HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

23 July 2014

ROACTEMRA 20 mg/ml, concentrate for solution for infusion

Box containing 1 vial of 4 ml (CIP: 34009 574 643 1 8)
Box containing 1 vial of 10 ml (CIP: 34009 574 6448 6)
Box containing 1 vial of 20 ml (CIP: 34009 574 645 4 7)

Applicant: ROCHE

INN	Tocilizumab
ATC Code (2014)	L04AC07 (immunosuppressant, interleukin-6 inhibitor)
Reason for the review	**Extension of indication**
List concerned	**Hospital use (French Public Health Code L.5123 2)**
Indication concerned	**ROACTEMRA, in combination with methotrexate (MTX), is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA) (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. ROACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial Marketing Authorisation: 16 January 2009 (centralised procedure) Extension of indication in polyarticular JIA: 30 May 2013
Prescribing and dispensing conditions/special status	Medicinal product reserved for hospital use Prescription reserved for specialists in rheumatology, internal medicine, or paediatrics. Medicine requiring special monitoring during treatment.

ATC Classification	2014 L : Antineoplastic and immunomodulating agents L04 : Immunosuppressants L04A : Immunosuppressants L04AC : Interleukin inhibitors L04AC07 : tocilizumab

02 BACKGROUND

The proprietary medicinal product ROACTEMRA (tocilizumab), biological therapy targeting interleukin-6 receptors, has been included on the list of medicines approved for hospital use in adults in the treatment of RA since 2009. It received its 1st indication extension in children in 2011 in systemic juvenile idiopathic arthritis.
This assessment concerns a new paediatric indication: polyarticular juvenile idiopathic arthritis from 2 years of age, MA obtained in May 2013. Other biological agents already have MA in this indication, in particular two anti-TNF treatments (from 2 years of age): etanercept and adalimumab and a T lymphocyte co-stimulation inhibitor: abatacept (from 6 years of age, anti-TNF failure).

03 THERAPEUTIC INDICATIONS

Indication forming the subject of the application:

"ROACTEMRA in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. ROACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. "

Other indications not related to the application:

Rheumatoid arthritis
"RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor 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. "

Systemic juvenile idiopathic arthritis
“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. "

04 DOSAGE

"The recommended posology is 8 mg/kg once every 4 weeks in patients whose body weight is more than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg. Dose interruptions of tocilizumab are recommended in patients with pJIA if laboratory abnormalities occur. As there are many co-morbid conditions that may affect laboratory values in pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the case-by-case medical assessment of the individual patient. "

05 THERAPEUTIC NEED

Polyarticular juvenile idiopathic arthritis (pJIA) is a chronic disease of unknown cause affecting children under 16 years of age with more than four joints affected during the first 6 months of the disease. It includes forms of arthritis with negative rheumatoid factor (including extended oligoarthritis) and forms with positive rheumatoid factor.

The aim of pJIA treatment is to combat inflammation, relieve pain and stiffness and prevent or slow down the progression of joint lesions. It makes use of fast-acting symptomatic treatments (NSAIDs, corticosteroids) and sometimes disease modifying treatments, depending on the form of the juvenile idiopathic arthritis (systemic, oligoarticular or polyarticular). NSAIDs are used as the first-line treatment, but they are not always effective. If required, they can be combined with intra-articular infiltrations of corticosteroids.

The reference disease modifying treatment is methotrexate (MTX), particularly where there is a polyarticular course without systemic signs.

Leflunomide, hydroxychloroquine, sulfasalazine, azathioprine, and ciclosporin are sometimes used (off-label) as alternatives to methotrexate, but their efficacy in pJIA is less well established.

Two anti-TNF treatments (adalimumab and etanercept) are used and have MA to treat progressive pJIA if treatment with other DMARDs fails:
- in children 2 years of age and older with an insufficient response or intolerance to MTX (ENBREL - etanercept),
- in children 2 years of age and older having had an insufficient response to one or several DMARDs (HUMIRA - adalimumab).

In patients having had an insufficient response to an anti-TNF (adalimumab or atanercept), the current alternatives are:
- the addition of a synthetic DMARD, in particular MTX, if the anti-TNF had been used as monotherapy,
- the use of a second anti-TNF which has not yet been used,
- the use of abatacept - ORENCIA (6 years of age and older, only the IV form has MA in children).

