment with MTX alone.	Yes

INN	Company	Indication	Date of relevant opinion	AB	IAB (wording)	Reimbursed Yes/No
HUMIRA (adalimumab) *Monoclonal antibody targeting TNF*	ABBVIE	HUMIRA in combination with methotrexate is indicated for: - the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate; - the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. **HUMIRA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.** HUMIRA 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.	02/11/2005	Substantial	Shares substantial IAB (level II) with ENBREL® in terms of clinical efficacy and slowing the progression of structural joint damage. As monotherapy, HUMIRA® has not been shown to be superior to methotrexate alone in patients naive to MTX.	Yes
CIMZIA (certolizumab) *Monoclonal antibody targeting TNF*	UCB	CIMZIA, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active RA in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate has been inadequate. **CIMZIA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.** CIMZIA 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.	10/03/2010	Substantial	No IAB (level V) in comparison with other TNF inhibitors (ENBREL®, HUMIRA® and REMICADE®) in the management of this condition.	Yes

INN	Company	Indication	Date of relevant opinion	AB	IAB (wording)	Reimbursed Yes/No
SIMPONI (golimumab) *Monoclonal antibody targeting TNF*	MSD	SIMPONI, in combination with MTX, is indicated for: - the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate; - the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX. SIMPONI, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.	01/02/2012	Substantial	No IAB (level V) in comparison with other TNF inhibitors in the management of patients in whom previous treatment with one or more conventional disease-modifying drugs, including methotrexate, used at the maximum tolerated dose has failed.	Yes

INN	Company	Indication	Date of relevant opinion	AB	IAB (wording)	Reimbursed Yes/No
KINERET (anakinra) *Interleukin-1 receptor antagonist*	SWEDISH ORPHAN BIOVITRUM	KINERET is indicated for the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone.	02/10/2013	Low	IAB level V (non-existent) in the therapeutic strategy for rheumatoid arthritis.	Yes

Table 2. Reminder of indications, actual benefit and improvement in actual benefit for “second line” biologics in RA

INN	Company	Indication	Date of relevant opinion	AB	IAB (wording)	Reimbursed Yes/No
ORENCIA IV (abatacept) *T-cell co-stimulation modulator*	BMS	ORENCIA in combination with MTX is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to or were intolerant to other disease-modifying anti-rheumatic drugs including MTX or a TNF inhibitor. A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and MTX.	14/03/2012	Substantial	- Substantial IAB (level II) in the therapeutic strategy for patients in whom other disease-modifying therapies including at least one TNF inhibitor have failed. - No IAB (level V) in adult patients who responded inadequately to previous therapy with one or more DMARDs including MTX or a TNF inhibitor.	Yes
ROACTEMRA (tocilizumab) *Monoclonal antibody targeting interleukin-6*	Roche	ROACTEMRA, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, ROACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. ROACTEMRA 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.	09/09/2009	Substantial	- No IAB (level V) in comparison with other TNF inhibitors in patients in whom previous therapy with one or more conventional disease-modifying drugs, including MTX, has failed. - Shares substantial IAB (level II) with ORENCIA® in the therapeutic strategy for patients in whom previous therapy with one or more TNF inhibitors has failed.	Yes
MABTHERA (rituximab) *Monoclonal antibody targeting B-cells*	Roche	MABTHERA in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies. MABTHERA 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.	13/12/2006	Substantial	Substantial IAB (level II) in comparison with the current strategy for patients in whom disease-modifying therapies including at least one TNF inhibitor have failed.	Yes

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The proprietary medicinal product ROACTEMRA is reimbursed under its Marketing Authorisation indications in most European countries.

Country	Reimbursed	
	Yes (start date) / No / Assessment in progress or change	Scope (indications) and special condition(s)
Austria	Yes (02.03.2009)	RA and JIA
Belgium	Yes (01.10.2009)	RA and JIA
Germany	Yes (15.02.2009) Assessment by IQWIG: "Biologic medications as second-line therapy for rheumatoid arthritis" (document in German). A re-assessment of biologics is in progress.	RA and JIA
Bulgaria	Yes (01.01.2013)	RA and sJIA
Denmark	Yes (23.03.2009)	RA and sJIA
Spain	Yes (08.07.2009)	RA and sJIA
Estonia	Yes (01.01.2011)	RA and sJIA
Finland	Yes (16.01.2009)	RA and sJIA
Greece	Yes (04.01.2010)	RA and sJIA
Hungary	Yes (01.06.2010)	RA
Ireland	Yes (01.05.2009)	RA and sJIA
Italy	Yes (03.04.2009)	RA
Latvia	Yes (01.01.2011)	RA
Lithuania	No	-
Luxembourg	Yes (01.04.2009)	RA and sJIA
Norway	Yes (21.04.2009)	RA and sJIA
Netherlands	Yes (01.02.2009)	RA and sJIA
Poland	No	-
Portugal	Yes (14.09.2010)	RA
Czech Republic	Yes (01.10.2010)	RA
Romania	No	-
United Kingdom	Yes (18.01.2010) Assessment: NICE: “Technology appraisal guidance 247”, does not cover monotherapy. A re-assessment of biologics is in progress. SMC: Advice No. 774/12 (see reference documents)	RA and sJIA
Slovakia	Yes (01.10.2009)	RA and sJIA
Slovenia	Yes (19.07.2010)	RA and sJIA
Sweden	Yes (15.02.2009)	RA and sJIA

