HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 May 2012

ROACTEMRA 20 mg/ml, concentrate for solution for infusion
B/1 vial of 4 ml (CIP code: 574 643-1)
B/1 vial of 10 ml (CIP code: 574 644-8)
B/1 vial of 20 ml (CIP code: 574 645-4)

Applicant: ROCHE SAS

tocilizumab
ATC code: L04AC07 (Interleukin 6 inhibitor)

List I

Medicinal product reserved for hospital use.
Prescription restricted to **paediatric**, rheumatology or internal medicine specialists.
Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation (centralised procedure): 16 January 2009

Date of last revision of Marketing Authorisation: 1 August 2011 (extension of the indication)

Reason for request: Inclusion on the list of medicines approved for hospital use in the extension of indication for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of old and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroid treatment. RoACtemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combinaison with MTX.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

tocilizumab

1.2. Indication

Rheumatoid arthritis:

Previous indication wording:

"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."

New indication wording:

Rheumatoid arthritis: "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." **(Indication non examined within the context of this opinion).**

Systemic juvenile idiopathic arthritis (new indication, which is the focus of this opinion):
"ROACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. ROACTEMRA can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX."

1.3. Dosage

"Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA or sJIA. All patients treated with ROACTEMRA should be given the Patient Alert Card."

sJIA patients:
The safety and efficacy of ROACTEMRA in patients below 2 years of age has not been established. No data are available.

The recommended posology is:
- 8 mg/kg once every 2 weeks in patients weighing ≥ 30 kg,
- or 12 mg/kg once every 2 weeks in patients weighing < 30 kg.

The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

Dose interruptions of ROACTEMRA for the following laboratory abnormalities are recommended in sJIA patients in the tables below.
If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and ROACTEMRA dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect laboratory values in sJIA, the decision to discontinue ROACTEMRA for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- *Liver enzyme abnormalities*

ALT / AST value	**Action**
> 1 to 3 x Upper Limit of Normal (ULN).	Dose modify concomitant MTX if appropriate For persistent increases in this range, interrupt ROACTEMRA until ALT / AST have normalized
> 3 x ULN to 5 x ULN	Dose modify concomitant MTX if appropriate Interrupt ROACTEMRA dosing until transaminases are < 3 x ULN and follow recommendations above for values > 1 to 3 x ULN
> 5 x ULN	Discontinue ROACTEMRA The decision to discontinue treatment with tocilizumab in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- *Low absolute neutrophil count (ANC)*

Number of neutrophils (cells x 10^9/l)	**Action**
ANC> 1	Maintain recommended dose
ANC 0,5 to 1	Interrupt ROACTEMRA dosing When ANC increases to >1X$10^{9/l}$, resume ROACTEMRA
ANC< 0,5	Discontinue ROACTEMRA The decision to discontinue RoACTEMRA in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- *Low platelet count*

Platelet count (cells x 10^3/µl)	**Action**
50 to 100	Dose modify concomitant MTX if appropriate Interrupt ROACTEMRA dosing When platelets count I >100 x10^3/µl, resume ROACTEMRA
< 50	Discontinue ROACTEMRA The decision to discontinue ROACTEMRA in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of the dose of ROACTEMRA due to laboratory abnormalities has not been studied in sJIA patients.

Available data suggest that clinical improvement is observed within 6 weeks of initiation of treatment with ROACTEMRA. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe."

Method of administration:
"After dilution, ROACTEMRA for RA and sJIA patients should be administered as an intravenous infusion over one hour.
RA Patients, ***and sJIA patients ≥ 30 kg****:*
ROACTEMRA should be diluted to a final volume of 100 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique.
For further information on dilution prior to administration, see section 6.6 of the SPC.
sJIA patients < 30 kg*:*
ROACTEMRA should be diluted to a final volume of 50 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

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

2.2. Medicines in the same pharmaco-therapeutic category

No other medicinal product in the same pharmaco-therapeutic category has marketing authorisation for the treatment of active systemic juvenile idiopathic arthritis in paediatric patients (≥ 2 years) who have had an inadequate response to a previous NSAIDs or corticosteroid treatment.

2.3. Medicines with a similar therapeutic aim

There is no other medicinal products with the same therapeutic aim, which has this specific indication for systemic JIA in failed treatment with NSAIDs and corticosteroids.

Note:
In practice, in low inflammatory polyarticular forms of systemic JIA, even though they frequently appear to be less effective than IL1 and IL6 inhibitors, and they often only have a partial effect even when administered concomitantly (methotrexate + TNF alpha inhibitor), medicinal products with marketing authorisation as disease-modifying treatments for polyarticular forms of JIA are used (expert opinions and PNDS[1]), in particular:

- classic disease-modifying anti-rheumatic drugs (DMARDs)
  Methotrexate: METHOTREXATE BELLON, METOJECT, LEDERTREXATE
- biological therapies:
  TNF Inhibitors: adalimumab (HUMIRA), etanercept (ENBREL)

The wording of their labels is not identical, and is found in the table below (Table 1. **Differences in label wording and a summary of the opinions for proprietary medicinal products with marketing authorisation for JIA.**).

