HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 September 2013

HUMIRA 40 mg, solution for injection in pre-filled syringe

B/2 x 0.8 ml pre-filled glass syringes with 2 alcohol wipes (CIP: 34009 362 230 5 9)

HUMIRA 40 mg, solution for injection in pre-filled pen

B/2 x 0.8 ml pens with 2 alcohol wipes (CIP: 34009 378 014 5 4)

HUMIRA 40 mg/0.8 ml, solution for injection for paediatric use

Pack of 2 boxes, each one containing one 0.8 ml vial of sterile solution with 2 alcohol wipes (CIP: 34009 418 517 2 8)

Applicant: ABBVIE

INN	**adalimumab**
ATC Code (2012)	**L04AB04 (tumour necrosis factor alpha (TNF-alpha) inhibitors)**
Reason for the review	**Extension of the indication for JIA in children from 2 to 4 years.**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)**
Indication concerned	**"HUMIRA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 2 to 17 years who have had an inadequate 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 aged less than 2 years."**

Actual Benefit	**The actual benefit is substantial when combined with methotrexate in the treatment of active polyarticular juvenile idiopathic arthritis (or as monotherapy, in cases of intolerance to methotrexate) in children from 2 years who have not had a satisfactory response to one or more disease-modifying treatments.**
Improvement in Actual Benefit	**In the absence of clinical data versus the only clinically relevant comparator, etanercept, HUMIRA does not provide an improvement in actual benefit (IAB V, non-existent) compared with ENBREL when combined with methotrexate in the treatment of active polyarticular juvenile idiopathic arthritis (or as monotherapy, in cases of intolerance to methotrexate) in children from 2 years who have not had a satisfactory response to one or more disease-modifying treatments.**
Therapeutic use	**For active polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 to 17 years, HUMIRA is a second-line disease-modifying treatment, for those who have not had a satisfactory response to one or more disease-modifying treatments. HUMIRA should preferably be used in combination with methotrexate, however may be given as monotherapy in cases of methotrexate intolerance or where continued treatment with methotrexate is inappropriate.**
Recommendations	**-**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised procedure): 8 September 2003 Date of revision of Marketing Authorisation concerned: 25 February 2013 (extension of the indication for juvenile idiopathic arthritis in children from 2 years) European risk management plan
Prescribing and dispensing conditions / special status	Exception drug status List I Initial annual hospital prescription Syringe and pen: specialists in rheumatology, gastroenterology, digestive surgery, dermatology, paediatrics and internal medicine. Vial: specialists in rheumatology, gastroenterology, digestive surgery, paediatrics and internal medicine.

ATC Classification	2012	
	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AB	Tumour necrosis factor alpha (TNF-alpha) inhibitors
	L04AB04	Adalimumab

02 BACKGROUND

In August 2008, the extension of the indication of HUMIRA (at a set dose of 40 mg every two weeks) in polyarticular juvenile idiopathic arthritis (JIA) was restricted by EMA to the age range of between 13 and 17 years due to there being insufficient data to specify a set dose and the absence of a form that allows the administration of a dose modified to body surface area as evaluated in the only efficacy clinical study available.

In March 2011, after having developed a new paediatric format with a graduated syringe enabling the necessary amount to be drawn based on body surface area, an extension of the indication to children from 4 to 12 years was approved on the basis of the main results from the DE038 study, which had previously been assessed by EMA in 2008 and by the Transparency Committee in 2009.
The Transparency Committee gave its opinion on this indication on 24 June 2009 and 21 September 2011 and stated that the actual benefit of HUMIRA was substantial and had level V IAB for its therapeutic use.

This review concerns a change to the inclusion conditions for the list of medicines approved for reimbursement through National Health Insurance and approved for hospital use for HUMIRA, following the extension of the indication for juvenile idiopathic arthritis in children from 2 years.

03 THERAPEUTIC INDICATIONS

Pre-filled syringe, pre-filled pen, solution for injection for paediatric use

Indication forming the subject of the application

Previous wording:
"Polyarticular juvenile idiopathic arthritis

HUMIRA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 4 to 17 years who have had an inadequate 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 aged less than 4 years."

New wording
"Polyarticular juvenile idiopathic arthritis

HUMIRA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 2 to 17 years who have had an inadequate 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 aged less than 2 years."