08 SUMMARY OF PREVIOUS ASSESSMENT IN RA

Date of opinion (reason for request)	**09/09/2009** Inclusion on the list of medicines approved for hospital use
Indication	ROACTEMRA, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs)* or tumour necrosis factor (TNF) antagonists. In these patients, ROACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
AB	Substantial
IAB	The Transparency Committee considers that: - in adults suffering from moderate to severe active RA who had either an inadequate response or intolerance to prior treatment with one or more conventional DMARDs including methotrexate at the maximum tolerated dosage, ROACTEMRA does not provide any improvement in actual benefit (**IAB V**) compared with TNF-alpha inhibitors; - in adults suffering from moderate to severe active RA who had either an inadequate response or intolerance to prior treatment with one or more TNF-alpha inhibitors, ROACTEMRA offers the **same improvement in actual benefit (IAB II) as ORENCIA** (abatacept) in therapeutic use.
Studies requested	The Transparency Committee would like to see a long-term follow-up study conducted for ROACTEMRA on patients being treated for rheumatoid arthritis using similar methods and protocols to the studies requested for other biotherapies in the treatment of rheumatoid arthritis. The Transparency Committee points out that the aims of such a study are to: - describe the prescription conditions (indication, dosage, concomitant medication, etc.) and the patients treated (socio-demographic data, patient history, history of the disease, comorbidities, etc.); - evaluate the impact of the treatment on the health of the population concerned in terms of morbidity and mortality (particularly disease progression, patient quality of life, monitoring of the onset of drug resistance, onset of long-term adverse events, etc.); - describe the treatment strategy and the use of healthcare services. If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, cannot answer all the questions raised by the Transparency Committee, a specific study must be conducted. The study duration must be justified by an independent scientific committee.

09 ANALYSIS OF AVAILABLE DATA

In support of its application for re-assessment of the IAB of tocilizumab (TCZ - ROACTEMRA) **as monotherapy** in the treatment of rheumatoid arthritis, the company has submitted the results of the following studies:

- **the ADACTA study**, a superiority study comparing TCZ with adalimumab as monotherapy in patients intolerant of MTX or in whom continued treatment with MTX was considered inappropriate (including those who responded inadequately to MTX)
- **the AMBITION study** (the results of which were already assessed by the Committee in 2009), which evaluated the non-inferiority (primary analysis) and then the superiority (secondary analysis) of TCZ to MTX in patients who had not been failed by MTX
- **the ACT-RAY study**, a superiority study comparing two TCZ treatment regimens, monotherapy versus combined therapy with MTX, in patients with an insufficient response to MTX
- the **ACT-SURE** (results already assessed by the Committee in 2009) and **ACT-STAR** open-label studies, which evaluated the safety of TCZ as monotherapy and in combination with a DMARD
- two Japanese studies already included with the 2009 application (**SAMURAI**, **SATORI**), one Japanese phase II extension study (**STREAM**) and a **meta-analysis** of six clinical studies which was used to support registration of ROACTEMRA in Japan.

The methodology of these studies is summarised in Table 3 below.

Table 3. Summary of the main studies of tocilizumab as monotherapy for rheumatoid arthritis.