1 HAS. Guide for doctors, ALD31. Juvenile Idiopathic arthritis. National diagnosis and healthcare protocol (PNDS). July 2009.

Table 1. Differences in label wording and a summary of the opinions for proprietary medicinal products with marketing authorisation for JIA.

Proprietary medicinal product	JIA Type	Age	Line of treatment	Opinion
HUMIRA Adalimumab	evolutive polyarticular JIA	**from 4 years**	Insufficient response to one or more disease-modifying treatments	21/09/2011 Substantial AB IAB V for treatment
ENBREL Etanercept	Active polyarticular JIA	**2 years and above**	Inadequate response or proven intolerance to methotrexate	02/10/2002 Substantial AB IAB II depending on treatment strategy
METHOTREXATE Bellon Methotrexate	Polyarticular forms of severe and active JIA	Not stated	Response to NSAID treatment judged as unsatisfactory.	4/01/2006 Substantial AB IAB II for treatment
METOJECT Methotrexate	Severe and active forms of polyarticular JIA	Not stated	Inadequate response to NSAIDs	14/03/2007 Substantial AB IAB IV compared with other MTX-based injectable proprietary medicinal products. For all of its indications
LEDERTHREXATE Methotrexate	Severe and active forms of polyarticular JIA	Not stated	Response to NSAID treatment judged as unsatisfactory.	18/11/2009 Substantial AB IAB V compared with other MTX-based injectable proprietary medicinal products, especially methotrexate Bellon

Other medicinal products:

Anakinra (KINERET, IL1 inhibitor) does not have marketing authorisation for JIA, but is suggested without marketing authorisation in the PNDS, based on expert opinions for forms of JIA with persistent systemic signs, as with tocilizumab (ROACTEMRA, IL 6 inhibitor).

ORENCIA (abatacept) has marketing authorisation for polyarticular JIA from 6 years (Opinion of 05/10/2011, substantial AB and IAB V in therapeutic use) but is not recommended in the PNDS or in reference publications for systemic JIA.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Efficacy data for tocilizumab (ROACTEMRA) in the treatment of systemic JIA is primarily based on the results from the TENDER Study (WA18221) versus placebo; the choice of placebo as a comparator medicine being justified due to the absence of a medicinal product with a marketing authorisation for the treatment of systemic JIA.
Results were also provided from studies carried out in Japan, a country where ROACTEMRA has had marketing authorisation for systemic JIA since April 2008:

- MRA011JP - phase II open-label study (n =11);
- MRA316JP - phase III study (n=56);
- MRA317JP - open-label extension of MRA011 and MRA 316 JP (n=60) and;
- MRA324JP - open-label phase III study (n=82) carried out to allow access to the product prior to commercialisation in Japan, the primary efficacy endpoint being tolerance. The results from this study are presented in section 3.2.

- **TENDER study (WA18221)[2]**

Primary objective:

The primary objective of this study was to evaluate the efficacy and safety of tocilizumab (TCZ) in children aged from 2 to 17 years, with active systemic JIA and who have had an inadequate response to NSAIDs or corticosteroid treatment, either due to the occurrence of a side effect or a lack of efficacy.

Methodology:

This study included 3 phases.

The first phase, which lasted for 12 weeks, controlled versus placebo, randomised and double blind, was followed by two open-label phases, one lasting 92 weeks followed by another lasting 156 weeks (3 years), during which all patients received TCZ. The follow-up phase is still in progress.

Inclusion and non-inclusion criteria

In the randomised phase 112 patients were included, aged from 2 to 17 years, with systemic JIA that was persistently active for at least 6 months prior to the first selection appointment and with an inadequate response to NSAIDs or corticosteroid treatment, or due to the occurrence of a side effect, or due to a lack of efficacy. Randomisation was stratified based on weight, the duration of the disease, the initial corticosteroid dose and the use of MTX.

Those not included were patients receiving treatment with a DMARD, other than MTX, or a biological therapy (abatacept, adalimumab, anakinra, etanercept or infliximab). Patients previously treated by these products, as well as those previously or currently being treated with MTX, could be included.

Treatments received:

Patients received an appropriate dosage of TCZ every two weeks for twelve weeks based on their weight: 12 mg/kg for children weighing < 30 kg (n = 38), and 8 mg/kg for those weighing ≥ 30 kg (n = 37) or the placebo (n = 37). No adjustment to the dose allocated during randomisation was possible during the controlled phase, even if the patient lost or gained weight during this time.

2 43 centres in 17 countries, no investigation centre in France

Note: the recommended dose for adults with RA is 8 mg/kg every 4 weeks.

The primary efficacy endpoint was a composite endpoint, corresponding to the proportion of patients with an ACR[3] paediatric 30 (ACRpedi30) response and no fever at Week 12.
The ACRpedi30 response was defined as an improvement ≥ 30%, in at least 3 of the 6 criteria in the ACR paediatric score, compared with inclusion, without worsening > 30% in more than one criterion. The 6 factors are as follows:

- overall assessment of disease severity by the physican (on a visual analogue scale VAS 0 – 10 cm)
- overall assessment of the patient's general well-being by the parent (on VAS 0 - 10 cm)
- patient's functional capacity (Disability index of Childhood Health Assessment Questionnaire – CHAQ)
- number of swollen joints
- number of joints with restricted mobility
- CRP (C-reactive protein)

The absence of fever was defined as a body temperature that was never ≥ 37.5ºC during the previous 7 days.