Indications not concerned by this assessment

- "Paediatric Crohn's disease

HUMIRA is indicated for the treatment of severe active Crohn's disease, in children and adolescents aged 6 to 17 years who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Pre-filled 40 mg syringe and pre-filled 40 mg pen

- Crohn's Disease

HUMIRA is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

- Rheumatoid arthritis

HUMIRA in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

HUMIRA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

HUMIRA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

- Axial spondyloarthritis

Ankylosing spondylitis (AS)

HUMIRA is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

HUMIRA is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

- Psoriatic arthritis

HUMIRA is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. HUMIRA has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical forms of the disease and to improve physical function.

- Psoriasis

HUMIRA is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

- Ulcerative colitis

HUMIRA is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies."

04 DOSAGE

HUMIRA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of polyarticular juvenile idiopathic arthritis. Patients being treated with HUMIRA will be given a special alert card.

Polyarticular juvenile idiopathic arthritis from 2 to 12 years:
The recommended dose of HUMIRA for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years is 24 mg/m^2 body surface area, up to a maximum single dose of 20 mg of adalimumab (for patients aged 2 to 4 years) and up to a maximum single dose of 40 mg of adalimumab (for patients aged 4 to 12 years) administered every other week via subcutaneous injection.
The volume for injection is selected based on the patients' height and weight (see table below). The paediatric 40 mg vial is available for patients who need a dose of less than the full 40 mg dose.

Height (cm)	Total body weight (kg)												
	10	15	20	25	30	35	40	45	50	55	60	65	70
80	0.2	0.3	0.3	0.3									
90	0.2	0.3	0.3	0.4	0.4	0.4							
100	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5					
110	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6		
120	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7
130		0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.7
140		0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*
150			0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*	0.8*
160			0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.8*	0.8*	0.8*	0.8*
170				0.6	0.6	0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*
180					0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*	0.8*

* Maximum single dose is 40 mg (0.8 ml)

Polyarticular juvenile idiopathic arthritis from 13 to 17 years:
For adolescents aged from 13 to 17 years, a dose of 40 mg is administered every other week, regardless of body surface area. The 40 mg pen and the pre-filled 40 mg syringe are available for patients to administer a full 40 mg dose.
The available data permit the assumption that a clinical response is usually achieved within 12 weeks of treatment. Continuation of treatment must be carefully reconsidered in patients who have not responded to the treatment within this period. There is no justified use of HUMIRA in children aged under 2 years in this indication.

For other indications: see SPC

05 THERAPEUTIC NEED

Juvenile idiopathic arthritis (JIA) 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.[1] It is a serious and debilitating chronic condition. Diagnosis of this disease is an exclusion diagnosis, which includes all forms of chronic arthritis in children with an unknown cause.

The aim of JIA treatment is to combat inflammation, relieve pain and stiffness and prevent or slow down the progression of articular lesions. It uses fast-acting symptomatic treatments (NSAIDs, corticosteroids) and sometimes disease-modifying treatments (methotrexate as a 1st line and TNF α inhibitors as 2nd line treatments), depending on the form of JIA (oligo or polyarticular).

Another TNF α inhibitor, etanercept, has Marketing Authorisation to treat polyarticular JIA in children from 2 years, who have not had a satisfactory response or are intolerant to methotrexate.

[1] Job Deslandre C. Arthrite juvénile idiopathique. Encyclopédie Orphanet, January 2007

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Indication	Date of Opinion	AB	IAB (Wording)
TNF alpha inhibitors (L04AB)				
ENBREL, solution for injection **(etanercept)** ***Pfizer***	**Treatment of active chronic polyarticular juvenile arthritis, in children aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. ENBREL has not been studied in children aged less than 4 years.**	**02/10/2002 (Inclusion)**	**Substantial**	**In the treatment of chronic polyarticular juvenile arthritis, ENBREL provides a substantial improvement in actual benefit (level II) compared with the treatment strategy for these patients.**
ENBREL, solution for injection **(etanercept)** ***Pfizer***	**Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.**	**11/04/2012 (Amendments to the inclusion conditions in the indication of JIA for proprietary medicinal products at a dose of 25 mg. The indication was widened to include children from 2 years.)**	**Substantial**	**The extension of the indication for the age range involving children aged 2 and 3 years does not change the assessment of the IAB for ENBREL in the treatment of active polyarticular juvenile idiopathic arthritis in cases of inadequate response to methotrexate (IAB II awarded in 2002).**
Selective immunosuppressants (L04AA)				
ORENCIA, powder for concentrate for solution for infusion **(abatacept)** ***Bristol-Myers Squibb***	**ORENCIA in combination with methotrexate is indicated for 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 including at least one TNF inhibitor. ORENCIA in children below 6 years of age has not been studied.**	**05/01/2011 (Extension of the indication)**	**Substantial**	**Although it is the first biotherapy with Marketing Authorisation for patients with juvenile idiopathic arthritis who have not had an adequate response to at least one TNF inhibitor, the Transparency Committee, in view of:** **- limited efficacy data that does not enable the benefit of ORENCIA (abatacept) to be assessed in this indication (only 16% of patients evaluated during the double-blind phase of the study corresponded to patients covered in the indication) and,** **- the low success and the uncertainties regarding its safety,** **considers that ORENCIA in combination with methotrexate does not provide an improvement in actual benefit (IAB V) in its therapeutic use.**