Study status	Type of study	Duration	Patients (ITT pop)	Population studied	Treatment regimen (number in group)			Primary endpoint
ADACTA Completed	Randomised, double-blind, double-dummy superiority study	6 months	326	Moderate to severe active RA, where MTX has failed (inadequate response, intolerance, continued treatment considered inappropriate) in patients naive to biologics.	TCZ 8 mg/kg + SC ADA placebo (n=163)	ADA 40 mg + IV TCZ placebo (n=163)		Change in DAS28-ESR from baseline to W24
AMBITION Completed (already assessed)	Randomised, double-blind, double-dummy non-inferiority study A superiority test could be performed if non-inferiority was demonstrated.	6 months (24 weeks)	570	Patients with moderate to severe RA who have not experienced failure of MTX (not treated with MTX within 6 months of randomisation and not having stopped treatment with MTX due to intolerance or lack of efficacy within 6 months of randomisation)	TCZ 8 mg/kg + oral MTX placebo (n=288)	TCZ 8 mg/kg + placebo (n=284)		ACR 20 response at W24
ACT-RAY Started in 2009, ongoing	Randomised, double-blind superiority study (TCZ + MTX versus TCZ monotherapy)	2 years	556	Patients with moderate to severe RA, inadequate response to MTX	TCZ 8 mg/kg + MTX (n=279)	TCZ 8 mg/kg + placebo (n=277)		DAS28 remission rate (DAS28 < 2.6) at W24
ACT-SURE Completed	Open-label	6 months	1681	Patients with moderate to severe RA, in whom **DMARDs and/or TNF inhibitors have failed**	TCZ 8 mg/kg monotherapy (n=239)	TCZ 8 mg/kg + ≥ 1 DMARD (n=1442)		**Safety at 24 weeks**
ACT-STAR Completed	Open-label, randomised	6 months	883	Patients with moderate to severe RA, in whom **DMARDs and/or TNF inhibitors have failed**	TCZ 8 mg/kg monotherapy (n=163)	TCZ 8 mg/kg + DMARD (n=358)	TCZ 4 mg/kg + DMARD (n=362)	**Safety at 24 weeks**
SAMURAI Completed, submitted with 2009 application	**Open-label, randomised**	1 year	302	Patients with severe active RA, in whom DMARDs have failed	TCZ 8 mg/kg (n=157)	Existing treatment with DMARDs (n=145)		Inhibition of structural damage at W52 (total Van der Heijde modified Sharp score)
SATORI Completed Submitted with 2009 application	Controlled, randomised, double-blind study versus MTX	6 months	125	Patients with moderate to severe active RA, in whom low-dose MTX has failed	TCZ 8 mg/kg (n=61)	Low-dose MTX (8 mg once/week) (n=64)		ACR 20 response at W24
STREAM[12] Completed	**Open-label** extension phase of a phase II study	5 years	143	Patients with severe active RA, in whom DMARDs have failed	TCZ 8 mg/kg			ACR 20 response, frequency and severity of adverse events

09.1 Efficacy

The efficacy of TCZ as monotherapy is mainly supported by the results of the ADACTA study. Supplementary data from the AMBITION and ACT-RAY studies, the Japanese SAMURAI and SATORI studies, the Japanese phase II extension study STREAM and from a meta-analysis of these were also submitted.
The results of the open-label ACT-SURE and ACT-STAR studies, which had the primary objective of evaluating the safety of TCZ, are presented in section 9.2.

9.1.1 ADACTA study[2]

Aim and method:
This was a phase IV, randomised, controlled, double-blind superiority study lasting 6 months, with the primary objective of demonstrating the superiority of TCZ to adalimumab (ADA), in terms of reducing disease activity, as monotherapy after 24 weeks of treatment.
The patients included had had moderate to severe active RA for more than 6 months, and were either intolerant of MTX or continued treatment was considered inappropriate (including patients who had responded inadequately to MTX). One of the non-inclusion criteria was that patients must not have been previously treated with a biologic agent.

Treatments
Patients received TCZ 8 mg/kg by IV infusion every 4 weeks in combination with placebo ADA, or ADA 40 mg as an SC injection every 2 weeks in combination with a placebo TCZ infusion.
From W16, patients who responded insufficiently (less than 20% improvement in the number of tender and swollen joints) could receive escape therapy in the form of weekly (rather than fortnightly) SC injections (adalimumab or placebo). Patients were authorised to receive corticosteroids (stable dose ≤ 10 mg/day prednisone or equivalent) and a stable dose of NSAIDs.

Efficacy endpoint
The primary efficacy endpoint was change in DAS28-ESR score at 24 weeks.

Statistical analysis
The analyses were performed in the ITT population.
Missing data were entered using the LOCF[3] method(including for patients who had received escape therapy).

Results
A total of 326 patients were included with 163 patients in each group.
One patient in the ADA group who was not treated was not included in the ITT analysis.
Patient characteristics were comparable across both groups: they had a mean age of 54 years, 56% were receiving concomitant corticosteroid treatment (mean dose 6.4 mg/day prednisone or equivalent), and the mean DAS28 score was 6.7.
After 24 weeks of treatment, the mean change in DAS28 score from baseline was -3.3 in the TCZ group and -1.8 in the ADA group, i.e. an adjusted mean difference of -1.5 (95% CI [-1.8; -1.1]) in favour of TCZ, $p < 0.0001$.
Analysis of the secondary endpoints confirmed the superiority of TCZ monotherapy to ADA monotherapy. Specifically:
- The proportion of patients in DAS28 remission (DAS28 < 2.6) was significantly higher in the TCZ group (39.9%) than in the ADA group (10.5%), $p < 0.0001$.
- The proportion of patients with low disease activity (DAS28 ≤ 3.2) was significantly higher in the TCZ group (51.5%) than in the ADA group (19.8%), $p < 0.0001$.