The secondary endpoints included:

- ACR paediatric 50/70/90 responses at Week 12
- the proportion of patients with fever at inclusion and absence of fever at Week 12
- the proportion of patients with a rash at inclusion and absence of rash at Week 12
- the change, compared with inclusion, in the number of swollen joints at Week 12
- the proportion of patients receiving oral corticosteroids with an ACRpedi70 response at Week 6 or 8, who then reduced their corticosteroid dose by at least 20% without destabilisation in ACRpedi30 response or the occurrence of systemic symptoms at Week 12.

Results:

Characteristics of patients included (see table 2).

Patients included had a mean age of 10 years (± 4.6 years) in the TCZ groups and 9.1 years (± 4.4 years) in the placebo group. Overall, one third of patients treated with TCZ were ≤ 6 years of age, one third were between 7 and 12 years and the remaining third were over 12 years old. They all had an active form of the disease. Forty three percent (43%) of patients in the TCZ group and 54% of patients in the placebo group had fever during the week prior to inclusion in the study. The proportion of patients with a rash in the 14 days prior to inclusion was different in the two groups: 28% in the TCZ groups versus 49% in the placebo group. The mean CRP level was higher in the TCZ groups (200.4 mg/l) than in the placebo group (95.6 mg/l).

Before entering the study, the majority of patients had previously been treated with biological therapies, including anakinra and TNF inhibitors (84%, including 73% with TNF inhibitors in the TCZ groups, and 78%, including 70% with TNF inhibitors in the placebo group). The reasons for stopping these treatments were not collected.

Before entering the study, patients included also started treatment with oral corticosteroids (90%), NSAIDs (73%) and MTX (70% in TCZ 8 mg/kg group and 50% with TCZ 12 mg/kg and 54% with placebo) and continued with these treatments after inclusion in the study. Two patients in the TCZ groups stopped treatment with MTX during the 12 week phase, versus 20 patients in the placebo group.

3 American College of Rheumatology

Table 2. TENDER Study – Patients characteristics at inclusion

Characteristics	Placebo N=37	TCZ (8 mg/kg) N=37	TCZ (12 mg/kg) N=38	TCZ (8 mg/kg and 12 mg/kg) N=75
Mean age (years) (SD)	9.1 (4.4)	13.5 (2.9)	6.6 (3.3)	10.0 (4.6)
Mean disease duration (years) (SD)	5.1 (4.4)	6.33 (4.4)	4.03 (3.2)	5.2 (4.0)
Mean weight (kg) (SD)	31.7 (16.8)	49.7 (20.1)	20.1 (5.9)	34.7 (20.9)
Fever (during the 7 days prior to inclusion)				
Present, n (%)	20 (54%)	12 (32%)	20 (53%)	32 (43%)
Absent, n (%)	17 (46%)	25 (68%)	18 (47%)	43 (57%)
Fever (during the 14 days prior to inclusion)				
Present, n (%)	24 (65%)	15 (41%)	26 (68%)	41 (55%)
Absent, n (%)	13 (35%)	22 (59%)	12 (32%)	34 (45%)
Rash				
Present, n (%)	18 (49%)	8 (22%)	13 (34%)	21 (28%)
Absent, n (%)	19 (51%)	28 (76%)	25 (66%)	53 (71%)
CRP level (mg/l)				
Mean (SD)	95.6 (68.7)	232.23 (534.9)	169.32 (269.0)	200.4 (419.9)
Median	77.2	95.2	123.2	115.6
(Min-Max)	(1.9-302.2)	(8.7-2525.4)	(5.4-1704.9)	(5.4-2524.4)
N mean number of swollen joints (SD)	16.9 (12.9)	23.5 (16.6)	19.2 (15.2)	21.3 (15.9)
Treatments previously received and stopped prior to entry in the study				
Patients who received at least one treatment with DMARDs (%)	25 (68 %)	29 (78%)	26 (68%)	55 (73%)
Number of DMARDs, mean (SD)	1.4 (1.4)	1.6 (1.2)	1.0 (0.8)	1.3 (1.1)
Patients who received at least one treatment with MTX n (%)	20 (54%)	26 (70%)	19 (50%)	45 (60%)
Patients who received at least one treatment with a biological therapy n (%)	29 (78%)	35 (95%)	28 (74%)	63 (84%)
N biological therapies, mean (SD)	1.6 (1.3)	2.5 (1.5)	1.4 (1.1)	1.9 (1.4)
Patients who received one treatment with Anakinra, n (%)	13 (35%)	21 (57%)	20 (53%)	41 (55%)
Patients who received at least one treatment with a TNF inhibitor, n (%)	26 (70%)	31 (84%)	24 (63%)	55 (73%)
Treatments previously received and being taken at the time of entry in the study, and concomitant therapies				
Patients who received at least one treatment with NSAIDs, n (%)	27 (73%)	26 (70%)	29 (76%)	55 (73%)
Oral corticosteroids, n (%)	31 (84%)	34 (92%)	36 (95%)	70 (93%)
Previous dose of oral corticosteroids (mg/kg/day), mean (SD)	0.27 (0.17)	0.21 (0.15)	0.36 (0.17)	0.29 (0.18)
Previous dose of oral corticosteroids				
< 0.3 mg/kg/day	19 (51%)	28 (76%)	10 (26%)	38 (51%)
≥ 0.3 mg/kg/day	18 (49%)	9 (24%)	28 (74%)	37 (49%)
MTX, n (%)	26 (70%)	21 (57%)	31 (82%)	52 (69%)

