HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

05 January 2011

ORENCIA 250 mg, soluble powder for dilution for infusion purposes
B/1 (CIP code: 570 892.7)

Applicant: BRISTOL-MYERS SQUIBB

abatacept
ATC code: L04AA24

List I

Medicinal product reserved for hospital use.
Prescription restricted to rheumatology or internal medicine specialists.

Date of Marketing Authorisation: 21 May 2007 (centralised procedure)

Date of latest revision of Marketing Authorisation: 20 January 2010 (extension of indication)

Reason for request: Inclusion on the list of medicines approved for hospital use in the extension of indication “treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Abatacept

1.2. Indications

Previous description of indication:

"Rheumatoid arthritis:
ORENCIA in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to, or did not tolerate, other disease-modifying treatments including at least one TNF inhibitor. A reduction in the progression of structural damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate."

New wording of indications:

Rheumatoid arthritis **(this indication has not been examined in the context of this opinion)**:
"ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a TNF inhibitor.
A reduction in the progression of structural damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate."

N.B.: the indication of ORENCIA in adults suffering from RA was amended on 01/07/2010 (addition of the third intention (failure of a TNF inhibitor) and the second intention (failure of conventional disease-modifying treatments including MTX)). **This change will be reviewed by the Transparency Committee in the context of an opinion on modification of the conditions of inclusion.**

Polyarticular juvenile idiopathic arthritis (new indication dealt with in this opinion):
"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 who have had an insufficient response to other DMARDs[1] including at least one TNF inhibitor". ORENCIA has not been studied in children aged less than 6 years."

1.3. Dosage

"Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. If a response to abatacept is not present within 6 months of treatment, the continuation of the treatment should be reconsidered.

[1] The French phrase 'traitement de fond' [disease-modifying treatment] of RA is generally used to describe a medicinal product which has a delayed effect on symptoms and which may have an impact on the progression of the disease, in particular radiographical progression of structural damage. The equivalent phrase in English is "DMARD" (disease-modifying anti-rheumatic drugs). Conventional disease-modifying treatments, as distinct from biotherapies (TNF inhibitors, rituximab, abatacept, tocilizumab, etc.), include MTX (conventional disease modifying reference treatment for RA), leflunomide, sulfasalazine, hydroxychloroquine, gold salts, azathioprine, D-penicillamine and tiopronine.

Adults
To be administered as a 30-minute intravenous infusion at the dose specified in table 1. Following the initial infusion, ORENCIA should be given 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Table 1. Dose of ORENCIA[a]

Body weight of patient	Dose	Number of vials[b]
< 60 kg	500 mg	2
≥ 60 kg to ≤ 100 kg	750 mg	3
> 100 kg	1,000 mg	4

[a] Approximately 10 mg/kg.
[b] Each vial provides 250 mg of abatacept.

No dosage adjustment is required when ORENCIA is used in combination with other disease modifying reference treatments, corticosteroids, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics.

Elderly patients
No dosage adjustment is required.

Paediatric patients
Juvenile idiopathic arthritis. **The recommended dose for patients 6 to 17 years of age with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg calculated based on the patient's body weight at each administration. Paediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen, not to exceed a maximum dose of 1,000 mg. ORENCIA should be administered as a 30-minute intravenous infusion. Following the initial infusion, ORENCIA should be given 2 and 4 weeks after the first infusion and every 4 weeks thereafter.**
The safety and efficacy of ORENCIA in children below 6 years of age have not been studied and therefore ORENCIA is not recommended for use in children under six years of age.

Renal and hepatic impairment
ORENCIA has not been studied in these patient populations. No dosage recommendations can be made.

Method of administration
Each vial of ORENCIA 250 mg must be reconstituted with 10 ml of water for injections, using the silicone-free syringe provided. The reconstituted solution must then be diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection, before administration by intravenous infusion."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

L: Antineoplastic and immunomodulating agents
L04: Immunosuppressants
L04A: Immunosuppressants
L04AA: Selective immunosuppressants
L04AA24: abatacept

2.2. Medicines in the same pharmaco-therapeutic category

There is no other medicine indicated in the treatment of JIA following inadequate response to, or intolerance of, a TNF inhibitor and which has the same mechanism of action as ORENCIA.