[2] Gabay C et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541-1550
[3] Last available observation carried forward

- The proportion of patients with a "good" EULAR response was significantly higher in the TCZ group (51.5%) than in the ADA group (19.8%), p < 0.0001.

9.1.2 Supplementary data on efficacy as monotherapy

AMBITION study[4]
The conclusions of the Committee on this study were as follows: "TCZ 8 mg/kg demonstrated its non-inferiority (PP analysis) compared with MTX for the primary endpoint. The proportion of ACR 20 responders at 24 weeks was 70.6% in the TCZ 8 mg/kg group and 52.1% in the MTX group (weighted difference of 0.21 95%CI [0.13, 0.29]).
The superiority of TCZ 8 mg/kg was also demonstrated (ITT analysis) compared with MTX for the primary endpoint: the proportion of ACR 20 responders at 24 weeks was 69.9% in the TCZ 8 mg/kg group and 52.5% in the MTX group, p<0.0001."

ACT-RAY study[5]
TCZ 8 mg/kg in combination with MTX was not shown to be superior to TCZ monotherapy in terms of DAS28-ESR remission rate (< 2.6) after 24 weeks of treatment: 40.4% for TCZ + MTX versus 34.8% for TCZ + PBO, p = NS. In addition, no difference was demonstrated between the two groups in terms of radiographic progression at 24 weeks.

Japanese studies

- SAMURAI study[6]

In this open-label study, the increase in total Sharp score at week 52 (primary endpoint) was significantly lower on TCZ 8 mg/kg (2.3 [1.5; 3.2]) than on DMARDs including MTX prescribed at a mean low dose of 8 mg/week[7](6.1 [4.2; 8]), p < 0.01.

- SATORI study[8]

In this study, conducted in a small number of patients (125) for whom low-dose MTX had failed, after 24 weeks of treatment, 80.3% of patients in the TCZ 8 mg/kg group (Marketing Authorisation dosage) obtained an ACR 20 response versus 25% in the low-dose MTX group (8 mg/week[7] in place of the usual mean dosage of 15 mg/week), p < 0.001.

- STREAM[9]

In this open-label 5-year extension phase of a phase II study, the 143 patients included were all treated with TCZ 8 mg/kg every 4 weeks as monotherapy. A total of 94 patients, i.e. 66%, completed the study after 5 years. Safety was the main reason for discontinuation (32 patients i.e. 22%). The proportion of patients who achieved an ACR 20 response was 84.0%, 69.1% for ACR 50 and 43.6% for ACR 70. DAS28 remission was observed in 55.3% of patients.

[4] Jones G. et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010;69:88-96.
[5] Dougados M. et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis 2013;72:43-50.
[6] Nishimoto N. et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 2007;66:1162-1167.
[7] The maximum MTX dosage authorised in Japan is 8 mg/week.
[8] Nishimoto N. et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19:12-19.
[9] Nishimoto N. et al. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. 99Ann Rheum Dis 2009;68:1580-1584.

Meta-analysis of Japanese studies[10]

This meta-analysis was performed from six Japanese clinical studies (including the SAMURAI and SATORI studies) and their extension phases, and allowed the company to obtain Marketing Authorisation for TCZ in Japan in 2008.
A total of 601 patients who received TCZ as monotherapy (2 mg/kg, 4 mg/kg or 8 mg/kg every 4 weeks during the studies, then 8 mg/kg during the extension phases) for a median duration of 3.8 years were included. These were patients with RA who had responded inadequately to at least one DMARD (80.8% had previously been treated with MTX).
The percentage of treatment discontinuations was 27.6% at 3 years and 35.7% at 5 years, including 19.6% due to AEs. At 5 years, the proportion of patients who achieved an ACR 20 response was 91.3%, 73% for ACR 50 and 51.3% for ACR 70. DAS28 remission (< 2.6) was observed in 59.7% of patients.

09.2 Safety/Adverse effects

9.2.1 Data from clinical studies

ADACTA study
During the 24-week double-blind period, 82% of patients treated with TCZ monotherapy versus 83% of those treated with ADA monotherapy had at least one adverse event (AE). Infection was the most common AE, with an incidence of 70% in the TCZ group versus 65% in the ADA group. A total of 54 patients stopped treatment prematurely: 24 (15%) in the TCZ group including 7% due to AEs and 30 (18%) in the ADA group including 7% due to AEs. Serious adverse events (SAEs) were reported in 12% of patients in the TCZ group and 10% of patients in the ADA group. The most common SAEs were “infections and infestations” (3.1% in both treatment groups). Two patients died in the TCZ group, with one of these deaths considered as possibly related to treatment.
General disorders and administration site conditions were reported more frequently in the ADA group, with 32 patients (19.8%) affected versus 16 patients (9.9%) in the TCZ group. Two patients in the TCZ group stopped treatment following hypersensitivity reactions associated with the infusion.