From now on, tocilizumab, interleukin-6 receptor inhibitor, has MA for the treatment of pJIA with MA wording similar to that of etanercept: patients (2 years of age and older) having responded inadequately to MTX.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators are the three other biological agents with MA in pJIA. There are:

- in the case of failure of DMARDs including methotrexate:

- the anti-TNFs (ENBREL - etanercept and HUMIRA - adalimumab) administered subcutaneously.

- in the case of failure of DMARDs including at least one anti-TNF:

- T lymphocyte co-stimulation modulator: ORENCIA (abatacept) IV (subcutaneous administration does not have MA in children)

They all have a substantial AB (see Table 1 below recalling the MA indications and the assigned IAB wording).

◗ Conclusion

The comparators listed are all clinically relevant.

1 Table 1. Assessment history of comparators by the Transparency Committee in polyarticular JIA

NAME INN	Company	Indication	Date of opinion from the TC	IAB (Wording)
ENBREL Etanercept	Pfizer	Treatment of active **chronic polyarticular juvenile arthritis** in children aged 4 to 17 years of age **in case of inadequate response or proven intolerance to methotrexate**. ENBREL has not been studied in children below 4 years of age.	**02/10/2002** Inclusion	In the treatment of chronic polyarticular juvenile arthritis, ENBREL presents **substantial improvement of the actual benefit (level II) in relation to the therapeutic strategy of these diseases.**
		Treatment of active polyarticular juvenile idiopathic arthritis in **children from the age of 2 years and adolescents in case of inadequate response or proven intolerance to methotrexate.** ENBREL has not been studied in children below 2 years of age.	**11/04/2012 Extension of the population (2 to 4 years of age)**	The indication extension for the age range concerned to children aged 2 and 3 years of age **is not likely to alter the assessment of the IAB of ENBREL in the treatment of progressive pJIA in case of insufficient response to methotrexate (IAB II allocated in 2002).**
HUMIRA Adalimumab	AbbVie	HUMIRA **in combination with methotrexate** is indicated for the treatment of **progressive polyarticular juvenile idiopathic arthritis in adolescents aged 13 to 17 years** in case of insufficient response to **one or more disease-modifying treatments**. HUMIRA can be given as **monotherapy** in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.	**24/06/2009 Extension of therapeutic indication in pJIA 13-17 years**	**HUMIRA does not provide an improvement in actual benefit (level V) in the therapeutic strategy.**
		HUMIRA in combination with methotrexate is indicated for the treatment of **progressive polyarticular juvenile idiopathic arthritis in children and adolescents aged 4 to 17 years** in case of insufficient response to one or more disease-modifying treatments. HUMIRA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. HUMIRA has not been studied in children below the age of 4 years.	**21/09/2011 Extension of the population (4 to 12 years of age)**	**HUMIRA does not provide an improvement in actual benefit (level V) in the treatment.**
		HUMIRA in combination with methotrexate is indicated for the treatment of **progressive polyarticular juvenile idiopathic arthritis in children and adolescents 2 years of age and older** in case of insufficient response **to one or more disease-modifying treatments**. HUMIRA can be given as **monotherapy** in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. HUMIRA has not been studied in children below the age of 2 years.	**18/09/2013 Extension of the population (2 to 4 years of age)**	**In the absence of clinical data versus the only clinically relevant comparator, etanercept, HUMIRA does not provide any improvement in actual benefit (level V, nonexistant) in comparison to ENBREL.**
ORENCIA Abatacept IV form	Bristol-Myers Squibb	ORENCIA in combination with methotrexate is indicated in the treatment of **moderate to severe, active polyarticular juvenile idiopathic arthritis** (JIA) **in paediatric patients 6 years of age and older having had an insufficient response to other DMARDs including at least one anti-TNF**. ORENCIA has not been studied in children below the age of 6 years.	**05/01/2011 Treatment indication extension in pJIA ≥ 6 years**	Even being the first biological therapy to be granted MA in patients with JIA having had an insufficient response to at least one anti-TNF, the Transparency Committee, in view of: - the limited efficacy data not enabling the benefit provided by ORENCIA (abatacept) to be assessed in this indication (only 16% of patients evaluated during the double-blind phase of the study corresponded to patients meeting the indication) and, - the short follow-up period and the uncertainties about safety, considers that ORENCIA in combination with methotrexate **does not**

				provide an IAB (V) in the therapeutic strategy.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

On the date of writing this document, the proprietary medicinal product ROACTEMRA is reimbursed for this new paediatric indication in 13 European countries. The assessment of its reimbursement is ongoing in seven countries.

