HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 September 2009

ROACTEMRA 20 mg/ml concentrate for solution for infusion
Pack of 1 bottle of 4 ml (CIP: 574 643.1)
Pack of 1 bottle of 10 ml (CIP: 574 644.8)
Pack of 1 bottle of 20 ml (CIP: 574 645.4)

Applicant : ROCHE

tocilizumab

ATC Code: L04AC07

List I
Medicinal product reserved for hospital use.
Prescription restricted to internal medicine or rheumatology specialists.
Medicinal product requiring special surveillance during treatment.

MA date: 16 January 2009 (centralised procedure)

Reason for request: Inclusion on the list of medicinal products approved for use by hospitals.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

tocilizumab

1.2. Background

Tocilizumab is a recombinant humanised monoclonal anti-IL-6 receptor antibody. It is the first of a new therapeutic class targeting interleukin-6, indicated in the treatment of rheumatoid arthritis (RA).

1.3. Indications

"ROACTEMRA combined with methotrexate (MTX), is indicated for the treatment of, moderate to severe active rheumatoid arthritis (RA) in adults who have either responded inadequately to,or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs)[1] 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".

1.4. Dosage

"The recommended dosage is 8 mg/kg body weight once every four weeks; the dosage must not be lower than 480 mg. Doses above 1.2 g have not been evaluated in clinical studies.

Dose adjustments due to laboratory abnormalities

•Liver enzyme anomalies

ALT/AST value	Recommended action
> 1 to 3 x upper limit of normal (ULN)	Dose modify concomitant MTX if appropriate For persistent increases in this range, reduce ROACTEMRA dose to 4 mg/kg or interrupt ROACTEMRA until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate.
> 3 to 5 x ULN (confirmed by repeated dosages)	Interrupt ROACTEMRA dosing until < 3 x ULN When value reach < 3 x ULN, resume ROACTEMRA at 4 mg/kg or 8 mg/kg dose For persistent increases > 3 x ULN, discontinue ROACTEMRA
> 5 x ULN	Discontinue ROACTEMRA

[1] The term disease-modifying anti-rheumatic drug is usually used to describe a drug that has a delayed action on symptoms and in theory an effect on the progress of the disease, particularly X-ray structural damage. Disease-modifying anti-rheumatic drugs (DMARDs), as opposed to biotherapies (TNF inhibitors, rituximab, abatacept, tocilizumab, etc.) include MTX (DMARD of choice in RA), leflunomide, sulfasalazine, hydroxychloroquine, gold salts, azathioprine, D-penicillamine and tiopronin

• Low absolute neutrophil count

Number of neutrophils (cells x 10^6/l)	Recommended action
> 1,000	Maintain dose
500 < neutrophils < 1,000	Interrupt ROACTEMRA When neutrophils increases > 1,000 x 10^6/l, resume ROACTEMRA at 4 mg/kg and increase to 8 mg/kg, as clinically appropriate
< 500	Discontinue ROACTEMRA

•Low platelet count

Platelet count (cells//µl)	Recommended action
50,000 < platelets < 100,000	Interrupt ROACTEMRA dosing When platelet count > 100,000/µl, resume ROACTEMRA at 4 mg/kg and increase to 8 mg/kgas clinically appropriate
< 50,000	Discontinue ROACTEMRA

Special populations

Paediatric patients: ROACTEMRA is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Elderly patients: No dose adjustment is required for patients aged 65 years and older.

Renal impairment: No dosage adjustment is necessary for 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.

Hepatic impairment: ROACTEMRA has not been studied in patients with hepatic impairment. Therefore, no dose recommendation can be made".

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L: Antineoplastic and immunomodulating agents
L04: Immunosuppressants
L04A: Immunosuppressants
L04AC: Interleukin inhibitors
L04AC07: tocilizumab

2.2. Medicines in the same therapeutic category

Tocilizumab is the first of a new therapeutic class of biotherapies targeting interleukin-6, indicated in the treatment of RA.

2.3. Medicines with a similar therapeutic aim

RA with inadequate response or intolerance to disease-modifying antirheumatic drugs (DMARDs)[2]

- combined with MTX:
  - TNF-alpha inhibitors: HUMIRA - adalimumab, ENBREL - etanercept, REMICADE- infliximab
  - interleukin-1 receptor antagonist: KINERET – anakinra

- in monotherapy:
  - TNF-alpha inhibitors: HUMIRA - adalimumab, ENBREL – etanercept.