AMBITION study
The overall incidence of AEs was similar in both groups: 79.9% in the TCZ monotherapy group versus 77.5% in the MTX monotherapy group. The most common AEs were infections (34.4% in the TCZ group versus 37.3% in the MTX group) and gastrointestinal disorders. The overall incidence of treatment-related AEs was similar in both groups: 56.6% in the TCZ group versus 49.6% in the MTX group. The proportion of treatment discontinuations due to AEs was 3.8% in the TCZ group versus 5.3% in the MTX group. Three deaths occurred in the TCZ group (including one treatment-related death following gastrointestinal perforation) versus one in the MTX group.
The proportion of SAEs was 3.8% in the TCZ group versus 2.8% in the MTX group, with severe infections accounting for 1.4% and 0.7% respectively.

ACT-RAY study
During the 24 weeks of the study, the proportion of patients who had at least one AE was comparable across both groups: 200 patients (72.5%) in the TCZ monotherapy group versus 194 patients (70%) in the TCZ + MTX group. The number of patients who stopped treatment due to AEs was 8 in the TCZ + PBO group and 11 in the TCZ + MTX group. SAEs were reported in 16 patients (5.8%) in the TCZ + PBO group versus 17 patients (6.1%) in the TCZ + MTX group. The most common SAEs were infections and cardiac disorders.
Three deaths occurred during the study and a fourth patient died after the 24-week study period. There were two deaths in each treatment group, with the following causes of death: sepsis,

[10] Nishimoto N. et al. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. Mod Rheumatol 2010;20:222-232.

myocardial infarction, sepsis with meningitis, and septic shock, preceded by a scrotal abscess, skin necrosis, acute kidney failure and congestive heart failure.

ACT-STAR study[11]
During the 24 weeks of the study, the proportion of patients who:
- had at least one AE was 80.8% in the TCZ 4/8 mg/kg + DMARD group, 81.1% in the TCZ 8 mg/kg + DMARD group, and 82.6% in the TCZ 8 mg/kg monotherapy group;
- stopped treatment due to AEs was 8.8% in the TCZ 4/8 mg/kg + DMARD group, 5% in the TCZ 8 mg/kg + DMARD group, and 6.5% in the TCZ monotherapy group;
- had an SAE was 8% in the TCZ 4/8 mg/kg + DMARD group, 8.4% in the TCZ 8 mg/kg + DMARD group, and 5.8% in the TCZ monotherapy group.

The SAEs were pneumonia (1%) and cellulitis (0.9%).
Two patients treated with TCZ 4 mg/kg died.

ACT-SURE study[12]

Of the 1681 patients included, 976 were naive to TNF inhibitors, 298 had been treated with TNF inhibitors (followed by withdrawal) and 407 had been recently treated with TNF inhibitors. The incidence of AEs was 74.4% in patients naive to TNF inhibitors, 80.2% in patients who had been previously treated with TNF inhibitors and 82.6% in patients who had recently been treated with TNF inhibitors (overall incidence: 77.4%).
The number of patients who stopped TCZ prematurely was 215 (12.8%), including 86 due to AEs; this latter figure includes 4 deaths (sepsis, sudden death, cardiac arrest and aortic dissection). Three deaths occurred in the group of patients naive to TNF inhibitors and one in the group who had recently received them. Reactions to the infusion were reported in 6.7% of patients.

Meta-analysis of Japanese studies
The incidence of AEs was 465.1 per 100 patient-years (10,176 AEs in 596 of the 601 patients treated with TCZ). The most common AEs were “infections and infestations” (129.2 per 100 patient-years). The most common severe infections were pneumonia, shingles and cellulitis. A total of 133 reactions to the infusion were observed in 93 patients (15.5%). Cases of anaphylaxis or anaphylactic reactions occurred in 3 patients.
Gastrointestinal perforations occurred in 5 patients, including 3 where an association with the treatment could not be ruled out. Cases of malignancy were reported in 19 patients (3.2%; 0.8 per 100 patient-years).

Pharmacovigilance data
The international pharmacovigilance data submitted by the company come from the last 3 biannual PSURs, covering the periods from 11 April 2011 to 10 October 2012. In each of these three 6-month periods respectively (11 April 2011 to 10 October 2011, 11 October 2011 to 10 April 2012 and 11 April 2012 to 10 October 2012), the following cases were reported to the company internationally:
- 2084 adverse effects, including 1217 serious adverse effects
- 2419 adverse effects, including 1726 serious adverse effects
- 3633 adverse effects, including 2393 serious adverse effects.