Table 2. Point about the administration of ROACTEMRA

Country	Reimbursement	
	Yes (start date)/No/Assessment in progress or change	Scope (indications) and special condition(s)
Austria	Yes (02.03.2009)	RA - sJIA - pJIA
Belgium	Yes (01.10.2009)	RA - sJIA
	Assessment in progress	pJIA
Croatia	Yes (01.01.2010)	RA
	Assessment in progress	sJIA - pJIA
Germany	Yes (15.02.2009)	RA - sJIA - pJIA
Bulgaria	Yes (01.01.2013)	RA - sJIA - pJIA
Denmark	Yes (23.03.2009)	RA - sJIA - pJIA
Spain	Yes (08.07.2009)	RA and sJIA
	Assessment in progress	pJIA
Estonia	Yes (01.01.2011)	RA - sJIA - pJIA
Finland	Yes (16.01.2009)	RA and sJIA
Greece	Yes (04.01.2010)	RA - sJIA - pJIA
Hungary	Yes (01.06.2010)	RA - sJIA
	Assessment in progress	pJIA
Ireland	Yes (01.05.2009)	RA - sJIA - pJIA
Italy	Yes (03.04.2009)	RA
	Assessment in progress	pJIA
Latvia	Yes (01.01.2011)	RA - sJIA - pJIA
Lithuania	N/A	-
Luxembourg	Yes (01.04.2009)	RA and sJIA
	Assessment in progress	pJIA
Norway	Yes (21.04.2009)	RA - sJIA - pJIA
Netherlands	Yes (01.02.2009)	RA - sJIA - pJIA
Poland	Yes (01.01.2013)	RA
	Assessment in progress	sJIA - pJIA
Portugal	Yes (14.09.2010)	RA
Czech Republic	Yes (01.10.2010)	RA - sJIA
Romania	N/A	-
United Kingdom	Yes (18.01.2010)	RA - sJIA - pJIA
Slovakia	Yes (01.10.2009)	RA - sJIA - pJIA
Slovenia	Yes (19.07.2010)	RA and sJIA
	Assessment in progress	pJIA
Sweden	Yes (25.11.2009)	RA - sJIA - pJIA

RA: rheumatoid arthritis, sJIA: systemic juvenile idiopathic arthritis and pJIA: polyarticular juvenile idiopathic arthritis

08 ANALYSIS OF AVAILABLE DATA

In support of the inclusion request for tocilizumab - TCZ (ROACTEMRA) in its new paediatric indication, namely the treatment of polyarticular juvenile idiopathic arthritis (pJIA), the company has provided the efficacy and safety results from the CHERISH -WA 19977 study and the safety data from the main and extension phases of an open-label Japanese study which included 19 patients.

08.1 Efficacy

The efficacy of TCZ in the treatment of pJIA is mainly supported by the results of the CHERISH study. This study was conducted between 14 October 2009 and 4 November 2011 in 58 centres, 4 of which in France. It was performed versus a placebo.

It should be noted that comparison with an active comparator (other biological therapy) was feasible insofar as etanercept had had MA in this indication since 2000.

8.1.1 CHERISH Study [1]

Aim and method:
Phase III, placebo-controlled, randomised, withdrawal study[2] lasting 104 weeks, performed in three parts: 16-week open-label part, 24-week double-blind part and a 64-week open-label follow-up part. The primary objective was to demonstrate the superiority of TCZ in comparison with a placebo in terms of paediatric ACR30 response in patients with pJIA.

Inclusion criteria:
- patients 2-17 years old with pJIA according to the International League of Associations for Rheumatology (ILAR) criteria for at least 6 months with at least five active joints and,
- having had an inadequate response or intolerance to MTX and,
- not having been treated with oral corticosteroids or having been administered at a stable dose of less then 10 mg/day for at least 4 weeks before the inclusion visit.

The patients could have been treated with a biological therapy however a withdrawal period before their inclusion in the study was required (≥ 1 week for anakinra, ≥ 2 weeks for etanercept, ≥ 5 weeks for rilonacept, ≥ 8 weeks for adalimumab and infliximab, ≥ 12 weeks for abatacept, ≥ 20 weeks for canakinumab).