SD: standard deviation

Permitted rescue treatments:

Before the end of Week 12, patients could receive a rescue treatment of TCZ in cases of:

- symptomatic serositis (increase of corticosteroid dose, over 14 or more consecutive days above the observed dose at inclusion, or administration of a dose of prednisone > 30 mg/day);
- fever persistence without infection (3 consecutive days > 38°C);
- worsening of the diseasecompared with inclusion according to ACR paediatric 30 score (ACRpedi30);

- any re-occurrence of symptomatic serositis;
- development of macrophage-activation syndrome (MAS) at Week 2 or after two weeks of treatment.

Overall 21 patients, including 20 in the placebo group, received a rescue treatment with TCZ before the end of the 12 weeks of assessment of the randomised phase due to the onset of fever or a deterioration in ACRpedi30 criteria, and were directly entered into the open-label phase. A single patient in the TCZ 8 mg/kg group had a rescue treatment, although the reason was not mentionned.

Three patients were withdrawn from the randomisation phase of the study before the end of the 12 weeks, for reasons other than those defined for receiving a rescue treatment;

- 1 patient from the placebo group and 1 patient from the TCZ group due to adverse events;
- 1 patient from the TCZ group for refusing to continue with the study.

Overall, 96% of patients from the TCZ group and 46% from the placebo group received treatment over the whole 12 weeks period of the randomised phase. Analysis of the results was carried out on an ITT basis for the 112 patients randomised.

- Primary efficacy endpoint results:

At Week 12, the superiority of TCZ over the placebo at the dosages of 8 mg and 12 mg/kg was demonstrated for the primary efficacy endpoint (ACRpedi30 + absence of fever), with an absolute difference in the proportion of responder patients compared with placebo of 61.5%. See Table 3.

Table 3. TENDER Study–primary efficacy endpoint results.

	Placebo N = 37	**TCZ 8 mg/kg N = 37**	**TCZ 12 mg/kg N = 38**	**TCZ (8 mg/kg and 12 mg/kg) N = 75**
Responder patients n (%) [95% CI]	9 (24.3%) [10.5-38.1]	28 (75.7%) [61.9-89.5]	36 (94.7%) [87.6-100.0]	64 (85.3%) [77.3-93.3]
Difference vs. placebo [95% CI]				61.5 [44.9-78.1]
p				<0.0001

As the aim of the study was to show a difference between TCZ (dose based on weight) and the placebo, was not to show a difference between each dose of TCZ and the placebo; no statistical investigations were carried out between each dose of TCZ and the placebo.

Additional analyses:

The clinical study report mentions sub-group analyses, whose level of evidence is low, which suggested that TCZ was highly effective for patients who were either previously treated or did not receive earlier treatment with MTX or other biological therapies:

- the percentage of responders for the primary efficacy endpoint (ACR 30 and fever) treated with TCZ was 94.8% for those previously treated with MTX vs. 97% for those who had never received MTX;
- the percentage of responders treated with TCZ was 90% for treatment naive patients and 95.6% for those who had received a previous biological therapy.

- Secondary endpoints results:

There was a statistically significant improvement for all the secondary endpoints in the TCZ group compared with the placebo group at Week 12, in particular those presented in table 4. The results for rash are to be interpreted with caution as the patient characteristics were not comparable at inclusion for this endpoint.

With regard to fever, clinical criteria interest for this disease, the proportion of patients with fever at inclusion and who no longer had fever at Week 12 was 35/41 in the TCZ group and 5/24 in the placebo group.

With regard to corticosteroid-sparing effet, another area of interest, it was observed that the proportion of patients receiving oral corticosteroids with a ACRpedi70 response at Weeks 6 or 8, who then reduced their corticosteroid use by at least 20% without destabilisation in ACRpedi30 response, or having any systemic symptoms Week 12, was higher in the TCZ group: 17/70 versus 1/31 in the placebo group.
These criteria were only evaluated as secondary endpoints; the results are therefore only exploratory.

Table 4. TENDER Study – Results for the secondary endpoints.

	Placebo N = 37	**TCZ (8 mg/Kg and 12 mg/kg) N = 75**	**p**
Level of ACR Paediatric response at Week 12			
ACRpedi50	10.8%	85.3%	<0.001
ACRpedi70	8.1%	70.7%	<0.001
ACRpedi90	5.4%	37.3%	<0.001
Patients with fever at inclusion and who no longer had one at Week 12	20.8%	85.4%	<0.001
Patients with a rash at inclusion and who no longer had fever at Week 12	11.1%	63.6%	0.0008
Change in the number of swollen joints	-32.7%	-70.6%	0.0012
Change in the number of joints with restricted mobility	-22.5%	-51.6%	0.0192
Patients able to reduce their corticosteroid dose by at least 20% without relapse	3.2%	24.3%	0.028

Non-comparative follow-up data showed sustained clinical response beyond 12 weeks for:

- 89.0% of patients (97/109) at Week 24;
- 86.1% of patients (93/108) at Week 36;
- 82.1% of patients (78/95) at Week 48;
- 89.3% of patients (50/56) at Week 60;
- 84.8% of patients (28/33) at Week 72.