Infections and infestations were the most common AE, accounting for between 20.5% and 21.3% of adverse effects and between 26.2% and 29.4% of serious adverse effects. General disorders and administration site conditions accounted for between 10.6% and 11.9% of adverse effects and between 7.7% and 8.1% of serious adverse effects. Gastrointestinal disorders accounted for between 9.2% and 9.5% of adverse effects and between 8.0% and 8.8% of serious adverse effects.

[11] Weinblatt ME. et al. Tocilizumab as monotherapy or in combination with nonbiologic disease-modifying antirheumatic drugs: Twenty-four-week results of an open-label, clinical practice study. Arthritis Care Res (Hoboken) 2013;65:362-371
[12] Bykerk VP. et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARD and/or TNF inhibitors: a large, open-label study close to clinical practice. Ann Rheum Dis 2012; 71:1950-1954.

In each of the three 6-month periods respectively (11 April 2011 to 10 October 2011, 11 October 2011 to 10 April 2012 and 11 April 2012 to 10 October 2012), the following fatal cases were reported to the company internationally:
- 51 fatal cases i.e. a notification rate of 0.14%
- 59 fatal cases i.e. a notification rate of 0.15%
- 110 fatal cases i.e. a notification rate of 0.24%.
The distribution of these fatal cases by system organ class (SOC) is comparable from one period to the next, with the following main SOCs: general disorders and administration site conditions (65 cases), infections and infestations (48 cases), respiratory, thoracic and mediastinal disorders (25 cases), and neoplasms benign, malignant and unspecified (excluding cysts and polyps) (23 cases).

The SPC for TCZ was amended on 25 May 2012 to add a precaution for use in patients with a history of interstitial lung disease. The Undesirable Effects section was amended to include the following information: “Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.”
On 22 November 2012, a special warning regarding symptoms suggestive of tuberculosis was added to section 4.4 of the SPC. On 13 December 2012, the efficacy and safety results of the ADACTA study were incorporated into section 5.1 of the SPC.

In France, during the 18-month period from 11 April 2011 to 10 October 2012, a total of 852 adverse effects including 371 serious adverse effects were reported. The estimated number of patients treated with ROACTEMRA was 4433, i.e. a notification rate of 8.9 cases per 100 patients exposed. The most frequent AEs were “infections and infestations”, accounting for 21.2% of adverse effects and 21% of serious adverse effects; “gastrointestinal disorders”, accounting for 12.3% of adverse effects and 11.9% of serious adverse effects; “skin and subcutaneous tissue disorders”, accounting for 9.9% of adverse effects and 8.6% of serious adverse effects; “blood and lymphatic system disorders”, accounting for 8.5% of adverse effects and 9.7% of serious adverse effects; and “general disorders and administration site conditions”, accounting for 7.9% of adverse effects and 7.3% of serious adverse effects. Five deaths, 5 cases of pregnancy with maternal exposure and 1 case of pregnancy with paternal exposure were reported. Thirteen cases of “anaphylactic reaction/hypersensitivity” were reported.
On the whole, the adverse effects reported in France are consistent with those reported in the rest of the world in terms of the SOCs most commonly involved in adverse effects.

09.3 Usage/prescription data

The REGATE post-listing study responding to the Committee’s 2009 request is in progress (sponsor = French Society of Rheumatology). Patient recruitment was completed in April 2013.

Data from market research in 2012 (A+A panel) submitted by the company provides information about the use of ROACTEMRA as monotherapy. According to these sources, patients treated with ROACTEMRA were:
- 75% female
- 39% treated with monotherapy
- 56% treated with TCZ + MTX
- 5% treated with TCZ + a DMARD other than MTX
- 51% of patients in whom DMARDs failed were treated with monotherapy
- 36% of patients in whom at least one TNF inhibitor failed were treated with monotherapy.

Characteristics of patients treated with monotherapy:
- The mean age of patients was 54.2 years.
- Their mean weight was 69.1 kg.
- The mean TCZ dosage was 7.7 mg/kg.
- 93.3% of patients were treated with TCZ 8 mg/kg every 4 weeks.

09.4 Summary & discussion

ADACTA study
The ADACTA study in 326 patients with moderate to severe active RA in whom MTX had failed (inadequate response, intolerance or continued treatment considered inappropriate) showed that tocilizumab (TCZ) monotherapy was superior to adalimumab (ADA) monotherapy in terms of mean change in DAS28 score at 24 weeks (the primary endpoint): -3.3 vs. -1.8, i.e. a difference of -1.5 (95% CI [-1.8; -1.1]), $p < 0.0001$.