Treatments
During the 16-week, open-label, part 1 of the study, all patients received an infusion of TCZ at weeks 0, 4, 8 and 12 at a dose depending on their weight:
- those weighing ≥ 30 kg received 8 mg/kg IV;
- those weighing < 30 kg were randomised to receive 8 mg/kg or 10 mg/kg IV.

At week 16, patients with at least a paediatric ACR30 response were selected as responders and were included in the double-blind part 2 of the study during which they were randomised to receive either TCZ (same dose as before) or the placebo. The concomitant administration of MTX and oral corticosteroids was authorised.
Then, the patients having completed part 2 were entered into the open-label, part 3 extension during which they all received TCZ at the same dose as before.

The patients were stratified depending on the concomitant administration of MTX and oral corticosteroids.

This withdrawal methodology has been used in studies evaluating the comparators (adalimumab, etanercept and abatacept) as part of their paediatric development and has been accepted by the MA by taking into account efficacy and safety established in adults.

[1] Hermine I Brunner et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis 2014; 0: 1-8.
[2] In withdrawal trials, all patients receive the tested treatment for a certain period, then this is stopped and replaced (withdrawn) by the placebo in a certain number of patients determined by randomisation.

This methodology has the advantage of limiting the exposure to the placebo but it does not allow a conventional demonstration of efficacy since it is not possible to assess the quantitative effect in the general population, only in patients responding to the studied treatment.
It is regrettable that the placebo was chosen as the comparator when other biological therapies were available.

Efficacy endpoint

The primary efficacy endpoint was the proportion of patients having experienced a paediatric ACR30 flare between week 16 and week 40.

The paediatric ACR30 criterion used in this study is common to the studies having evaluated the comparators.

The paediatric ACR30 flare was defined as deterioration ≥ 30% of at least three of the six components of the ACR score without improvement > 30% of more than one of the remaining components.

Les 6 composantes du score ACR sont les suivants :

- Overall assessment of well-being by the patient (or their family) (visual analogue scale VAS 0-100 mm)
- Overall assessment of disease severity by the doctor (on a visual analogue scale VAS 0-100 mm).
- Assessment of physical functions by the patient or their family (CHAQ questionnaire)
- Number of active joints,
- Number of joints with limitation of movement
- Inflammation markers (ESR or CRP; the ESR was used in this study).

Secondary endpoints:

Twelve (12) secondary endpoints were analysed according to a predefined hierarchy. If the first test was statistically significant, the second hypothesis could be tested with the same $\alpha = 0.05$ and so forth unless statistical significance was not reached for one criterion from the list**:**

1. proportion of patients with a paediatric ACR50 response at week 40
2. proportion of patients with a paediatric ACR50 response at week 40
3. proportion of patients with a paediatric ACR70 response at week 40
4. Mean variation at week 40 in comparison with inclusion of the number of active joints
5. Mean variation at week 40 in comparison with inclusion of the disease severity (physician VAS)
6. Mean variation at week 40 in comparison with inclusion of pain (patient VAS)
7. Mean variation at week 40 in comparison with inclusion of the number of joints with limitation of movement
8. Mean variation at week 40 in comparison with inclusion of patient well-being (parent VAS)
9. Mean variation at week 40 in comparison with inclusion of ESR
10. Mean variation at week 40 in comparison with inclusion of the CHAQ-DI score
11. proportion of patients with a paediatric ACR90 response at week 40
12. proportion of patients with inactive disease at week 40

Statistical analysis:

The analyses were performed in the intention-to-treat (ITT) population. The ITT population was defined in this study as the entire randomised population having received at least one dose of treatment (which is therefore closer to a modified ITT).
The sample size (60 patients in each group) was determined based on a hypothesis of

ACR30 flare rate of 35% with TCZ and 65% with the placebo to demonstrate a statistically significant difference with a power of 80% and an alpha risk of 0.05. On this basis, 188 patients were enrolled in part 1 to be sure that there were a sufficient number of patients at the time of randomisation.

Results

In conclusion, 188 patients were included in part 1 and treated with TCZ, 153 of which received a dose of 8 mg/kg and 35 received a dose of 10 mg/kg (<30 kg). At the end of part 1 (week 16), 22 patients had stopped treatment, 15 of which for an insufficient response to TCZ, 3 for adverse events, 1 lost to follow-up and 3 patients refused to continue the study.
Consequently, of the 188 patients initially included, 166 patients were randomised in part 2: 82 patients in the TCZ groups (66 patients treated with 8 mg/kg and 16 with 10 mg/kg) and 84 in the placebo group.