RA with inadequate response or intolerance to one or more TNF inhibitors

- combined with MTX:
  - MABTHERA – rituximab (only severe RA)
  - ORENCIA – abatacept

- in monotherapy: none.

Table 1. Comparison of indication wording for ROACTEMRA compared to other biotherapies

Products	MA indications
ROACTEMRA (tocilizumab) Monoclonal interleukin-6 antibody	Moderate to severe RA: - combined with MTX • refractory to at least one DMARD or • refractory to at least 1 TNF inhibitor - in monotherapy when intolerance or inadequate response to MTX • refractory to at least one DMARD or • refractory to at least 1 TNF inhibitor
ORENCIA (abatacept) T-cell co-stimulation inhibitor	Combined with MTX, indicated in the treatment of moderate to severe active RA in adult patients who had an inadequate response or intolerance to other disease-modifying drugs including one or more TNF inhibitor therapies. A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept with MTX.
MABTHERA (rituximab) Monoclonal B-cell antibody	MabThera in combination with MTX is indicated for the treatment of adult patients with severe active rheumatoid arthritis who had an inadequate response or intolerance to other disease-modifying drugs, including one or more TNF inhibitor therapies.

ENBREL (etanercept) Soluble tumour necrosis factor (TNF) receptor	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 antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate . Enbrel can be given as a 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..
REMICADE (infliximab) Monoclonal TNF antibodies	Remicade, in combination with methotrexate, is indicated for: the reduction of signs and symptoms as well as the improvement in physical function in: adult patients with an active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate adult patients with a severe, active and progressive disease not previously treated with methotrexate or other DMARDs. A reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated in these patient populations.
HUMIRA (adalimumab) Monoclonal TNF antibodies	HUMIRAin combination with methotrexate, is indicated for: the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying 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.
KINERET (anakinra) Interleukin-1 receptor antagonist	KINERET is indicated in the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with inadequate response to methotrexate alone.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The company has submitted five randomised, double-blind controlled studies evaluating the efficacy of tocilizumab (TCZ) - ROACTEMRA in reducing signs and symptoms of RA.
A total of 4,211 patients aged 18 years and older, diagnosed with active RA according to ACR criteria[3] and with at least 8 tender joints and 6 swollen joints were included in these studies.
The patients included:

- had shown inadequate response to one or more DMARD in the OPTION[4], TOWARD[5] and LITHE[6] studies,
- had shown inadequate response to one or more TNF inhibitor (RADIATE study[7]),
- had not been treated with MTX within 6 months prior to randomisation and had not discontinued previous MTX treatment as a result of intolerance or lack of efficacy * – AMBITION study[8].

The methodologies of these five studies are described in table 2 below.

[3] ACR (American College of Rheumatology): this score assesses the response to treatment. It takes into the tender joints count, the swollen joints count, the patient's-assessment of pain, the patient and the physician's global assessment of disease activity, the functional status and the biological inflammation.
[4] S Smolen et al. Effect of inteleukin-6-receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. Lancet 2008;371:987-997.
[5] Genovese MC. et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying anti-rheumatic drugs. Arthritis rheum 2008;58;(10):2968-2980.
[6] Not published; available solely as abstract
[7] Emery P. et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biologicals: results from a 24 week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67;1516-1523.
[8] Stones G. et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. Ann Rheum Dis 2009

Table 2. Summary of 5 phase III studies evaluating the efficacy of ROACTEMRA in RA