During previous assessments, in the absence of any clinical studies comparing ROACTEMRA directly with other biologics and especially TNF inhibitors, and taking into account some uncertainties as to its long-term safety in actual practice (particularly regarding reactions to the infusion), the Committee had had difficulty defining its role in an optimal strategy for managing RA, in particular in relation to TNF inhibitors.

This study shows that ROACTEMRA offers a minor improvement over adalimumab in terms of efficacy where monotherapy is considered in patients for whom MTX has failed (contraindication, intolerance or continued treatment considered inappropriate). However, in the absence of any direct comparison, its role in relation to other TNF inhibitors still cannot be defined.

The AMBITION study (already assessed by the Committee), conducted in patients who had not experienced failure of MTX (patients naive to MTX or not taking MTX in the 6 months preceding randomisation, and not having stopped treatment with MTX due to intolerance or lack of efficacy), TCZ (8 mg/kg) monotherapy was shown to be non-inferior and then superior (planned superiority analysis) to MTX in terms of the ACR 20 response rate at 24 weeks (the primary endpoint): 69.9% vs. 52.5%, $p < 0.0001$.

In **the ACT-RAY study**, in patients who had responded inadequately to MTX, TCZ monotherapy was not statistically different to TCZ combined with MTX in terms of DAS28 remission rate (< 2.6) at 24 weeks: 34.8% versus 40.4%, p = NS.

A meta-analysis of Japanese studies in 601 patients in whom DMARDs had failed, who were treated with TCZ monotherapy for a median duration of 3.8 years, supported the efficacy of TCZ as monotherapy at 5 years (ACR 20 response: 91.3%, DAS28 < 2.6 remission rate: 59.7%).

In the ADACTA study, the incidence of AEs was similar with TCZ and adalimumab for AEs as a whole (82% vs. 83%) and for serious AEs (12% vs. 10%). Infections were more common with TCZ than with adalimumab (70% vs. 65%) but the incidence of serious infections was similar (3.1% in each group).
The safety data submitted were consistent with those expected according to the SPC for tocilizumab. Infections were the most common AEs.

09.5 Planned studies

The REGATE study, which follows the Committee's request for post-listing data, is in progress.

Studies are under way in the context of obtaining Marketing Authorisation in polyarticular JIA and in early RA (Marketing Authorisation expected March 2014). A new subcutaneous form is in development (Marketing Authorisation expected February 2014).

010 THERAPEUTIC USE

According to the wording of its Marketing Authorisation, ROACTEMRA (tocilizumab) may be used at the same stage in the therapeutic strategy for moderate to severe active rheumatoid arthritis as TNF inhibitors, that is in patients for whom a conventional disease-modifying anti-rheumatic drug such as methotrexate has failed (inadequate response or intolerance), or after failure of at least one TNF inhibitor. It may be used as monotherapy and in combination with methotrexate.
In one study, in patients in whom MTX had failed (inadequate response, intolerance, continued treatment considered inappropriate) and who required treatment with a biologic, ROACTEMRA monotherapy was shown to be superior to adalimumab in terms of ACR 20 response. Nonetheless, no studies comparing it with other TNF inhibitors are available.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

- Rheumatoid arthritis is a serious and disabling chronic disease.
- This medicinal product is a disease-modifying therapy.
- Its efficacy/adverse effects ratio is high.
- There are treatment alternatives.

- Public health benefit:

  Rheumatoid arthritis is a serious and disabling chronic disease which is a major cause of disability. It is responsible for a markedly reduced quality of life and its psychological impact is substantial. It has considerable economic consequences, both in terms of consumption of healthcare and lost working days. In 2009, bone and joint disorders (rheumatoid arthritis, ankylosing spondylitis, severe scoliosis) were the sixth most common cause of new admissions to the long-term condition (LTC) plan, with almost 30,000 LTCs.[13] The public health burden of rheumatoid arthritis is therefore substantial. The public health burden in the subpopulation likely to benefit from ROACTEMRA is moderate, due to the more limited number of patients concerned.

  Reducing the functional impairment and disability caused by rheumatoid arthritis, as well as improving quality of life for people with chronic diseases, is a public health need that is an established priority (objective 83 of the Law of 9 August 2004 on public health policy, Plan to Improve the Quality of Life of Patients with Chronic Diseases 2007-2011) despite the existence of available therapies. Similarly to TNF inhibitors and other biologics, the proprietary medicinal product ROACTEMRA helps to partially meet the public health need identified.

  The results of the ADACTA study showed that ROACTEMRA monotherapy is superior to adalimumab monotherapy. Consequently, a small additional impact in terms of morbidity is expected from the proprietary medicinal product ROACTEMRA as monotherapy.

  Monotherapy is not expected to have any particular impact on the organisation of the healthcare system.

  Consequently, in the subpopulation likely to be treated with monotherapy, it is not expected that the proprietary medicinal product ROACTEMRA will benefit public health.