The demographic and medical characteristics of the patients included in part 1 were as follows: the 188 patients included in part 1 were 11 years old on average with an average disease duration of 4 years and active disease (in particular the number of active joints was 20). The majority of patients (71%) had already been treated with a DMARD and 32% with a biological agent. Nine percent (9%) of patients had been treated with three biological agents or more, 56 patients with an anti-TNF, 5 with anakinra, 5 with abatacept and 1 with canakinumab. The majority of them (79%) had received concomitant treatment during the study with MTX and an oral corticosteroid (46%).

The demographic and medical characteristics of the randomised patients in the two TCZ and placebo groups during part 2 were similar and are presented in table 3.

Table 3. Characteristics of patients in the double-blind part of the CHERISH study

	Placebo n=81	**TCZ n=82**
Mean age (SD)	11.2 (4.09)	11.1 (3.67)
Female, n(%)	62 (77)	66 (80)
Mean weight (kg) (SD)	39.40 (16.38)	41.43 (17.15)
Mean height (cm) (SD)	141.32 (21.27)	143.30 (21.12)
Body surface area (m^2), mean (SD)	1.23 (0.35)	1.27 (0.35)
Mean duration of disease (years) (SD)	4.20 (3.92)	4.48 (3.69)
Mean number of active joints (SD)	20.4 (13.8)	21.2 (13.6)
Mean number of joints with limitation of movement (SD)	17.0 (13.88)	16.5 (13.81)
Overall assessment of well-being (patient VAS), mean (SD)	58.6 (23.35)	45.5 (23.11)
Overall assessment of disease severity (physician VAS), mean (SD)	64.0 (19.31)	57.8 (20.30)
CHAQ-DI score, mean (SD)	1.50 (0.73)	1.22 (0.67)
JADAS-27 score, mean (SD)	26.83 (10.66)	24.64 (8.42)
Mean ESR (mm/h) (SD)	36.29 (25.67)	31.70 (22.87)
Number of DMARDs previously received (SD) Number of patients having previously received a DMARD/category n (%) 0 1 2 ≥ 3	1.1 (0.96) 23 (28) 32 (40) 19 (23) 7 (9)	1 (0.92) 25 (30) 36 (44) 15 (18) 6 (7)
Number of patients having previously received at least one biological therapy, n (%) Number of patients having previously received a biological therapy/category n (%) 0 1 2 ≥ 3	23 (28) 58 (72) 15 (19) 5 (6) 3 (4)	27 (33) 55 (67) 14 (17) 10 (12) 3 (4)
Number of patients receiving MTX, n (%)	**64 (79)**	**67 (82)**

Mean dose of MTX (mg/m²/week) (SD)	**13.56 (7.93)**	**12.31 (3.19)**
Number of patients receiving at least one oral corticosteroid, n (%) Mean dose of oral corticosteroids (mg/kg/day) (SD)	**38 (47)** **0.13 (0.05)**	**33 (40)** **0.13 (0.05)**

Results for the primary endpoint

At week 40, the superiority of TCZ compared with the placebo was demonstrated: the proportion of patients with a paediatric ACR30 flare was 25.6% in the TCZ group (all doses included) and 48.1% in the placebo group, p=0.0024 which is a weighted difference of 21%. However, the flare rates observed in the two groups were different to those expected and used to calculate the number of subjects required: 25.6% versus 35% in the TCZ group and 48.1% versus 65% in the placebo group.

Results on secondary endpoints (see Table 4)

According to the predefined sequential approach, the absence of statistical significance for one criterion did not allow the following criterion on the list to be analysed. Only six criteria were significant.