Study	Study type	Patients N	Population studied / inclusion criteria	Treatment regimens	Primary endpoint
OPTION WA 17822	randomised, placebo-controlled double-blind	623	**Adult patients with moderate to severe active RA for at least 6 months** **Who had received MTX at stable dose within at least 8 weeks and who had previously experienced an inadequate response to treatment with MTX**	**Combined with MTX** (oral or parenteral, 10 to 25 mg x 1/week): - TCZ 8 mg/kg + **MTX** - n= 205 - TCZ 4 mg/kg + **MTX** - n= 214 - Placebo + **MTX** - n= 204	ACR 20 at W24
LITHE WA 17823	randomised, placebo-controlled double-blind	1196		**Combined with MTX** (10 to 25 mg x1/week): TCZ 8 mg/kg + **MTX** - n= 401 TCZ 4 mg/kg + **MTX** - n= 401 Placebo + **MTX** - n= 394	ACR 20 at W24 X-ray assessment W52 and W104 Physical function at W52 to W104
TOWARD WA 18063	randomised, placebo-controlled double-blind	1220	**Adult patients with moderate to severe active RA for at least 6 months** **Who had received DMARDs* at stable dose within at least 8 weeks and who had previously experienced an inadequate response to treatment with DMARDs**	**Combined with DMARD*** (stable dose) TCZ 8 mg/kg + **DMARD** - n= 805 Placebo + **DMARD** -n= 415 **DMARDs given**: MTX: 73.6 to 76%, chloroquine: 19.9 to 20.5%, Sulfasalazine: 13.2 to 14%, Leflunomide: 12 to 15.7%, gold salts: 0.2 to 0.7%, azathioprine 2.2%	ACR 20 at W24
RADIATE WA 18062	randomised, placebo-controlled double-blind	499	**Adult patients with moderate to severe active RA for at least 6 months** **Who had received MTX at stable dose within at least 8 weeks and who had previously experienced an inadequate response to treatment with at least one TNF inhibitor**	**Combined with MTX** (10 to 25 mg x1/week): TCZ 8 mg/kg + **MTX** (n= 175) TCZ 4 mg/kg + **MTX** (n= 163) Placebo + **MTX** (n= 160)	ACR 20 at W24
AMBITION WA 17824	Randomised, MTX controlled double-blind, Non-inferiority study	673	**Adult patients with moderate to severe active RA for at least 3 months not treated with MTX within the 6 months prior to randomisation and who had not discontinued MTX treatment due to intolerance or lack of efficacy over the 6 months prior to randomisation**	**In monotherapy:** - TCZ 8 mg/kg + placebo - MTX (dose of 7.5 mg to 15 mg/week then 20 mg/week according to clinician) + placebo	ACR20 at W24

*Disease-modifying antirheumatic drugs including methotrexate (MTX), sulfasalazine, leflunomide, chloroquine/hydroxychloroquine, gold salts, etc.
TCZ: tocilizumab

Results: (ITT analysis)

3.1.1. Efficacy of tocilizumab combined with a DMARD

- **In patients not responding to at least one DMARD (OPTION, LITHE and TOWARD studies)**

➢ Characteristics of patients included in the three studies.

The initial patient characteristics were similar in the three studies. Mean age was around 52 years, mean weight 72 kg and mean time since onset of RA was 7 to 10 years. The patients had very active RA (mean DAS 28[9] of around 7), with a mean of 30 tender joints, 19 swollen joints and a mean HAQ[10] disability index of around 1.5. The prior disease-modifying drugs are described in table 3.

Table 3. History of DMARDs at baseline into OPTION, LITHE and TOWARD studies – patients with inadequate response to one or more DMARD

	OPTION			**LITHE**			**TOWARD**	
	TCZ 8 mg/kg +MTX	TCZ 4 mg/kg +MTX	Pbo +MTX	TCZ 8 mg/kg +MTX	TCZ 4 mg/kg + MTX	Pbo +MTX	TCZ 8 mg/kg +DMARD	Pbo +DMARD
MTX (%)	100	100	99	100	99.7	100	76	73.6
Mean MTX dose mg/week	14.5	14.7	14.8	15.4	14.9	14.9	14.7	14.9
DMARD other than MTX (%)	74.8*	77.8*	77*	75.4	78.4	71.	65.3	67.9
TNF inhibitor (%)	5	10	9	10.8	11.8	11.5	17.3	14.7

DMARD: disease-modifying antirheumatic drug

* corresponding to prior DMARDs other than MTX/TNF inhibitors in clinical report

➢ Primary endpoint results:

In each of these three studies, the proportion of ACR 20[11] responders was statistically higher with TCZ administered at doses of 4 and 8 mg/kg every 4 weeks combined with a DMARD than with a DMARD alone; see Table 4 below.

[9] The DAS (Disease activity score) is a validated score measuring RA activity. It is calculated based on 28 joints and counts the number of tender joints, the number of swollen joints, and the patient's assessment of pain intensity and sedimentation rate ESR or C Reactive Protein - CRP. The disease is very active if the score is greater that 5.1 and inactive if the score is below 2.6. It is also used as a criterion for clinical remission; the RA is considered to be in remission when the DAS28 is below 2.6.