2.3. Medicines with a similar therapeutic aim

These are medicinal products which have been granted marketing authorisation for disease-modifying treatment of JIA:

- TNF inhibitors: ENBREL (etanercept) and HUMIRA (adalimumab)
- methotrexate: METHOTREXATE BELLON, METOJECT, LEDERTREXATE

The indication wordings of these medicinal products are not identical. Details are given in the table below.

Table 1. Similar medicinal products

Proprietary medicinal products	**JIA indication**	**Dose** **Interval between doses** **Route**
ORENCIA (abatacept)	Active polyarticular JIA – ≥ 6 years – In the event of inadequate response to other disease-modifying treatments, including at least one TNF inhibitor. – Combined with MTX	10 mg/kg D1, D15 and every four weeks thereafter intravenous
HUMIRA (adalimumab)	Active polyarticular JIA – 13 to 17 years – In the event of insufficient response to one or more disease-modifying treatments o Combined with MTX o As monotherapy (without MTX) in cases of intolerance of MTX or when continuation of MTX is inappropriate	40 mg Once every two weeks subcutaneous
ENBREL (etanercept)	Active polyarticular JIA – 4 to 17 years – In the event of an inadequate response to or intolerance of MTX o Combined with MTX o As monotherapy (without MTX)	0.4 mg/kg (up to 25 mg) Twice a week subcutaneous
METHOTREXATE Bellon METOJECT LEDERTHREXATE (methotrexate)	– Active polyarticular JIA – In the event of inadequate response to NSAIDs	10 mg/m^2 (max 20 mg/m^2) Once a week, orally or by IM or SC route

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy of abatacept (ORENCIA) in the treatment of juvenile idiopathic arthritis (JIA) has been evaluated in a clinical study (IM 101 033[2]) performed between February 2004 and May 2008. The primary aim of this study was to compare the efficacy of abatacept with that of placebo in patients aged at least six years who had been selected as responding to abatacept during an open pre-inclusion period of four months.

Methodology: Controlled, randomised study with three periods, A, B and C. Periods A (selection of responsive patients) and C (extension) were open-label, while period B was double-blind.

Period A:
Open-label pre-inclusion period of four months, the aim of which was to select patients who responded to abatacept.

The following patients were included:

- patients aged between 6 and 17,
- patients with JIA, with active arthritis in at least two joints[3] and limited mobility in two joints,
- patients whose had an inadequate response to, or were intolerant of, disease-modifying treatment (conventional treatment or biotherapy). Patients were therefore not necessarily required to have had an inadequate response to, or have been intolerant of, TNF inhibitors in order to take part in the study.

190 patients were included in total to receive 10 mg/kg of abatacept in 30-minute infusions on D1, D15, D29, D57 and D85. Their demographic and medical characteristics are described in table 2. The average age of the patients was 12.4 years, and most of them (64%) had polyarticular and active JIA (16 joints with active arthritis and limited mobility). The patients had been suffering from the disease for 4.4 years on average. On inclusion into the study, 96% of them were receiving disease-modifying treatment, primarily methotrexate (74%). The only disease-modifying treatment which patients were permitted to continue taking during the study was methotrexate (MTX). Only 56 of the 190 patients included had previously been treated with a TNF inhibitor and could be regarded as meeting the criteria for the introduction of abatacept treatment which are laid down in the marketing authorisation.

N.B.: The failure criteria (insufficient response or intolerance) were not defined in the clinical report. Failure was evaluated by the investigating physician.

[2] Ruperto et al. abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. The Lancet 2008; 372(9636): 383 – 391.

[3] Active arthritis: swelling or limitation of mobility together with pain and/or stiffness.