Table 4. Results for secondary endpoints in the CHERISH study

	Criteria	**Placebo n=81**	**TCZ n=82**	**p-value**
1	Paediatric ACR30 response , n (%)	44 (54.3 %)	61 (74.4 %)	
	Weighted difference (95% CI)	19% (5%; 33%)		0.0084
2	Paediatric ACR50 response, n (%)	42 (51.9%)	60 (73.2%)	
	Weighted difference (95% CI)	20% (6%; 34%)		0.0050
3	Paediatric ACR70 response, n (%)	34 (42.0 %)	53 (64.6 %)	
	Weighted difference (95% CI)	22% (7%; 37%)		0.0032
4	Mean variation in comparison with inclusion of the number of active joints	-11.4	-14.3	
	Weighted difference (95% CI)	-2.9 (-5.7; -0.1)		0.0435
5	Mean variation in comparison with inclusion of the disease severity (physician VAS)	-35.2	-45.2	
	Weighted difference (95% CI)	-9.9 (-16.5; -3.4)		0.0031
6	Mean variation in comparison with inclusion of pain (patient VAS)	-22.3	-32.4	
	Weighted difference	-10.2 (-17.6; -2.7)		0.0076
7	Mean variation in comparison with inclusion of the number of joints with limitation of movement	-7.7	-9.5	
	Weighted difference (95% CI)	-1.8 (-4.1; 0.5)		NS
8	Mean variation in comparison with inclusion of patient well-being (parent VAS)	-24.7	-32.1	
	Weighted difference	-7.4 (-14.8; 0.0)		*******
9	Mean variation in comparison with inclusion of ESR	-12.0	-26.3	
	Weighted difference (95% CI)	-14.3 (-19.6; -9.0)		*******
10	Mean variation in comparison with inclusion of the CHAQ-DI score	-0.6	-0.8	
	Weighted difference (95% CI)	-0.2 (-0.4; 0.01)		*******
11	Paediatric ACR90 response, n (%)	19 (23.5%)	37 (45.1%)	
	Weighted difference (95% CI)	21% (7%; 35%)		*******

12	Proportion of patients with inactive disease, n (%)	12 (14.8%)	26 (31.7%)	
	Weighted difference (95% CI)	16% (3%; 29%)		*******
The response differences for the secondary endpoints between the two groups was adjusted for stratification factors at inclusion (MTX and corticosteroids). ******* p-value not available given that the associated parameter was evaluated after break of statistical significance of the sequential approach.				

Results of the other analyses:
The patients were stratified according to whether or not MTX or corticosteroids were used.
The analyses performed on low numbers suggested that:
- patients treated with TCZ in association with methotrexate had a lower ACR30 fare rate than those treated with monotherapy.

	Placebo (n=81)		TCZ (n=82)	
MTX associated	Yes (n=64, 79%)	No (n=17)	Yes (n=67, 82%)	No (n=15)
Paediatric ACR30 flare, n (%)	25 (39.1)	14 (82.4)	13 (**19.4**)	8 (**53.3**)
Paediatric ACR30 response, n (%)	39 (60.9)	5 (29.4)	53 (79.1)	8 (53.3)

- patients treated with TCZ in combination with a corticosteroid had the same flare rate as those not treated concomitantly.

	Placebo (n=81)		TCZ (n=82)	
Oral corticosteroid associated	Yes (n=38)	No (n=43)	Yes (n=33)	No (n=49)
Paediatric ACR30 flare, n (%)	21 (55.3)	18 (41.9)	8 (24.2)	13 (26.5)
Paediatric ACR30 response, n (%)	18 (47.4)	26 (60.5)	24 (72.7)	37 (75.5)

An analysis was performed in the patients previously treated with biological therapy and suggested that the flare rate was higher and the proportion of paediatric ACR30 responders was lower in these patients than in those patients who had never received biological therapy.

	Placebo (n=81)		TCZ (n=82)	
Previous treatment with a biological agent	Yes (n=23)	No (n=58)	Yes (n=27)	No (n=55)
Paediatric ACR30 flare, n (%)	18 (78.3)	21 (36.2)	12 (44.4)	9 (16.4)
Paediatric ACR30 response, n (%)	6 (26.1)	38 (65.5)	15 (55.6)	46 (83.6)

However, it should be noted that the results of these analyses are to be interpreted with caution given the small cohort sizes.

The results of the extension open-label phase (on-going) are not provided in this file.

No study has compared TCZ withother available biological therapies in the treatment of pJIA.

08.2 Safety/Adverse effects

8.2.1 Data obtained from the pivotal study

Given the withdrawal methodology, all patients were exposed to tocilizumab (TCZ) during the CHERISH study. On the database provided by the company, the median duration of exposure was 48 weeks. During the study, 159 (84.6%) patients had at least one adverse event (AE). Definitive treatment cessation due to an AE concerned seven patients and temporary cessation around 13% of patients.
The most frequently reported system organ classes were:
- "Infections and infestations": 61.2%;
- "Musculoskeletal and connective tissue disorders": 34.0%;
- Gastrointestinal disorders: 31.9%;
- Skin and subcutaneous tissue disorders: 22.3%;
- Respiratory, thoracic and mediastinal disorders: 21.3 %;
- Central nervous system disorders: 19.7%;
- General disorders and administration site conditions: 16.5%.