NAME (INN) *Company*	Indication	Date of Opinion	AB	IAB (Wording)
Anti-metabolites (L01B)				
METHOTREXATE BELLON 2.5 mg, tablet **(methotrexate)** ***Sanofi-Aventis***	**Polyarticular forms of severe and active juvenile idiopathic arthritis, when the response to NSAIDs is judged as unsatisfactory.**	**04/01/2006** **(Renewal of inclusion)**	**Substantial**	**Level II improvement in actual benefit in the treatment of these conditions**
METOJECT, solution for injection **(methotrexate)** ***NORDIC PHARMA***	**Polyarticular forms of severe and active juvenile idiopathic arthritis, when the response to NSAIDS is inadequate.**	**10/05/2006** **(Inclusion)**	**Substantial**	**For all of the Marketing Authorisation indications, METOJECT does not provide an improvement in actual benefit (IAB V) compared with other methotrexate-based proprietary medicinal products for injection.** **The Committee highlights that METOJECT can specifically be administered subcutaneously and does not require being prepared beforehand by a trained professional.**
METOJECT, solution for injection **(methotrexate)** ***NORDIC PHARMA***	**Polyarticular forms of severe and active juvenile idiopathic arthritis, when the response to NSAIDS is inadequate.**	**17/03/2007** **(Re-assessment of IAB following the submission of new data)**		**In view of:** **- a subcutaneous administration regimen that does not require preparation beforehand,** **- the results from a study demonstrating the superiority of methotrexate administered subcutaneously compared with orally,** **the Transparency Committee considers that METOJECT, in all of its Marketing Authorisation indications, provides a minor improvement in actual benefit (IAB IV) compared with other methotrexate-based proprietary medicinal products for injection.**
METOJECT, solution for injection **(methotrexate)** ***NORDIC PHARMA***	**Polyarticular forms of severe and active juvenile idiopathic arthritis, when the response to NSAIDS is inadequate.**	**09/05/2012** **(Renewal of inclusion)**	**Substantial**	**-**
LEDERTREXATE, solution for injection **(methotrexate)** ***BIODIM***	**Polyarticular forms of severe and active juvenile idiopathic arthritis, when the response to treatment with NSAIDS is judged as unsatisfactory.**	**18/11/2009** **(Extension of indication)**	**Substantial**	**In the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis and psoriasis, LEDERTREXATE proprietary medicinal products for injection do not provide an improvement in actual benefit (IAB V) compared with other methotrexate-based proprietary medicinal products, and in particular METHOTREXATE BELLON.**

06.2 Other health technologies

Not applicable

◗ Conclusion

Etanercept (ENBREL), the only other TNF α inhibitor indicated in the treatment of polyarticular juvenile idiopathic arthritis in children from 2 years, is the clinically relevant comparator product.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Marketing Authorisation:

Country	Marketing Authorisation	
	Date	Population(s) That of the Marketing Authorisation or restricted
European Union	**08/09/03**	**Rheumatoid arthritis (RA), Psoriatic arthritis (Pso arth), Ankylosing spondylitis (AS), Crohn's disease, Psoriasis Juvenile idiopathic arthritis (JIA) Ulcerative colitis (UC)**
United States	**31/12/02**	**Rheumatoid arthritis (RA), Psoriatic arthritis (Pso arth), Ankylosing spondylitis (AS), Crohn's disease, Psoriasis, Juvenile idiopathic arthritis (JIA) Ulcerative colitis (UC)**
Australia	**10/12/03**	**Rheumatoid arthritis (RA), Psoriatic arthritis (Pso arth), Ankylosing spondylitis (AS), Crohn's disease, Psoriasis, Juvenile idiopathic arthritis (JIA)**
Japan	**16/04/08**	**Rheumatoid arthritis (RA), Psoriatic arthritis (Pso arth), Ankylosing spondylitis (AS), Crohn's disease, Psoriasis**
Canada	**24/09/04**	**Rheumatoid arthritis (RA), Psoriatic arthritis (Pso arth), Ankylosing spondylitis (AS), Crohn's disease, Psoriasis**