Table 2. Patient characteristics at inclusion (period A)

Number of patients included in period A	190
Age (years) - mean (SD) Min-max	12.4 (3.0) 5-17
Average weight (kg)	42 (15)
Duration of disease (years) - mean (SD)	4.4 (3.8)
Breakdown into various forms of JIA Polyarticular RF- - n(%) Polyarticular RF+ - n(%) Systemic - n(%) Extensive oligoarticular - n(%) Persistent oligoarticular - n(%)	 84 (44.2) 38 (20.0) 37 (19.5) 27 (14.2) 3 (1.6)
Number of joints with active arthritis - mean (SD)	16.2 (12.7)
Number of joints with mobility limitation - mean (SD)	16.3 (14.5)
Overall evaluation of disease activity by the doctor (100-mm VAS) - mean (SD)	54.2 (20.3)
Evaluation of the child's well-being by the parents (100-mm VAS) - mean (SD)	44.5 (24.6)
CHAQ score (score of 0 to 3) - mean (SD)	1.3 (0.8)
CRP (mg/dL) - mean (SD)	3.2 (4.4)
SR (mm/hr) - mean (SD)	32.0 (26.8)
Previous disease-modifying treatments Methotrexate – n(%) DMARDs other than MTX - n(%) TNF inhibitor	 140 (74) 2 (1.1) 56 (29) *
Associated disease-modifying treatment MTX, n (%) Dosage (mg/m²/week) - mean (SD)	 138 (72.6) 13.2 (4.7)

* alone or in combination with MTX

Patients with a paediatric ACR 30 response were regarded as responsive to abatacept. This value represents an improvement of at least 30% compared to the initial scores for three of the six factors, and a worsening of no more than one factor in the paediatric ACR score.

The 6 factors were:

- overall evaluation of disease severity by the doctor (on a 0 - 10 cm visual analogue scale (VAS))
- overall evaluation of the patient's general well-being by a parent (on a 0 - 10 cm VAS)
- 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)

170 of the 190 patients included completed period A. The main reason for discontinuing treatment was lack of efficacy (8.9%), as shown in table 3.

Table 3. Discontinuation of treatment in period A

	Abatacept
Number of patients included in period A	190
Treatment discontinuations - n (%) Reason - n (%) Adverse event Insufficient efficacy Withdrawal of consent Other	20 (10.5) 1 (0.5) 17 (8.9) 1 (0.5) 1 (0.5)

In total, 123 of the 190 patients (64.7%) had a paediatric ACR 30 response at four months (improvement of at least 30% compared to the initial scores for three of the six factors, and a worsening of no more than one factor in the paediatric ACR score). Approximately 74% of these patients were treated with a combination of abatacept and MTX at an average dosage of 13 mg/m²/week (the standard dosage for JIA).

Sub-group analyses were performed in order to evaluate the percentage of patients in the relevant population (patients previously treated with a TNF inhibitor) who responded to abatacept. In this sub-group of 56 patients, 22 had a paediatric ACR 30 response at four months; this is a 39% response rate. For information, the proportion of patients with a paediatric ACR 30 response in the sub-group of patients who had not previously received TNF inhibitor treatment (off-label use) was 101 in 133 (76%).

Period B:
Six-month randomised double-blind period aimed at comparing the efficacy of abatacept with placebo on patients selected as responsive to abatacept in period A.
The primary efficacy endpoint in this double-blind phase was the time to onset of the first inflammatory flare-up. An inflammatory flare-up was defined as:

- an aggravation of at least 30% for at least 3 of the 6 factors in the “ACR paediatric” score, and
- an improvement of $\geq$ 30% in a maximum of 1 factor out of 6 in the “ACR paediatric” score.
- an aggravation of at least 2 cm on the 10-cm VAS if the overall evaluation by the doctor or parents was used to define the flare-up.
- an aggravation of at least two joints if the number of swollen joints or joints with restricted mobility was used to define the flare-up.

The proportion of patients presenting with inflammatory flare-up was evaluated as a secondary endpoint.

As one of the 123 patients found to be responsive on the basis of the paediatric ACR 30 score in period A withdrew consent, 122 patients were randomised to receive 10 mg/kg of abatacept or placebo once a month during the six months of the study or until the onset of inflammatory flare-up. Only 20 (16%) of these patients had previously been treated with a TNF inhibitor (8 out of 60 patients in the abatacept group and 12 out of 62 patients in the placebo group) and only one in each group had previously been treated with two TNF inhibitors. During this phase, 81.7% (n=49/60) of patients treated with abatacept were on a combination regimen also involving MTX at an average dose of 13.5 mg/m²/week (usual dosage). Consequently, not all patients were treated with abatacept in combination with MTX, as is recommended by the SPC. Patient characteristics are shown in table 4.