Seventeen (17) patients reported 22 serious AEs, 5 of which were considered as being possibly related to treatment according to the investigator: benign intracranial hypertension, uveitis, renal calculus, pneumonia and cellulitis. The incidence of uveitis will be monitored and analysed in the RMP.
The most common infections were nasopharyngitis and upper respiratory tract infections. There was one case of primary tuberculosis in an endemic region.
Eleven (11) patients experienced an AE during TCZ infusion (hypotension, headaches, nausea) and 38 during the 24 hours following the infusion (gastrointestinal disorders and general disorders and administration site conditions). No serious hypersensitivity reaction requiring treatment cessation was reported. Two cases of thrombocytopenia of low intensity were reported and considered as being possibly linked to TCZ according to the investigator.
Two patients experienced a hepatic AE (hepatotoxicity of low intensity, sclerosing cholangitis with elevated transaminase leading to treatment cessation). Constipation considered as severe was reported.
One patient developed anti-TCZ antibodies without having a hypersensitivity reaction and stopped treatment.
Reduced neutrophils were reported in 3.7%. Elevated hepatic transaminase ALT was observed in 3.7% of patients and AST in less than 1% of patients
Elevated total cholesterol > 1.5 to 2 x ULN was observed in one patient and an elevation of LDL cholesterol > 1.5 to 2 x ULN was observed in one patient.

Japanese study
In this study and its extension phase performed in 19 patients, 142 AEs were reported, the majority of these AEs were considered to be of low intensity (136/142). The most commonly reported adverse event was nasopharyngitis (15/19 patients). Six serious AEs were reported in four patients including four infections. No deaths were reported during the study Eighteen (18) patients reported an AE which could be related to the treatment, infections, particularly nasopharyngitis, were the most common adverse effects.

Pharmacovigilance data
No analysis of pharmacovigilance data specific to the new pJIA indication has been provided.

Conclusion
The analysis of TCZ safety data in the treatment of pJIA did not reveal any new safety signal in comparison with the known TCZ safety profile in systemic JIA and rheumatoid arthritis. The adverse events observed are coherent with the known TCZ safety profile to date. Infections were the most commonly reported adverse effects. Infusion reactions were reported during the studies but no anaphylactic shock was reported. The risk management plan for ROACTEMRA is common to all its indications and administration routes and includes monitoring of identified significant adverse events particularly "serious infections, serious hypersensitivity reactions, neutropaenia and diverticulitis complications" and potential AEs particularly "malignancies, skeletal development of children".

08.3 Summary & discussion

The efficacy of tocilizumab-TCZ in the treatment of pJIA was mainly evaluated in the phase III CHERISH study versus placebo. In this withdrawal study, conducted in three parts, over a total duration of 104 weeks, 188 patients with active pJIA having not responded satisfactorily to methotrexate were included. The patients could have been treated with biological therapies, this was the case for 32% of included patients.
At the end of the 16-week, open-label part 1, during which all patients were treated with TCZ, only the ACR30 responders (168/188, 89.4% of the initial population) were included in part 2 of the study lasting 24 weeks, randomised versus placebo (82 patients were treated with TCZ and 84 with placebo) then in an open-label part 3.
The studies which evaluated the comparators used the same withdrawal methodology (selection of responders before randomisation) and were performed versus placebo. This methodology only enabled assessment of the quantative effect to the evaluated treatment in responders. The choice of a placebo as a comparator posed a problem due to the existence of these treatment alternatives.

The superiority of TCZ in comparison with the placebo was demonstrated for the primary endpoint: paediatric ACR30 flare rate at week 40 was 25.6% in the TCZ group and 48.1% in the placebo group, which is a weighted difference of 21% (95% CI = [-35%; -8%], p=0.0024). This criterion is modest given the therapeutic objective of obtaining remission but is common to all the studies having evaluated the biological therapies in pJIA. In the CHERISH study, the flare rates in the two groups were different to the hypotheses defined in the statistical plan (placebo 48.1% vs. 65%) and TCZ (25.6% vs 35%).