Reimbursement abroad for JIA:

Country	Reimbursed YES/No/Assessment in progress			
	JIA 2-4 years	JIA 4-12 years		JIA 13 -17 years
	Paediatric vial	Paediatric vial	Syringe or pen	Syringe or pen
Germany	Yes	Yes	Yes	Yes
Austria	No	Yes	Yes	Yes
Denmark	Yes	Yes	Yes	Yes
Finland	Assessment in progress	Yes	Yes	Yes
Greece	No	No	Yes	Yes
Ireland	Yes	Yes	Yes	Yes
Italy	Assessment in progress	Yes	Yes	Yes
Norway	Yes	Yes	Yes	Yes
The Netherlands	Yes	Yes	Yes	Yes
Portugal	Assessment in progress	Yes	Yes	Yes
Sweden	Yes	Yes	Yes	Yes
United Kingdom	Yes	Yes	Yes	Yes

08 REMINDER OF PREVIOUS ASSESSMENTS FOR HUMIRA IN JIA

Date of Opinion	24/06/2009 (inclusion in the extension of the indication for JIA in adolescents from 13 to 17 years)
Indication	Polyarticular juvenile idiopathic arthritis HUMIRA, combined with methotrexate, is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in adolescents aged 13 to 17 years who have not had a satisfactory response to one or more disease-modifying treatments. HUMIRA may be given as monotherapy in cases of methotrexate intolerance or where continued treatment with methotrexate is inappropriate.
Actual Benefit (AB)	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. These are serious and disabling chronic conditions. HUMIRA is intended for symptomatic treatment. The efficacy/adverse effects ratio for these medicinal products is high. These products are a second-line treatment following the failure of classic disease-modifying treatments including methotrexate. There is only one alternative medicine with Marketing Authorisation that specifically includes children at this stage of the disease: ENBREL (etanercept). The actual benefit of these products in this indication is substantial.
Improvement in Actual Benefit (IAB)	In the treatment of active polyarticular juvenile idiopathic arthritis in adolescents aged 13 to 17 years, in cases of an inadequate response to one or more disease-modifying treatments, HUMIRA does not provide an improvement in actual benefit (level V) in the therapeutic strategy.
Studies requested	The Transparency Committee would like to receive the results of the everyday clinical practice study requested by EMA (register) in the context of the Risk Management Plan.

Date of Opinion (reason for the review)	21/09/2011 (Amendments to the inclusion conditions in the indication of juvenile idiopathic arthritis (JIA): extension to children and adolescents aged 4 to 12 years)
Indication	Polyarticular juvenile idiopathic arthritis HUMIRA combined with methotrexate, is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents aged 4 to 17 years who have not had a satisfactory response to one or more disease-modifying treatments. HUMIRA may be given as monotherapy in cases of methotrexate intolerance or where continued treatment with methotrexate is inappropriate (for efficacy as monotherapy, see SPC). HUMIRA has not been studied in children aged less than 4 years.
Actual Benefit (AB)	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. These are serious and disabling chronic conditions. HUMIRA is intended for symptomatic treatment. The efficacy/adverse effects ratio for these medicinal products is high. These products are a second-line treatment (following the failure of classic disease-modifying treatments including methotrexate.) Alternative medicinal products exist. The actual benefit of these products in this indication is substantial.
Improvement in Actual Benefit (IAB)	HUMIRA does not provide an improvement in actual benefit (level V) in the treatment of active polyarticular juvenile idiopathic arthritis in adolescents aged 4 to 12 years who have not had a satisfactory response to one or more disease-modifying treatments.
Studies requested	As stated in the previous Opinion, the Transparency Committee would like to receive the results of the everyday clinical practice study, with a follow-up period lasting 10 years, requested by EMA in the context of the Risk Management Plan (RMP) on patients with JIA aged 13 to 17 years (STRIVE register). Furthermore, the Committee would like to be sent the same long-term follow-up data of the safety of HUMIRA in children aged 4 to 12 years. This data can be collected within the context of the study scheduled in the RMP, on the condition that it covers children aged 4 to 12 years.