Table 4. Baseline characteristics of patients included in period B

	Abatacept	**Placebo**
Number of patients included in period B*	60	62
Age (years) - mean (SD) min-max	12.6 (3.0) 6-17	12.0 (3.0) 5-17
Duration of disease (years) - mean (SD)	3.8 (3.7)	3.9 (3.5)
Number of joints with active arthritis - mean (SD)	18.2 (11.5)	14.7 (12.8)
Number of joints with mobility limitation - mean (SD)	17.3 (13.2)	14.3 (13.7)
Overall evaluation of disease activity by the doctor (100-mm VAS) - mean (SD)	53.5 (17.8)	52.7 (21.1)
Evaluation of the child's well-being by the parents (100-mm VAS) - mean (SD)	41.8 (22.5)	39.9 (24.7)
CHAQ score (score of 0 to 3) - mean (SD)	1.3 (0.7)	1.2 (0.8)
CRP (mg/dL) - mean (SD)	2.9 (4.6)	2.7 (3.4)
SR (mm/hr) - mean (SD)	30.8 (26.9)	31.4 (27.7)
Treatments received by patients on randomisation for period B: Methotrexate – n(%) Other DMARDs - n(%) Corticosteroids - n(%) NSAIDs - n(%)	 49 (81.7) 0 (0) 28 (46.7) 53 (88.3)	 47 (75.8) 1 (1.6) 27 (43.5) 58 (93.5)
Previous biological treatment received prior to inclusion: TNF inhibitors - n(%)	8 (13.3)	13 (21.0)

SD: standard deviation; Rf: rheumatoid factor; VAS : visual analogue scale; CHAQ: Childhood Health Assessment Questionnaire; CRP: C-reactive protein; SR: sedimentation rate; DMARD: Disease Modifying Anti-rheumatoid Arthritis Drugs; NSAIDs: non-steroidal anti-inflammatories

The percentage of patients discontinuing treatment was high, mainly because of lack of efficacy (17% in the abatacept group), as shown in table 5.

Table 5. Discontinuation of treatment in period B

	Abatacept	**Placebo**
Number of patients included in period B	60	62
Treatment discontinuations - n (%) Reason - n (%) Insufficient efficacy Withdrawal of consent	11 (18.3) 10 (16.7) 1 (1.7)	31 (50.0) 31 (50.0) -

- Results for the primary efficacy endpoint (time to onset of first flare-up):

Analysis was performed in ITT. The median time to onset of flare-up in the abatacept group could not be estimated as less than 50% of patients experienced a flare-up in the six-month follow-up period.

Proportion of patients experiencing flare-up (secondary endpoint):

Most (over 80%) of the study population was being treated on an off-label basis. After six months, the proportion of patients experiencing flare-up was significantly lower in the abatacept group (12/60; 20%) than in the placebo group (33/62; 53.2%); p<0.001. As over 80% of these patients had been treated by a combination regimen also involving MTX, the therapeutic response observed must be interpreted as a response to the combination of abatacept + MTX.

Only 20 of the 122 patients included in this phase met the criteria laid down in the marketing authorisation. Sub-group analyses showed that 2 out of 8 patients treated with abatacept experienced an inflammatory flare-up, compared to 8 out of 12 treated with placebo. Among those patients who had not previously received TNF inhibitor treatment, it was seen that 19.2% (10/52) of patients in the abatacept group experienced inflammatory flare-up, compared with 51% (25/49) in the placebo group.

Consequently, very little clinical data is available to allow assessment of the quantitative effect of abatacept in the treatment of JIA in patients who were insufficiently responsive to, or intolerant of, TNF inhibitor treatment.

Period C[4] :
Open-label extension phase involving treatment with 10 mg/kg abatacept for up to five years. The aim of this period was to evaluate the tolerance of abatacept. Patients who had completed the six-month double-blind period (period B) were eligible for period C. In addition, patients experiencing an inflammatory flare-up in period B could be immediately enrolled in period C, as could patients who presented an inadequate response during the pre-inclusion phase (period A).

A total of 153 patients were treated with abatacept in this extension phase. The average length of treatment was approximately 35 months (minimum length of treatment 21 months). 42 (27.5%) of the 153 patients included in this phase stopped treatment, mainly because of insufficient efficacy (13.1%).
As the primary objective of this phase was to evaluate tolerance, the results are discussed in section 3.2.