Monitoring is still in progress, with this analysis being intermediate.

- **Additional studies**

❖ **Study MRA316JP[4] (carried out in Japan between 2004 and 2005)**

The primary objective of this study was to evaluate the efficacy and the safety of TCZ for systemic JIA in children and adolescents with intolerance or an inadequate response to corticosteroid therapy.

Patients included were aged from 2 to 19 years and had active systemic JIA.[5]

Patients had not previously received corticosteroid therapy, immunosuppressants or a DMARD in the two weeks prior to the first injection of TCZ, or a TNF inhibitor in the 12 weeks prior to treatment. The oral corticosteroid dose was stable in the 2 weeks before starting the study.

- Methodology:

This study consisted of 2 phases.

The first half of the study was an open-label phase, lasting 6 weeks, during which all patients received TCZ at a dosage of 8 mg/kg every 2 weeks. The primary efficacy endpoint was the percentage of patients with an ACRpedi30 response and CRP < 5 mg/l at Week 6.

For responder patients, this phase was followed by a second 12 weeks, double-blind, randomised phase versus placebo. The primary efficacy endpoint for this phase was the proportion of children in each group with an ACRpedi30 response and CRP < 15 mg/l at Week 12, without needing a rescue treatment.

- Results:

Fifty six (56) patients were included in the study. Among these, 6 did not complete the first phase; 2 due to intolerance, 1 for ineffective treatment, and 3 due to developing anti-TCZ antibodies.

Among the 50 patients who completed the first phase, 44 (79%) met the primary efficacy endpoint at Week 6 (ACRpedi30 response and CRP < 5 mg/l). The six non-responder children all had a body weight < 30 kg, which showed a decrease in TCZ efficacy administered at the dosage of 8 mg/kg for children with a low body weight.

Thus, forty four (44) patients were then randomised to continue with the second phase of the trial; 21 in the TCZ group and 23 in the placebo group. After randomisation, one patient in the TCZ group was excluded due to unintentional unblinding

In this second phase of the study, the superiority of TCZ over the placebo was demonstrated for the primary efficacy endpoint: at Week 12 the proportion of responders was 16/20 in the TCZ group versus 4/23 in the placebo group ($p<0.001$).

4 Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 2008 22; 371: 998-1006.

5. An active disease was defined by the presence of CRP levels ≥ 15 mg/l and an inadequate response to treatment with corticosteroid therapy for more than 3 months at a dosage ≥ 0.2 mg/kg of equivalent prednisolone.

❖ **The open-label extension phase of the Japanese studies MRA316JP4 and MRA011JP = MRA317JP**

During this open-label extension phase, 60 patients with systemic JIA who had a clinical response to TCZ during study MRA016JP described above (n =50), and during study MRA011JP[6] (n =10), were treated with TCZ every 8 weeks. The results from this extension phase were in favour of a sustained ACR 30 paediatric response, of approximately 85% between 24 and 324 weeks after the start of treatment. Given the open-label nature of the study, the scope of these results is limited.

3.2. Adverse effects

Given the different methodologies used, the safety results from the Japanese studies (non-comparative) and the TENDER pivotal study are presented separately.

- **TENDER study (WA18221)**

During the double-blind, controlled 12 weeks phase of this study, 75 children were treated with 8 or 12 mg/kg of TCZ depending on their weight. Patients were included in the open-label follow-up phase after completing these 12 weeks, or due to a worsening in their condition (a rescue treatment being required). Only results from an intermediate analysis of this extension phase at 72 Weeks are available, as this study is still in progress.

During the controlled phase of the study, adverse events (AE) were reported by 89.2% (33/37) of patients in the TCZ 8 mg/kg group, 86.8% (33/38) of patients in the TCZ 12 mg/kg group and by 62.2% (23/37) in the placebo group. The most commonly reported AEs were:

- Upper respiratory tract infections (13.3% in the TCZ groups versus 10.8% in the placebo group);
- rhinopharyngitis (10.7% in the TCZ groups versus 2.7% in the placebo group);
- headaches (9.3% in the TCZ groups versus 8.1% in the placebo group) and;
- diarrhoea (6.7% in the TCZ groups versus 2.7% in the placebo group).

The majority of these AEs were mild to moderate in nature. Serious adverse events were reported by 3/75 (4%) patients treated with TCZ (one case of bacterial arthritis, one case of urticaria accompanied by an angioedema and one case of varicella, which progressed favourably) versus none in the placebo group.

Adverse events of special interest or Serious adverse events (SAEs)

Infections:
The overall rate of infection during the comparative phase was 344.7 for 100 patient-years in the TCZ group including 11.5 for 100 patient-years for serious infections and 287.0 for 100 patient-years in the placebo group (the incidence of serious infections in patient-years for the placebo arm was not provided).