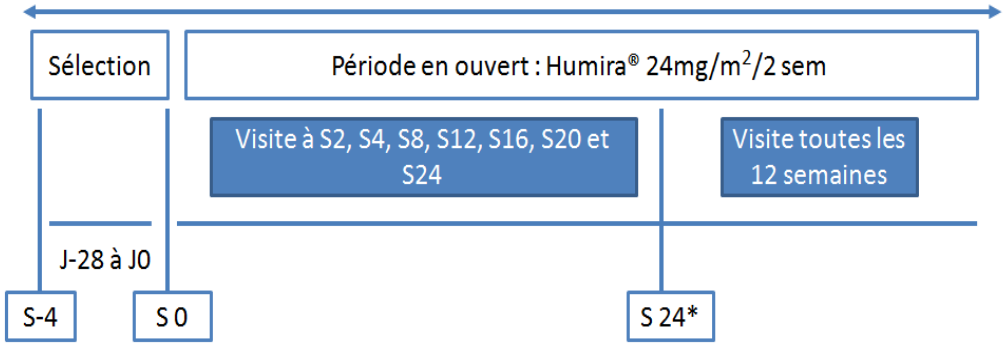
09 ANALYSIS OF AVAILABLE DATA

09.1 Efficacy

The assessment of the efficacy of adalimumab (HUMIRA) in JIA in children aged 2 to 4 years is based on a compassionate use study (M10-444) carried out at the request of the regulatory authorities (FDA and EMA). The study started prior to Marketing Authorisation being awarded, in August 2011, for ENBREL in this indication. Consequently, there has been no study carried out comparing HUMIRA and ENBREL. For ethical reasons, a placebo was not selected as a comparator.
The study, which started in 2009, has not yet finished; the results presented are interim results (last patient/last visit at 24 weeks: 9 September 2011).

The primary aim of this study was to evaluate the safety of HUMIRA in patients aged from 2 to under 4 years, or older than 4 years and weighing less than 15 kg, with moderately to severely active polyarticular juvenile idiopathic arthritis. Secondary efficacy endpoints included individual efficacy indicators and the proportion of patients showing a paediatric ACR 30/50/70/90 response.

	Study M10-444
Primary study objective	To evaluate the safety of HUMIRA in patients aged from 2 to under 4 years, or older than 4 years and weighing less than 15 kg, with moderately to severely active polyarticular juvenile idiopathic arthritis.
Method	International, multicentre, open-label phase IIIb study
Main inclusion criteria	- Patients with a diagnosis of polyarticular juvenile idiopathic arthritis or moderate to severe polyarticular progression (arthritis defined as affecting at least five joints at the time of starting treatment). These criteria correspond to ILAR categories for polyarticular juvenile arthritis with rheumatoid factor positive or negative (RF+ or RF-) and oligoarticular arthritis. - Patients aged from 2 to under 4 years, or older than 4 years weighing less than 15 kg. - Patients who tested negative for Intra-Dermo-Reaction. - In Europe, patients presenting with a history of failure, inadequate response, or intolerance to at least one disease-modifying treatment (DMARD: Disease Modifying Anti-Rheumatic Drug).
Main non-inclusion criteria	- Patients who had already been treated with TYSABRI (natalizumab), RAPTIVA (efalizumab) or with other biological treatments such ORENCIA (abatacept), KINERET (anakinra), ROACTEMRA (tocilizumab) or RITUXAN (rituximab). - Patients who had already been treated with a TNF inhibitor, including ENBREL (etanercept), REMICADE (infliximab), CIMZIA (certolizumab), SIMPONI (golimumab) or HUMIRA (adalimumab).
Course of the study	The dosage of adalimumab was 24 mg/m² of the body surface area, up to a maximum single dose of 20 mg, administered every other week via subcutaneous injection.