- ROACTEMRA is a second-line or subsequent therapy in patients with rheumatoid arthritis in whom previous treatment with methotrexate or at least one TNF inhibitor has failed and in whom treatment with a biologic as monotherapy is envisaged (intolerance or contraindication to MTX).

Consequently, the Committee considers that the actual benefit of ROACTEMRA is substantial in the treatment of rheumatoid arthritis in patients requiring treatment with a biologic as monotherapy.

[13] L'état de santé de la population en France. Suivi des objectifs annexes à la loi de santé publique. Rapport 2011. Direction de la recherche, des études, de l'évaluation et des statistiques [Directorate for Research, Surveys, Assessment and Statistics].

The Committee recommends continued inclusion on the list of medicines approved for hospital use in the indication "treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs including methotrexate or a TNF-alpha inhibitor" and at the dosage in the Marketing Authorisation.

011.2 Improvement in actual benefit (IAB)

In patients requiring a biologic as monotherapy, taking into account its superiority to adalimumab as monotherapy, the Transparency Committee considers that the proprietary medicinal product ROACTEMRA (tocilizumab) as monotherapy provides a minor improvement in actual benefit (level IV) in comparison with adalimumab in terms of efficacy.

011.3 Target population

According to the wording of its Marketing Authorisation indication, the target population for ROACTEMRA consists of adult patients with moderate to severe active RA who have had an inadequate response or intolerance to one or more conventional disease-modifying anti-rheumatic drugs or in whom one or more TNF inhibitors have failed.
Patients likely to be treated with ROACTEMRA as monotherapy make up a subpopulation of this target population which has previously been assessed by the Committee.

Subpopulation of patients in whom conventional disease-modifying drugs, including methotrexate, have failed

According to an old epidemiological study (Guillemin and Saraux[14]), in 2001 the prevalence of rheumatoid arthritis in France was estimated to be 0.31% of the population aged over 18 years. If this figure is applied to INSEE data from 1 January 2013 (50,980,000), the French population with RA can be estimated as 158,000 patients. Given the age of the source epidemiological data, this is likely to be an underestimate, considering the current number of patients reimbursed under the long term condition (LTC) plan for severe progressive RA.

The prevalence may be better approached from more recent CNAMTS data on the number of people under the LTC plan for severe progressive RA, which came to 189,148 people in 2011.[15] An increase of 6.9% was observed from 2008 to 2009; between 2009 and 2010 it was 5.2% and from 2010 to 2011 it was 4.8%. Supposing that the number of people under the LTC plan for RA has continued to increase at a rate of 6% per year, the number of people reimbursed under the LTC plan for severe progressive RA would be about 200,497 in 2012 and 212,527 in 2013.

On this basis, considering that the CNAMTS data cover 88% of the French population, the number of people with severe progressive RA in France in 2013 can be estimated as 241,000.

According to expert opinion, 45% to 60% of these patients are currently treated with methotrexate. Treatment fails in about 18% of patients on methotrexate (expert opinion), i.e. a population of between 19,500 and 26,000 patients.

Starting from the assumption that MTX is the standard conventional disease-modifying anti-rheumatic drug, the population with RA in whom at least one conventional disease-modifying anti-rheumatic drug has failed and who are likely to be treated with ROACTEMRA can be estimated as a maximum of between 19,500 and 26,000 patients.

[14] Guillemin F, Saraux A. et al. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis 2005; 64: 1427-1430.
[15] Ameli website.

Subpopulation of patients in whom TNF inhibitors have failed

Starting from the previous data, the population of patients with RA in whom at least one conventional disease-modifying anti-rheumatic drug has failed and who are likely to be treated with TNF inhibitors can be estimated as between 19,500 and 26,000 patients.

According to experts, 30% of patients treated with TNF inhibitors have an inadequate response or intolerance to these treatments, i.e. about 6,000 to 8,000 patients.

In these patients, the treatment options are to use a second TNF inhibitor or a biologic that does not target TNF, i.e. abatacept, rituximab or tocilizumab. No data are available that could be used to estimate the proportion of patients likely to benefit from treatment with tocilizumab at this stage of the disease. It should be noted that those patients who received tocilizumab as a 2nd line therapy cannot receive it as a 3rd line therapy.

The population of patients in whom TNF inhibitors have failed and who are likely to be treated with tocilizumab is therefore between 6,000 and 8,000 patients.

Conclusion

On the basis of these data, the target population for ROACTEMRA as monotherapy is included in the total target population for ROACTEMRA which is estimated as:

- **19,500 to 26,000 for patients who responded inadequately to previous therapy with a DMARD, including MTX;**
- **6,000 to 8,000 for patients who have had an inadequate response or intolerance to disease-modifying anti-rheumatic drugs including at least one TNF inhibitor.**