3.2. Tolerance

The tolerance of abatacept in the paediatric population was evaluated in a clinical study carried out on 190 patients treated with abatacept for an average of 35 months (4 months in period A, 6 months in period B and at least 21 months in period C).

Adverse events were reported in 70% (133/190) of patients treated with abatacept in period A. 27.4% of these events were regarded as treatment-related. Most of the adverse effects were of mild to moderate intensity and did not require the discontinuation of treatment, except for one case of leukaemia which occurred in period A.

During this clinical study, the adverse effects most often reported with abatacept were similar in nature to those observed in adults (infections, gastrointestinal disorders and infusion reactions). The only exception was fever. Very common adverse effects (≥1/10) were headaches and nausea, and common adverse effects (≥1/100 to < 1/10) were diarrhoea, cough, upper respiratory tract infections, fever, rhinopharyngitis and epigastric pain.

Reactions within an hour of infusion were reported for 4% of patients during period A and 2% of patients during period B. These reactions were similar to those reported in adults. Reactions occurred within 24 hours after infusion. Most of these were headaches, affecting 16% of patients treated with abatacept in period A and 3% of patients in period B.

One case of chickenpox was reported in period A and one case of multiple sclerosis was reported in period C.

Antibodies against abatacept were detected in 0.5% of patients in period A, 13% in period B and 11.4% of patients in period C. The presence of antibodies was not associated with a change in the efficacy of abatacept.

Abatacept has been on the US market for JIA in patients aged six or over since April 2008 and in Canada since July 2008. Post-marketing data available from December 2005 to June 2008 for patients aged 16 or under highlighted 10 adverse effects, including two cases of purpura, one of uveitis, one of thrombocytopenia and one of lymphopenia (the number of

[4] Ruperto et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum. 2010; 62 (6): 1792-1802.

patients exposed was not recorded). Analysis of the most recent PSUR[5] covering the period from June 2008 to December 2008 resulted in warnings being added to the SPC and the RMP on the risk of progressive multifocal leukoencephalitis.
A joint European risk management plan for the adult indication has been set up, aimed primarily at monitoring the occurrence of infections, cancers and effects on the immune system. The pharmaceutical firm is currently setting up a register.

3.3. Conclusion

The efficacy and tolerance of abatacept (ORENCIA) in the treatment of juvenile idiopathic arthritis (JIA) have been evaluated in a placebo-controlled clinical study of children who responded to abatacept. The study included 190 patients aged between 6 and 17 years with active JIA (average number of joints with active arthritis and limited mobility: 16), mainly polyarticular in nature (64%), who did not respond adequately to, or were intolerant of, at least one prior "non-biological" disease-modifying treatment such as methotrexate or a "biological" treatment such as a TNF inhibitor or anakinra. There were three phases to the study: phase A (open-label phase in which responsive patients were selected), phase B (double-blind) and phase C (open-label extension phase).

During phase A, which was carried out in order to select patients responding to abatacept, the 190 eligible patients were treated with abatacept (10 mg/kg in 30-minute infusions) for four months. Approximately 74% of patients were also treated with MTX (13.2 mg/m²/week). Patients with a paediatric ACR 30 response[6] at four months were regarded as responsive to abatacept. The paediatric ACR 30 response had been defined as an improvement of at least 30% compared to baseline with respect to 3 of the 6 factors and aggravation of a maximum of one factor of the ACR paediatric score. The proportion of patients responding to abatacept (paediatric ACR 30 at four months) was 64.7% (123/190).

During phase B, the 122 patients who were classed as responsive on the basis of the paediatric ACR 30 score (apart from one patient who withdrew consent) were randomised to receive either abatacept (10 mg/kg) or placebo on a double-blind basis for 6 months. Most patients were also being treated with methotrexate (81.7% in the abatacept group and 75.8% in the placebo group). The proportion of patients experiencing an inflammatory flare-up during these six months was significantly ($p<0.001$) lower in the abatacept group (12/60; 20%) than in the placebo group (33/62; 53.2%). As more than 80% of these patients had been on a combination regimen also involving MTX, the therapeutic response observed can be interpreted as a response to the combination of abatacept + MTX.
During phase C, which was conducted to evaluate the tolerance of abatacept, any patient wishing to be treated, including those who did not respond in period A, were given abatacept on an open-label basis (10 mg/kg). 13.1% of the 153 patients who took part in this phase and were treated for an average of 35 months stopped treatment because of a lack of efficacy.