[10] Health Assessment Questionnaire assessing functional incapacity, HAQ >2 = severe disability, HAQ <1 = minor disability, decrease in HAQ ≥ 0.22 = clinically significant response. This questionnaire is completed by the patient.

[11] The ACR 20 response corresponds to a 20% improvement in the number of swollen and tender joints and a 20% improvement in at least three of the following:

- ESR or CRP (C-Reactive Protein)
- disease activity assessed by patient using VAS,
- disease activity assessed by physician using VAS,
- pain assessed using VAS,
- disability index
-

Table 4. Proportion of patients achieving a response of ACR 20 at 24 weeks (primary endpoint) in the OPTION, LITHE and TOWARD studies

	TCZ 8 mg/kg +DMARD	TCZ 4 mg/kg* +DMARD	Placebo + DMARD
OPTION	58.5%**	47.90%**	26.50%
LITHE	56.30%**	50.60%**	27%
TOWARD* **	60.8%**	_____	24.5%

*the MA-recommended dosage is 8 mg/kg
** p<0.0001 vs. placebo + DMARD. DMARD = disease-modifying anti-rheumatic drug
*** in the TOWARD study, TCZ was studied in combination with MTX (73 to 76%) or a DMARD other than MTX; the aim of this study was to obtain the indication "in combination with DMARDs" but the EMEA did not grant this indication due to the low number of patients treated with a DMARD other than MTX

- Other primary endpoint in the LITHE study – total Sharp Genant score[12]

The effect of TCZ 8 mg/kg combined with MTX on reducing the joint damage was also evaluated as a primary endpoint in the LITHE study, using the total Sharp-Genant score at 52 weeks. X-ray progression was statistically lower in the groups treated with TCZ 8 mg/kg + MTX than in the group treated with placebo + MTX, p<0.0001.

Table 5. Mean X-ray changes over the 52 weeks of the LITHE study

	TCZ 8 mg/kg + MTX N = 398	Placebo + MTX (+TCZ from week 24) N = 393
Total Sharp-Genant score	0.29 *	1.13
Erosion score	0.17 *	0.71
Joint narrowing score	0.12 **	0.42

** p ≤ 0.0001 ** p < 0.005*

- Secondary endpoint results:

TCZ 8 mg/kg combined with a DMARD was also superior to the DMARD alone for the secondary endpoints in each of the three studies; see table 6.

Table 6. Secondary endpoint results of OPTION, LITHE and TOWARD studies

	OPTION		**LITHE**		**TOWARD**	
	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + DMARD	Placebo + DMARD
	N=205	N=204	N=398	N=393	N=803	N=413
ACR 50	44% *	11%	32% *	10%	38% *	9%
ACR 70	22% *	2%	13% *	2%	21% *	3%
Remission (DAS28<2.6)	28% *	1%	33% *	4%	30% *	3%

*p<0.0001. DMARD = Disease-modifying anti-rheumatic drugs including MTX, sulfasalazine, leflunomide, chloroquine/hydroxychloroquine, gold salts, etc. MTX: methotrexate

[12] Radiographic score evaluating joint damage. 14 joints in the hands, 6 in the feet are scored 0 to 98 for damage. Thirteen joints in the hands are scored 0 to 104 for narrowing. The total score therefore varies between 0 and 200. An increase in SST of one unit indicates the onset of joint bone erosion. A 7-point increase indicates destruction of almost the entire joint.

- **<u>Patients not responding to at least one TNF inhibitor (RADIATE study)</u>**

  - Patient characteristics (see Table 7)

Table 7. Baseline patient characteristics in RADIATE study

Baseline characteristics	TCZ 8 mg/kg + MTX N=175	TCZ 4 mg/kg + MTX N=163	Placebo + MTX N=160
Age (Mean in years)	53.9	50.9	53.4
Weight (Mean in kg)	74.3	76.4	75.4
Time since onset of RA (mean in years)	12.59	10.98	11.36
History of MTX treatment (%)	100	100	100
Mean dose of MTX in mg/week	15.7	16.2	16.5
History of DMARDs other than MTX (%)	81.7	81.6	83.8
History of TNF inhibitor treatment (%)	100	99.4	100
Number of prior TNF inhibitors (n,%)			
1	85 (50%)	75 (47%)	67 (42%)
2	55 (32%)	66 (41%)	69 (44%)
3 or more	30 (18%)	20 (12%)	22 (14%)
Positive RF number (%)	134 (79%)	117 (73%)	118 (75%)
DAS28 (mean score)	6.80	6.78	6.80
Tender joint count (TJC) (mean)	31.7	31.3	30.4
Swollen joint count (SJC) (mean)	18.9	19.5	18.9
ESR (mean in mm/h)	49.1	51.3	54.6
CRP (mean in mg/dL)	2.80	3.11	3.70
HAQ (mean)	1.7	1.7	1.7