During the open-label extension phase, which is still in progress, at one year the overall rate of infection was 306.6 for 100 patient-years, including 11.3 for 100 patient-years for serious infections.

The nature of the serious infections reported was similar to those observed in patients with RA, with the addition of herpes zoster and otitis media (source - SPC). One serious case of varicella and one case of otitis were reported in the TCZ 12 mg/ml group.

6 Phase II open-label study that included 11 patients with systemic JIA and who had had an inadequate response to corticosteroids

Infusion reactions

During the 12 weeks controlled phase:

- Four percent (4%) (3/75) of patients in the TCZ group reported events during infusion (in total 5 reactions occurred during the second, third, fourth and fifth infusion) versus 2 patients in the placebo group (those who received a rescue treatment of TCZ had 3 infusion reactions during the third and fourth infusions). One event (Quincke's oedema) was considered as serious, resulting in a life-threatening prognosis, and the patient stopped the study treatment.
- Sixteen percent (16%) (12/75) of patients in the TCZ group and 5.4% (2/37) of patients in the placebo group reported an event in the 24 hours after infusion. In the TCZ group, the following events were the most commonly observed: rash, urticaria, diarrhoea, abdominal pain, arthralgia and headaches. Urticaria was considered as being serious.

Clinically significant hypersensitivity reactions associated with TCZ and requiring discontinuation of treatment were reported by 1 patient out of 112 (<1%) treated with TCZ during the controlled and the open-label extension phase of the clinical study.

Death:

No deaths attributable to TCZ occurred during the initial phase of the study. A death due to pneumothorax was reported at Week 72, but this was not linked to TCZ.

Neutropenia
At Week 12, a case of neutropenia was reported by 1 patient in the placebo group, by 2 patients in the TCZ 8 mg/kg group and by 2 patients in the TCZ 12 mg/kg group. Neutropenia led to discontinuation of treatment; however, no relationship between neutropenia and the occurrence of serious infections was established.

Gastrointestinal disorders:
At Week 12, the incidence of gastrointestinal events (diarrhoea, vomiting, abdominal pain) was 18.7% in the TCZ groups and 5.4% in the placebo group.

Immunogenicity:
The presence of anti-tocilizumab antibodies was investigated for all 112 patients at inclusion. Two patients developed anti-tocilizumab antibodies, including one who had a hypersensitivity reaction which led him to leave the study. According to the SPC, "the incidence of anti-tocilizumab antibody formation might be underestimated because of interference of tocilizumab with the assay and higher drug concentration observed in children compared to adults".

Hepatic transaminase elevations
During routine laboratory analysis in the 12 weeks controlled phase, ALT or AST elevations ≥ 3 x ULN were observed in 5% and 3% of patients in the TCZ groups respectively, and none in the placebo group. During the open-label extension phase, which is still in progress, elevations in ALT or AST ≥ 3 x ULN were observed in 12% and 4% of patients in the TCZ groups respectively.

- **Japanese studies; MRA316JP, MRA317JP, MRA324JP and MRA011JP.**

During the additional Japanese studies, 149 patients received treatment with TCZ over a median duration of 2.1 years. Among those, 28.9% received treatment for less than 1 year.

The AEs reported were mainly rhinopharyngitis (59.1%; 88 patients), upper respiratory tract infections (46.3%; 69 patients), gastroenteritis (40.3%; 60 patients) and pharyngitis (33.6%; 50 patients). "Skin and sub-cutaneous tissue disorders" were reported by 67.1% of patients, mainly involving eczema (28.9%; 43 patients) and urticaria (16.8%; 25 patients). Finally, "gastrointestinal disorders" such as diarrhoea, nausea and vomiting, constipation, stomatitis and/or abdominal pain were reported by 57% of patients.

Sixty two (62) patients (41.6%) reported 105 SAEs. Among them, 45 patients (30.2%) reported 68 AEs, for which the realation with the treatment has not been ruled out. The most common SAE included “infections and infestations"; gastroenteritis (7.4% of patients) and pneumonia (3.4% of patients).

Ten (10) patients discontinued their treatment due to EIs during these studies. In studies MRA011JP, MRA316JP and MRA317JP there were 2 anaphylactic reactions, one duodenal perforation, one gastrointestinal haemorrhage, one case of herpes zoster and one case of hepatic enzyme elevation that required discontinuation of treatment and a favourable outcome was reached for the patients concerned. Only the link between treatment and the case of hepatic enzyme elevation has not been ruled out. In study MRA324JP, 4 patients stopped treatment due to reactions at the injection site (for 2 patients, with favourable outcome), one due to haemophagocytic histiocytosis (possibly linked to treatment) and one due to cardiac amyloidosis (considered as not being related to treatment); the latter two cases led to the deaths of the patients concerned.

- **World-wide pharmacovigilance data (PSUR)**

Analysis of the pharmacovigilance cases covering the period of 1October 11th 2010 to April 10th 2011 (6 months) reported within the context of the use of TCZ for JIA around the world has been carried out. It highlighted 140 adverse effects, including 78 that were serious. The System Organ Classes with the most frequently reported SAEs were "infections and infestations" (23.1%), "gastrointestinal disorders" (12.8%), "general disorders and administration site conditions" (9%).