The main shortcoming of this study is the small number of patients evaluated who met the criteria for the introduction of abatacept treatment defined in the marketing authorisation (inadequate response to or intolerance of disease-modifying treatments, including at least one TNF inhibitor). Only 56 of the 190 patients in phase A and 20 of the 122 patients in phase B had previously undergone TNF inhibitor treatment. In addition, approximately 20%

[5] Periodic safety update report

[6] ACR: American College of rheumatology. The 6 factors making up the paediatric ACR score are:

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

of patients were not treated in a combination regimen also involving MTX as recommended by the marketing authorisation.
A sub-group analysis was performed in order to evaluate the percentage of patients in the relevant population (patients previously treated with a TNF inhibitor) who responded to abatacept:

- in phase A, 22 of the 56 patients had a paediatric ACR 30 response at four months (39%), and
- in phase B, the proportion of patients experiencing an inflammatory flare-up was 2/8 for abatacept versus 8/12 for placebo.

Consequently, very little clinical data is available to allow assessment of the quantitative effect of abatacept in the treatment of JIA in patients who were insufficiently responsive to, or intolerant of, TNF inhibitor treatment (target population according to the marketing authorisation). Its efficacy has not been studied in patients under the age of 6.

Tolerance was similar to that observed in adults. The very common adverse effects (≥1/10) reported were headaches and nausea. The common adverse effects (≥1/100 to < 1/10) were diarrhoea, cough, upper respiratory tract infection, fever, rhinopharyngitis and epigastric pain. One case of chickenpox and one case of leukaemia were reported in period A and one case of multiple sclerosis was reported in period C. Reactions within an hour of infusion were reported for 4% of patients during period A and 2% of patients during period B.
Antibodies against abatacept were detected in 0.5% of patients in period A, 13% in period B and 11.4% of patients in period C. However, the presence of antibodies was not associated with a change in the efficacy of abatacept.
Since abatacept was placed on the market for JIA in the United States and Canada (more than two years ago), ten reports of adverse effects have been submitted. They include two cases of purpura, one case of uveitis, one case of thrombocytopenia and one case of lymphopenia. The number of patients exposed has not been recorded.

Global tolerance data for abatacept (all indications) led to a revision of the summary of product characteristics (SPC) and the creation of a risk management plan (RMP) to incorporate the risk of progressive multifocal leukoencephalitis.
Infections remain the primary known risk associated with administration of ORENCIA. Other concerns related to abatacept's mechanism of action include the long-term possibility of cancer and auto-immune reactions.
The RMP monitors these risks via extensions of clinical studies, register-based pharmacoepidemiological studies, immunological studies and routine drug tolerance monitoring. A register to monitor paediatric patients is currently being set up.

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 with a duration of more than 6 weeks[7]. These are serious and disabling chronic conditions.

ORENCIA is intended as symptomatic therapy.

In view of:

- the limited efficacy data available for the relevant population (patients aged six and over who have not responded adequately to other disease-modifying treatments including at least one TNF inhibitor), and
- the fact that tolerance information is only available for a short period and is inconclusive,

the Transparency Committee considers that the efficacy/adverse effects ratio of this proprietary medicinal product is moderate.

Public health benefit

The burden on public health caused by juvenile idiopathic arthritis is small because of the small number of patients affected (orphan condition).

Improving the management of this orphan disease is part of established public health priorities (National Rare Diseases Plan 2005-2008, Arrangements for paediatric medicines).

Given the limited amount of data available for patients who have failed treatment with a TNF-alpha inhibitor and the inadequate amount of data available on the longer-term tolerance and efficacy of abatacept, it is impossible to assume that there will be any additional impact on morbidity and quality of life for patients treated with ORENCIA as part of a combination regimen in this indication.

No impact on the organisation of the healthcare system is expected.
It is therefore impossible to know whether ORENCIA will be able to contribute to meeting the identified public health need when used in this indication.

Consequently, in the current state of knowledge and in view of the restricted size of the population concerned, it is not expected that ORENCIA will benefit public health in this indication.