  - Primary endpoint results

The proportion of ACR 20 responders at 24 weeks was significantly higher in the TCZ 8 mg/kg + MTX (50%) and TCZ 4 mg/kg + MTX groups (30.4%) than in the placebo + MTX group (10.1%), p< 0.0001.
The mean MTX dose in this study was in line with the SPC, between 15.6 and 16.5 mg/week over the 24 weeks of the study.

  - Secondary endpoint results

TCZ 8 mg/kg + MTX was also superior to MTX + placebo for the secondary endpoints (see table 8).

Table 8. Secondary endpoint results in RADIATE study (ITT population)

Endpoints	TCZ 8 mg/kg + MTX N=170	TCZ 4 mg/kg + MTX N=161	Placebo + MTX N=158
ACR 50 (%)	28.8*	16.8*	3.8
ACR 70 (%)	12.4*	5.0 (p=NS)	1.3
Remissions (DAS28<2.6) (%)	30.1*	7.6 (p=NS)	1.6

*p≤ 0.0001

3.1.2. Efficacy of tocilizumab in monotherapy – non-inferiorty study versus MTX (AMBITION)

AMBITION Study

The aim of this randomised, double-blind, non-inferiority, controlled study was to evaluate the efficacy of TCZ in monotherapy compared to MTX efficacy in reducing signs and symptoms of active RA.

The patients included were adults suffering from RA for the past 3 months at least. They should not have been given MTX within the 6 months prior to randomisation and should not have stopped MTX treatment due to intolerance or lack of efficacy.

At baseline (see table 9), 66% of patients were new to MTX and 33% had been treated with MTX. The patients were divided into 2 groups and were given either TCZ 8 mg/kg intravenously every 4 weeks, or MTX per os with an increase in weekly dose of 7.5 mg to 20 mg over an 8-week period. The mean dose of MTX during the study was 15.5 mg/week in the MTX monotherapy group.

Table 9. Baseline patient characteristics in AMBITION study - PP population

Baseline characteristics	TCZ 8 mg/kg N=265	MTX N=259
Age (mean in years)	51.1	50.1
Weight (mean in kg)	73.4	72.6
Time since onset of RA (mean in years)	6.43	6.31
DAS28 (mean score)	6.779	6.777
Mean swollen joint count (SJC)	19.3	18.9
Mean tender joint count (TJC)	32.2	31.1
HAQ (mean)	1.6	1.5
Proportion of patients new to MTX	176 (66%)	171 (66%)
History of DMARD treatment excluding MTX	171 (59.4%)	153 (53.9%
History of TNF inhibitors	24 (8.3%)	21 (7.4%)

Primary endpoint: ACR 20 response rate at week 24. It was hypothesised that TCZ would be considered non-inferior to MTX if the lower 95% confidence interval limit of the difference between the two treatments was greater than 0.12, without any reason (PP analysis). A superiority test (ITT analysis) could be conducted if non-inferiority was demonstrated.

Results:

TCZ 8 mg/kg demonstrated its non-inferiority (PP analysis) compared to 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 to 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, $p<0.0001$.

3.1.3. Efficacy results for TCZ after 24 weeks

In a blind extension phase of the LITHE study (patients who had an insufficient response to MTX), the proportion of ACR 20 responders was maintained at 52 weeks: 55.8% in the TCZ + MTX group, compared to 24.7% in the MTX group, $p<0.0001$. A total of 15 patients discontinued treatment due to lack of efficacy, of which 12 in the MTX + placebo group.

Three open-label extensions to 5 years are underway for the patients included in the 5 efficacy studies.

3.2. Comparative data comparing versus other biotherapies

No studies have directly compared TCZ with other biotherapies available for the treatment of RA. The company proposes an indirect comparison of TCZ with other RA biotherapies[13]. This

[13] not published, conducted by REES (health economics evaluation network)

indirect comparison is methodologically suitable. However, the low number of studies available on patients with inadequate response to TNF inhibitors limits the use of models enabling the heterogeneity of the studies to be taken into account (random effects model), despite these models being preferable. Overall, the authors' findings are acceptable: TCZ is not significantly superior to other biotherapies.