There is no French pharmacovigilance data concerning the use of tocilizumab in JIA.

- **Risk management plan (RMP)**

The label extension of ROACTEMRA for systemic JIA has not resulted in an amendment to the RMP for this medicinal product.

It should be noted that the European RMP for this proprietary medicinal product recommends the monitoring of the following identified risks:
- Serious infections;
- Serious hypersensitivity reactions;
- Diverticulitis complications.

The RMP also recommends the monitoring of the following potential risks:
- Neutropenia and the potential risk of infection;
- Thrombocytopenia and the potential risk of bleeding;
- Elevation in hepatic transaminases and bilirubin and hepatotoxicity;
- Elevations in lipid parameters and the potential risk of cardiovascular and cerebrovascular events;
- Malignancies;
- Demyelinating diseases;
- Immunogenicity / development of anti-TCZ antibodies;
- The potential risk of interaction with CYP 450 substrates.

The monitoring of these risks has been maintained.

It should be noted that, as for other biological therapies indicated for RA, a long-term follow-up study of ROACTEMRA was requested by the Committee in 2009 (the protocol for this study was validated by the ISPEP group.

3.3. Conclusion

Tocilizumab-TCZ (ROACTEMRA) in the treatment of active systemic JIA was evaluated in a phase III clinical study (TENDER; WA18211), including 112 patients aged at least 2 years, who have had an inadequate response to a previous treatment with NSAIDs and/or systemic corticosteroids. The majority of patients treated with tocilizumab (TCZ) had previously been treated with biological therapies: anakinra or TNF inhibitors (84% of patients) and classic disease-modifying treatments (73%), mainly MTX (60%). During the study, the majority of patients treated with TCZ continued to be treated with MTX (69%), NSAIDs (73%) or corticosteroids (93%).

During the first comparative phase of 12 weeks, the superiority of TCZ (8 mg and 12 mg/kg) was demonstrated over the placebo for the primary efficacy endpoint: percentage improvement of clinical symptoms (ACR paediatric 30 and fever) 85.3% (64/75) versus 24.3% (9/37), $p<0.0001$. During the second, open-label phase, in which patients received TCZ at a dosage based on their weight, the clinical response was maintained by more than 80% of patients in the group initially treated with TCZ.

TCZ in the treatment of active systemic JIA was also evaluated in a Japanese study (MRA316JP) which included an initial open-label phase, followed by a double-blind, randomised phase versus placebo. Among the 50 patients who completed the initial open-label phase, 44 (79%) met the primary efficacy endpoint at Week 6 (ACRpedi30 response and CRP < 5 mg/l). In the second phase, the superiority of TCZ over placebo was demonstrated for the primary efficacy endpoint at Week 12: the proportion of responders was 16/20 in the TCZ group versus 4/23 in the placebo group ($p<0.001$).

Finally, data gathered during the open-label extension phases of the Japanese studies (MRA316JP and MRA011JP[7]) suggested that the efficacy of tocilizumab is maintained up to 324 weeks.

Safety data (from clinical studies and pharmacovigilance information) were comparable with those already available for this medicinal product in rheumatoid arthritis; the most common adverse effects were infections, gastrointestinal disorders and reactions to the infusion including some serious events (Quincke's oedema, hypersensitivity reactions). Neutropenia and transaminase elevations were also noted.

7Japanese open-label phase II study that included 11 patients with systemic JIA and who had had an inadequate response to corticosteroids.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Juvenile idiopathic arthritis is the term used for all inflammatory conditions of the joints without an identified cause, starting before the age of 16 years and which last for more than 6 weeks.[8] The systemic form of JIA (Still's disease) occurs most often between the ages of 1 and 5 years.[1] The disease is characterised by the presence of at least one arthritic episode lasting at least 6 weeks plus extra-articular signs, dominated, in the main, by fever and skin disorders.[9]

ROACTEMRA is intended for symptomatic treatment.

The efficacy/adverse effects ratio for this medicinal product is high.

Public health benefit

The burden on public health caused by juvenile idiopathic arthritis is low because of the small number of patients affected as it is an orphan disease. The burden represented by the indication of ROACTEMRA, for children who have had an inadequate response to a previous treatment with NSAIDs or systemic corticosteroids, remains low.

Improvement in the management of this orphan disease is an integral part of public health priorities ("rare diseases" plan, paediatric medicinal products).

In view of the available data from trials versus placebo, it is expected that the impact of ROACTEMRA on morbidity will be moderate. The additional impact of ROACTEMRA compared with normal treatment for children with JIA is yet to be determined. An impact on quality of life may be expected, but it is not quantifiable. The transferability of data into current clinical practice is assured.
Furthermore, ROACTEMRA provides a partial response to an identified public health need.

Consequently, in the current state of knowledge and in view of the restricted size of the population concerned,a low public health benefit is expected for ROACTEMRA in this indication.

This medicinal product is indicated as a second-line treatment for systemic JIA, in patients who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.