This proprietary medicinal product is a third-line treatment for JIA. It is designed for patients who have not responded sufficiently to, or have not tolerated, other disease-modifying treatment including at least one TNF inhibitor.

No other medicine has been granted marketing authorisation specifically for children at this stage of the disease.
The actual benefit of this proprietary medicinal product for this indication is substantial.

[7] Job deslandre et al. Juvenile idiopathic arthritis. Encyclopédie orphanet. September 2003.

4.2. Improvement in actual benefit (IAB)

Though this is the first biotherapy to be granted marketing authorisation for use in patients suffering from juvenile idiopathic arthritis who have not responded sufficiently to at least one TNF inhibitor, the Transparency Committee is of the opinion that, given:

- the limited efficacy data which make it impossible to evaluate the benefits of ORENCIA (abatacept) in this indication (only 16% of the patients evaluated during the double-blind phase of the study matched the patients targeted in the indication), and
- the fact that tolerance information is only available for a short period and is inconclusive,

ORENCIA in combination with methotrexate provides no improvement in actual benefit (IAB V) in terms of therapeutic strategy.

4.3. Therapeutic use[7, 8, 9]

Current management

The aim of the treatment of juvenile idiopathic arthritis (JIA) is to combat inflammation, relieve pain and stiffness and prevent or slow down the progression of articular 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 first-line treatment but their efficacy is not reliable. 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 cyclosporin are sometimes used on an off-label basis as an alternative to methotrexate, but their efficacy in polyarticular JIA is less well established.

TNF inhibitors (adalimumab and etanercept) are used to treat patients with polyarticular JIA who have failed on other disease-modifying treatments, and have been granted marketing authorisation for JIA:

- in children aged 4 to 17 years with an insufficient response to or intolerance of MTX (ENBREL - etanercept),
- only in children aged 13 to 17 years with an insufficient response to one or more conventional disease-modifying treatments (HUMIRA - adalimumab).

The alternatives for patients who do not respond sufficiently to a TNF inhibitor (adalimumab or etanercept) are:

- addition of a non-biological disease-modifying treatment, especially MTX, if the TNF inhibitor had been used as monotherapy,
- administration of the second TNF inhibitor which has not yet been used,
- administration of abatacept.

Role of abatacept in treatment strategy

Abatacept is the only medicinal product which has been granted marketing authorisation for patients aged six and over who have not responded adequately to at least one TNF inhibitor.

[8] Hull RG; British Paediatric Rheumatology Group. Guidelines for management of childhood arthritis. Rheumatology 2001; 40 (11): 1309-12

[9] Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. JAMA 2005; 294(13): 1671-84

However, limited efficacy data is available for abatacept in the strict indication specified in the marketing authorisation. In the clinical study referred to in the dossier (N = 190), few patients failed at least one TNF inhibitor; only 20 patients selected as responding to abatacept (paediatric ACR 30 response at four months) and included in the double blind phase fell into this category. The proportion of these patients experiencing an inflammatory flare-up at six months was 2/8 in the abatacept group versus 8/12 in the placebo group. In addition, the amount of tolerance data available is still limited (short duration of treatment and small number of patients exposed). The risks of infection, cancer and auto-immune reactions must be taken into consideration.

4.4. Target population

The prevalence of JIA in France is estimated to be approximately 2 to 3/10,000 children.[10,11]
According to data from the French National Demographic Studies Institute (INED), there were 9,500,000 children aged between 6 and 17 in France on 1 January 2010. Consequently, the population of JIA patients aged between 6 and 17 would be 2,000 to 3,000.
Approximately 30% of them would require disease-modifying treatment with methotrexate, and approximately 30% would, according to the expert consensus, be found to be insufficiently responsive to or intolerant of methotrexate. The population of patients failing on MTX would not exceed 300 children.
According to the EMA report (EPAR[12]), 10 to 20% of patients would fail TNF inhibitor treatment. On the basis of the above, the maximum target population for abatacept would be 60 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services.

[10] Prieur AM. Management of children with chronic rheumatism. Similarities and differences with rheumatoid arthritis. Revue du rhumatisme 1990; 57 :280-286.
[11] Job Deslandre et al. Juvenile idiopathic arthritis. Encyclopédie orphanet. September 2003.
[12] EMA. Assessment report for Orencia February 2010.