3.3. Safety

The analysis of the safety of ROACTEMRA (tocilizumab –TCZ) took into account the data from controlled clinical studies and extension phases, and also the data from the Japanese postmarketing surveillance study.

3.3.1 Clinical trial safety

A total of 3,778 patients received at least one dose of TCZ 4 mg/kg or 8 mg/kg. In the controlled studies, 3% of patients discontinued treatment due to undesirable effects with placebo + DMARDs, compared to 5% with TCZ.
The most frequent adverse drug reactions with TCZ (frequency ≥ 5 %) were: upper respiratory tract infections, nasopharyngitis, headaches, hypertension and increased ALT.

In the long-term safety population (core and extensions studies), the rate of serious infections observed with TCZ + DMARDs was 3.9 events for 100 patient year exposure. Reported serious infections included pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis.

In the controlled studies, complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess, have been reported uncommonly (≥ 1/1,000, < 1/100) with TCZ.

Adverse events associated with infusion (selected events occurring during or within 24 hours of the infusion, mainly hypertension but also headaches and skin reactions) in 6.9% of patients in the TCZ 8 mg/kg + DMARD group and 5.1% of patients in the placebo + DMARD group.

Appreciatively 24% of patients receivingTCZ in the clinical studies experienced a sustained elevation in total cholesterol ≥ 6.2 mmol/l and 15% experienced a sustained increase in LDL cholesterol ≥ 4.1 mmol/l. The SPC recommends evaluating lipid parameters 4 to 8 weeks after initiating TCZ treatment.

Transient elevation in ALT/AST > 3 x ULN were observed in 2.1% of patients treated with TCZ 8 mg/kg monotherapy compared to 4.9% of patients on MTX and in 6.5% of patients who received TCZ 8mg/kg + DMARDs, compared to 1.5% of patients on placebo + DMARDs.

Hypersensitivity requiring treatment discontinuation was reported in a total of 13 out of 3,778 patients treated with TCZ (0.3%) during the controlled and open label clinical studies.

The clinical data are insufficient to assess the precise risk of malignancies related to TCZ. Long-term EMEA safety evaluations are on going.

The risk management plan incorporates the monitoring of identified and potential risks:
"Identified risks:

- severe infections,
- serious hypersensitivity reactions,
- complications of diverticulitis.

Potential risks:

- neutropenia,
- thrombocytopenia,
- elevated liver transaminases,
- elevated lipids,
- the immunogenicity of ROACTEMRA,
- malignancies,
- risk of demyelinisation,
- effects on CYP 450 liver enzymes."

3.3.2 Further safety data from the Japanese postmarketing surveillance sudy – CHMP report of July 23, 2009

The CHMP analysed 318 cases of serious adverse effects reported with tocilizumab in 5,426 patients with rheumatoid arthritis, monitored (exposure duration 2,668 patient year exposure) for the purpose of a Japanese postmarketing surveillance registry. The analysis of this data did not modify the product's efficacy/safety balance.

3.4. Conclusion

The efficacy and safety of ROACTEMRA (tocilizumab - TCZ) combined with MTX and in monotherapy for the treatment of moderate to severe active RA in adults patient who have either responded inadequately to a DMARD or a TNF inhibitor were evaluated in five randomised, double-blind controlled clinical studies including 4,211 patients.

In those patients who have responded inadequately to disease-modifying anti-rheumatic drugs (three studies) the proportion of ACR 20 responders at 24 weeks (primary endpoint) was higher in the TCZ 8 mg/week + DMARD group (59.20%) than in the placebo + DMARD group (25.80%), $p<0.0001$ – pooled analysis of three studies: OPTION, LITHE and TOWARD.

In those patients who have responded inadequately to TNF inhibitors (RADIATE study) the proportion of ACR 20 responders at 24 weeks (primary endpoint) was higher in the tocilizumab 8 mg + MTX group (50%) than in the placebo + MTX group (10%), $p<0.0001$.