For the 12 secondary efficacy endpoints evaluated with a sequential approach during part II, 6 were statistically significantly improved in the TCZ group compared with the placebo group, in particular the paediatric ACR30, ACR50 and ACR70 response rates at W40 (more relevant than ACR30), number of active joints, overall assessment of the severity of the disease and pain evaluation.

The patients were stratified according to whether or not MTX or corticosteroids were used.
The analyses performed in the different subgroups suggested that the efficacy of TCZ was better in combination with methotrexate in patients not having previously received biological therapy and independent of the concomitant use of corticosteroids. However, the results of these analyses are to be interpreted with caution given the low population numbers and the possible differences in terms of severity of the patients and the disease characteristics in these subgroups.

No study compared ROACTEMRA with other biological agents, in particular anti-TNFs, it is therefore difficult to define its role in comparison with these medicinal products as part of an optimal therapeutic strategy.

Analysis of safety data for TCZ in the treatment of pJIA did not reveal any new safety signal. The adverse events observed are coherent with the known TCZ safety profile to date. The most common AEs were infections, mainly nasopharyngitis and upper respiratory tract infections.

08.4 Planned studies

A monitoring register of paediatric patients, including those with pJIA and treated with TCZ is planned and will be implemented as part of the RMP.
A study is on-going with the subcutaneous form in polyarticular and systemic JIA.

09 THERAPEUTIC USE

In the absence of a study comparing TCZ with available alternatives, in particular other biological agents (anti-TNF, abatacept: T lymphocyte co-stimulation modulator), the role of ROACTEMRA IV infusion (interleukin-6 receptor inhibitor) in the therapeutic strategy for polyarticular juvenile idiopathic arthritis cannot be specified.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual benefit

- Polyarticular juvenile idiopathic arthritis is a severe and debilitating chronic disease.
- ROACTEMRA is intended as a symptomatic treatment.
- Its efficacy/adverse effects ratio is high.
- There are treatment alternatives.
- In the current state of this file, the role of this medicinal product cannot be specified.
- Public health benefit:

  The public health burden caused by juvenile idiopathic arthritis is small because of the low number of patients affected (rare disease).
  Improvement of the management of this disease is part of established public health priorities ("rare diseases" plan, paediatric medicinal products).
  In view of the available data (study versus placebo, no comparative data) and the intravenous administration route, it is not possible to assume an additional expected benefit in terms of morbidity and quality of life for the proprietary medicinal product ROACTEMRA in the management of patients.
  Consequently, in the current state of knowledge and in view of the restricted size of the population concerned, it is not expected that ROACTEMRA will benefit public health in this indication.

Consequently, the Committee considers that the actual benefit of ROACTEMRA is substantial in the MA indication, namely the treatment of progressive polyarticular juvenile idiopathic arthritis in combination with methotrexate (or as monotherapy, in case of intolerance to methotrexate) in children 2 years of age and older in case of insufficient response to methotrexate.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in this extension of the indication and at the dosages in the Marketing Authorisation.

- **Proposed reimbursement rate: 65%**

010.2 Improvement in actual benefit (IAB)

In the absence of direct comparison with other available biological agents in the treatment of polyarticular JIA and given its intravenous administration route requiring hospitalisation and monitoring, the Transparency Committee considers that ROACTEMRA IV infusion does not provide an improvement in actual benefit (level V, non-existent) in the management of this new paediatric indication.

010.3 Target population

According to the wording of the MA indication, the target population of ROACTEMRA is made up of patients aged 2 to 17 years with progressive polyarticular JIA responding insufficiently to methotrexate.

A systematic literature review in 2014[3] revealed that the incidence and prevalence of juvenile idiopathic arthritis in Europe was very variable, estimated in 2010 at 1.6 to 23/100,000 and 3.8 to 400/100,000 respectively, due to the differences in estimation methodology between the publications.

In France, the prevalence of JIA is estimated at around 2 to 3/10,000 children (ORPHANET data, consulted in June 2014).
According to the INSEE data, on 1 January 2013, there were 12,522,078 children aged between 2 and 17 years of age. Amongst them, around 30% are said to require a disease modifying treatment like methotrexate and around 30% would supposedly have an inadequate response or proven intolerance to methotrexate (source: expert opinion).

Based on this, the target population of ROACTEMRA in juvenile idiopathic arthritis in children aged 2 to 17 years of age would be a maximum of 340 children.

[3] S Thierry et al. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine. 2014; 81: 112-7.