There is no other medicinal products with a specific marketing authorisation for the treatment of systemic JIA. According to experts, even thought IL1 inhibitors do not have marketing authorisation, they may be used in this indication. Methotrexate and TNF inhibitors may be used, even though they appear to be less effective than IL1 and IL6 inhibitors, with their effect often being only partial, even when used associated (methotrexate + TNF alpha inhibitor).

The actual benefit of this proprietary medicinal product is substantial.

8. Job Deslandre et al. Juvenile idiopathic arthritis. Orphanet encyclopaedia. September 2003.
9. Heyman R, Prieur AM. Les formes systémiques d'arthrite juvénile idiopathique: diagnostic et prognostic [systemic forms of juvenile idiopathic arthritis: diagnosis and prognosis] . Med Ther Pediatr 2006; 9(1): 16-22. 9

4.2. Improvement in actual benefit (IAB)

Taking into account:

- the important size effect versus placebo in one clinical study;
- the absence of alternative therapies with specific marketing authorisation for this condition;
- and the risks, especially from infections, linked to biological therapies to be monitored in this paediatric population

The transparency Committee considers that ROACTEMRA (tocilizumab) provides a moderate improvement in actual benefit (IAB III) in the treatment of active systemic juvenile idiopathic arthritis in children aged 2 years and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.

4.3. Therapeutic use [7,8]

Current management

The aim of treatments for systemic JIA is to manage joint and systemic issues (fever, asthenia, anaemia). Immediate-action symptomatic treatments (NSAIDs and corticosteroids) are first-line treatments.

NSAIDs are used as first-line treatments, unless contraindicated or severity criterion, but their efficacy is inconsistent. Systemic corticosteroid therapy is indicated, following a specialist opinion, in the treatment of systemic issues in instances of hepatotoxicity from NSAIDs, insufficient efficacy or intolerance to NSAIDs, the presence of severity signs (significant alteration in general health,, weight loss, systemic toxicity, severe anaemia or significant serositis symptoms) or the occurrence of macrophage-activation syndrome. When the disease is being controlled, the dose of corticosteroids may be progressively reduced, based on the development of systemic clinical and biological signs (ALD [chronic condition] guide edited by HAS).

In cases of arthritic pain, analgesia using non-opioid based products, mild opioids or strong opioids may also be given. Symptomatic treatments may also be combined with intra-articular infiltrations of corticosteroids, when one or many joints are affected.

Classic disease-modifying treatments, such as methotrexate and TNF-α inhibitors, only have marketing authorisation for polyarticular JIA. According to experts and the ALD (Chronic condition) guide edited by HAS, their use for systemic JIA is possible in polyarticular forms with mild inflammation, but their efficacy is inconstant: Anakinra (KINERET, IL1 receptor antagonist) has no marketing authorisation for JIA but is proposed (without marketing authorisation in the PNDS) based on experts opinions, for forms of JIA with persistent systemic signs, as with tocilizumab (ROACTEMRA, IL 6 inhibitor)[8].

Role of tocilizumab in treatment strategy:

Tocilizumab is the only product with marketing authorisation for children aged 2 years and above, with systemic JIA inadequately responding to previous NSAID or systemic corticosteroid treatments. This proprietary medicinal product is administered via intravenous infusion every two weeks at a variable dose, based on the weight of the patient (8 mg/kg for patients weighing ≥ 30 kg, or 12 mg/kg for those weighing < 30 kg). If no improvement is seen after six weeks, continuation with treatment should be reconsidered. Potential adverse events associated with this medicinal product are mainly infections. Serious reactions to the infusion (Quincke's oedema and hypersensitivity reactions) were also reported.

In general, its use should be considered by taking into account the risks of infection and allergic reaction.

4.4. Target population

Given the wording in the marketing authorisation, the target population of ROACTEMRA comprises patients aged from 2 to 17 years with systemic JIA who have had an inadequate response to NSAID or corticosteroid treatments.

According to INED data, on January 1st 2012 in France there were approximately 12,320,000 children aged from 2 to 17 years. The prevalence of JIA in France is estimated at approximately 2 to 3/10,000 children.[8] The population of children aged from 2 to 17 years with any form of JIA will therefore be between 2,500 and 3,700 patients. On December 31th 2008, 3,641 patients had an off list ALD (ALD 31) and were treated for JIA.[8]
The systemic form of the disease represents 15% of all cases of JIA[7]; or 375 to 555 patients. Among these patients, the proportion of patients with an inadequate response to NSAIDs and corticosteroids can not be precisely established.

In summary, the target population of tocilizumab in this indication would be a maximum of 600 patients.

This data is confirmed by the estimation of the prevalence of systemic JIA published by Orphanet[10], which was 5 /100,000, or 616 patients.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the new indication and at the dosage in the Marketing Authorisation.

4.5.1 Post-inclusion data
The Committee would like to be informed of the results from studies carried out within the context of the RMP, especially from European registers.

10. Orphanet documents– Prevalence of rare diseases: Bibliographic data – November 2011 – Numéro.http://www.orpha.net/orphacom/cahiers/docs/FR/Prevalence_des_maladies_rares_par_prevalence_decroissante_ou_cas.pdf . *Consulted on 22 March 2012.*