In monotherapy, in patients who have not received MTX over the 6 months prior to randomisation (66%) and have not discontinued MTX due to lack of efficacy or intolerance, TCZ was not inferior to MTX in terms of ACR 20 response (difference of 0.21 95%CI [0.13; 0.29]. Its superiority over MTX was also demonstrated by ITT analysis: the proportion of ACR 20 responders at 24 weeks was 69.9% with TCZ compared to 52.5% with MTX, $p<0.0001$.

The efficacy of TCZ on reducing the progression of structural joint damage was evaluated in the LITHE study (n=1,196), on patients responding inadequately to MTX. The total Sharp-Genant score progression was significantly lower in patients treated with TCZ + MTX (0.29) than in those treated with MTX + placebo (1.13), $p<0.0001$.

There is no study available directly comparing tocilizumab to other biotherapies. However, a meta-analysis conducted by the company demonstrated that the efficacy of TCZ is comparable to that of other biotherapies, both for patients who have responded inadequately to DMARDs and those who have responding inadequately to TNF inhibitors.

An analysis of the adverse effects reported with TCZ throughout a Japanese postmarketing surveillance programme was conducted by the CHMP. The analysis of this data did not modify this product efficacy/ safety ratio.

The risk management plan incorporates the monitoring of identified and potential adverse effects with ROACTEMRA.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Rheumatoid arthritis is a serious incapacitating chronic disease.
The efficacy/adverse effects ratio for this medicinal product is high.

Public health benefit:

Rheumatoid arthritis, a serious incapacitating chronic disease, represents a substantial public health burden. The burden of the subpopulation liable to benefit from the treatment is moderate.

There are alternative rheumatoid arthritis treatments. However, there is still a therapeutic need but which does not constitute a public health need.

Given the absence of any additional impact compared to other biotherapies (absence of direct comparison, non-inferiority according to meta-analysis), and long-term safety uncertainties, ROACTEMRA is not expected to have any benefit on public health.

There are alternative treatments.
The actual benefit of ROACTEMRA is substantial.

4.2. Improvement in actual clinical benefit

The Transparency committee feels 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 DMARDs including methotrexate at the maximum tolerated dose, ROACTEMRA does not provide any improvement in actual benefit (IAB V) compared to 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.

4.3. Therapeutic use

The current management of rheumatoid arthritis consists of prescribing a fast-acting anti-inflammatory drug (NSAIDs, corticosteroids) and a disease-modifying drug in order to induce remission in clinical and laboratory parameters. Methotrexate is one of the most effective disease-modifying therapies for rheumatoid arthritis. It may be associated with other disease-modifying therapies provided there is strict clinical and laboratory monitoring. The maximum tolerated dose is 25 mg per week, but it must be adjusted to the clinical situation and tolerance of the treatment. Parenteral (IM and SC) forms can be used in case of insufficient response to the oral form.

If methotrexate produces an inadequate response or is contraindicated, another disease-modifying drug is used in monotherapy or combined with a TNF inhibitor, depending on the clinical/laboratory characteristics of the disease and the patient's physiopathological predisposition.
Specialist opinion, however, is that approximately 30% of patients have an inadequate or insufficient response to TNF inhibitors after 2 years.

When patients are refractory to TNF inhibitors, possible alternatives are:
- the use of another TNF inhibitor,
- the use of one of the two "third-line" biotherapies available: rituximab (a B cell monoclonal antibody) or abatacept (T cell co-stimulation inhibitor).

Therapeutic use of ROACTEMRA in RA

In RA patients refractory to DMARDs, the therapeutic use of ROACTEMRA compared to TNF inhibitors is difficult to determine given the absence of studies directly comparing ROACTEMRA to these drugs and due to the lack of follow-up efficacy and long-term safety data compared to TNF inhibitors.
However, according to the results of an indirect meta-analysis comparison, the efficacy of ROACTEMRA is similar to that of TNF inhibitors. The long-term safety and efficacy data for ROACTEMRA is nonetheless limited (treatment duration and low number of patients exposed, long-term consequences of lipid anomalies caused by ROACTEMRA).

The decision whether to prescribe ROACTEMRA will depend on the patient's predisposing factors, the patient's wishes and the choice of the prescriber.

In RA patients refractory to one or more TNF inhibitors, no studies have directly compared ROACTEMRA to other products with the same indication, i.e. abatacept and rituximab. However, the results of a meta-analysis have demonstrated that the efficacy of these biotherapies was similar. Consequently, the choice between these three products can be based on the type of administration and any contraindications.
These three products are contraindicated in the event of severe infections. Furthermore, MABTHERA carries a specific contraindication in the event of "severe heart failure or severe uncontrolled heart disease".

In these two indications, ROACTEMRA can be used in monotherapy in cases of intolerance to MTX, or when it is unsuitable to continue MTX treatment.

Reminder : ROACTEMRA has not been granted a MA for patients not previously treated with a disease-modifying anti-rheumatic drug, including MTX.

Product name	**Dosage and method of administration in RA**
KINERET	Combined with MTX 100 mg once daily as a subcutaneous injection
ENBREL 25 and 50 mg	Combined with MTX or in monotherapy 25 mg twice weekly as a subcutaneous injection or 50 mg once weekly
HUMIRA	Combined with MTX or in monotherapy 40 mg every two weeks as a subcutaneous injection
REMICADE	Combined with MTX 3 mg/kg administered by intravenous infusion over 2 hours followed by further 3 mg/kg infusions in weeks 2 and 6 after the first infusion, and then every 8 weeks.
MABTHERA	Combined with MTX 1,000 mg by IV infusion followed by a second 1,000 mg IV infusion two weeks later. The gap between two courses of treatment should not be less than 16 weeks.
ORENCIA	Combined with MTX ORENCIA must be administered by a 30 minute IV infusion (dose according to weight). After the first infusion, ORENCIA must be administered at weeks 2 and 4 then every 4 weeks.
ROACTEMRA	**Combined with MTX or in monotherapy** **8 mg/kg administered once every four weeks, through a 1-hour IV infusion.**

4.4. Target population

According to the wording of its MA indication, the target population of ROACTEMRA is comprised of patients who have responded inadequately or who are intolerant to one or more DMARD and those refractory to one or more TNF inhibitors.

Estimated target population of ROACTEMRA for the subpopulation of patients refractory to DMARDs

The prevalence of rheumatoid arthritis in France can be estimated based on the Guillemin and Saraux study of 2001[14] as 0.31% of the population over the age of 18.
By applying this data to the INSEE 2009 data (48,750,000), the population of RA patients in France can be estimated as 151,000 patients.
Furthermore, based on the CNAMTS[15] data on the number of RA patients classified as having a chronic condition, after adjustments, the population of patients with serious progressive RA in 2009 can be estimated as around 200,000.

Indeed, according to CNAMTS data, the number of people with serious progressive RA classified as having a chronic condition was 150,032 in 2007; an increase of 6.2% was observed between 2005 and 2006, and between 2006 and 2007, an increase of 6.8%. If we presume that the increase in chronic rheumatoid arthritis patients continued to increase at a rate of 6% per year, the number of chronic serious RA patients in 2009 is around 168,576.

Considering that the CNAMTS data covers 88% of the French population, the number of people suffering from serious progressive rheumatoid arthritis in France in 2009 can be estimated as 191,000.

The expert opinion is that 45% to 60% of these patients are currently being treated with methotrexate. Around 18% of patients treated with methotrexate drop out of treatment (expert opinion), i.e. between 16,000 and 20,000 patients.
Going on the principle that MTX is the DMARD of choice, it can be estimated that the population of RA patients refractory to at least one DMARD and liable to be treated by ROACTEMRA is at most between 16,000 and 20,000 patients.

Estimated target population of ROACTEMRA for the subpopulation of patients refractory to TNF inhibitors

Based on the above data, the population of RA patients refractory to at least one DMARD and liable to be treated with TNF inhibitors can be estimated at between 16,000 and 20,000 patients.
According to experts, 30% of patients treated with TNF inhibitors have an inadequate response or intolerance to these treatments, i.e. between 5,000 and 7,000 patients roughly.

For these patients, the treatment options are a second TNF inhibitor or a third-line biotherapy with abatacept, rituximab or tocilizumab. There is no data available to estimate the proportion of patients liable to benefit from treatment with ROACTEMRA at this stage of the disease. It should be noted that patients given ROACTEMRA in second-line treatment can no longer be given it in third-line treatment.
The population of patients refractory to TNF inhibitors and liable to be treated with ROACTEMRA is therefore between 5,000 and 7,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and dosages of the MA.

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

[14] Guillemin F, Saraux A. et al. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis 2005; 64 : 1427-1430.
[15] Points de repère n° 20 - November 2008 – persons suffering from a chronic condition on December 31, 2007.

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.),
- assess 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 effects, 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.