	 *Les patients sont suivis pendant 24 semaines quel que soit leur âge. A la semaine 24 si le patient est âgé de moins de 4 ans et pèse moins de 15 kg, l'étude se poursuit. Quand le patient atteint l'âge de 4 ans et pèse au moins 15 kg, il peut être suivi une année supplémentaire pour permettre la transition jusqu'a à un traitement approprié. Sélection = Selection Période en overte: Humira 24 mg/m^2/2 sem = Open-label period: HUMIRA 24 mg/m^2/2 weeks J-28 to J0 = Day 28 – Day 0 S-4 = Week 4 S 0 = Week 0 Visite a S2, S4, S8, S12, S16, S20 et S24 = Visit at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24 Visites toutes les 12 semaines = Visits every 12 Weeks S24 = Week 24 * The patients are monitored for 24 weeks regardless of their age. At Week 24, if the patient is aged under 4 years and weighs less than 15 kg, they continue with the study. When the child reaches the age of 4 years and weighs at least 15 kg, they can be monitored for an additional year to enable a transition to an appropriate treatment to be made.
Primary efficacy endpoint	Incidence of serious adverse events (SAE) and adverse events (AE).
Secondary endpoints included	Paediatric ACR 30/50/70/90 response rate measured at Weeks 12 and 24 for all patients, then every 12 weeks for patients continuing with the study. Condition of joints: at baseline then at Weeks 12 and 24: SJC66: Swollen Joint Count corresponding to the number of swollen joints LOM69: Limitation On passive Motion corresponding to the number of joints with reduced mobility POM75: Pain On passive Motion corresponding to the number of painful joints TJC75: Tender Joint Count corresponding to the number of tender joints Overall assessment of the severity of the disease by the parents (on a visual analogue scale (VAS) 0-100 mm) Assessment of pain by the parents (VAS) Overall assessment of the disease by the doctor (VAS) DICHAQ (assessment of child's disability questionnaire by the parents)
Calculation of the number of patients needed	Due to the low incidence and prevalence of juvenile idiopathic arthritis in patients aged 2 to 4 years, the number of patients needed was chosen based on the anticipated availability of patients to participate in the 3 year study. The total number of patients anticipated was approximately 30 patients worldwide, including between 1 and 3 in France.
Statistical analysis	The efficacy analyses were carried out on the intention to treat (ITT) population, defined as all patients included in the study who received at least one dose of HUMIRA. In order to minimise the bias inherent to missing data, two statistical methods were used in addition to observed data to compensate for the lack of data for certain parameters: - the Last Observation Carried Forward (LOCF) method - the Non Responder Imputation (NRI) method

Results from the study:

- **Patient characteristics**

The study included 32 patients; 28 were children aged between 2 and 4 years and 4 children were aged over 4 years and weighing less than 15 kg (Table 1). The majority of the children were girls (87.5%). The mean age of the 32 children was 3 years and their mean weight was 13.4 kg.

Table 1: Main demographic characteristics for patients included in study M10-144

Demographic characteristics N=32	
Gender n(%)	
Girl	28 (87.5)
Boy	4 (12.5)
Age n (%)	
< 4 years	28 (87.5)
≥ 4 years	4 (12.5)
Mean (± SD)	3.04 ± 0.723
Median	3.15
Min-max	2.0 - 4.6
Weight (kg) n (%)	
Mean (± SD)	13.4 ± 1.96
Median	13.0
Min-Max	10.4 - 18.9
Height (cm) n (%)	
Mean (± SD)	93 ± 6.09
Median	93.5
Min-Max	83 – 104.0
BMI* (kg/m²)	
Mean (± SD)	15.5 ± 1.27
Median	15.3
Min-Max	13.1 – 18.5
Body surface area (m^2)	
Mean (± SD)	0.6 ± 0.06
Median	0.6
Min-Max	0.5 – 0.7

**BMI = Body Mass Index*

Four patients (12.5%) discontinued the study prematurely (1 before the end of the 24 weeks and 3 after) and 11 patients completed the study. No patient discontinued the study due to adverse events. The reasons for discontinuation of the study were: withdrawal of consent, lost to follow-up, Marketing Authorisation obtained and the weight and age of the child were above the set limits of the study.

At the time of injection of the first dose of HUMIRA, the disease had been diagnosed for an average of 12.3 months (Table 2). Patients included had active JIA that was moderate to severe in intensity. With the exception of one child, all were rheumatoid factor negative and the large majority had normal C reactive protein levels.

Table 2: Main characteristics of disease activity

Variable	**HUMIRA N=32**
Time between JIA diagnosis and the 1st dose injected (months)	
Mean ± SD	12.3 ± 9.26
Median	10.3
Min - Max	2.3 – 40.8
TJC75: (Tender Joint Count) number of tender joints	
Mean ± SD	3.8 ± 5.02
Median	2.0
Min - Max	0 - 19
SJC66: (Swollen Joint Count) number of swollen joints	
Mean ± SD	8.9 ± 7.37
Median	7.0
Min – Max	0 - 36

LOM69: (Limitation On passive Motion) number of joints with reduced mobility	
Mean ± SD	8.5 ± 7.70
Median	6.5
Min - Max	0 - 32
POM75: (Pain On passive Motion) number of painful joints	
Mean ± SD	5.1 ± 4.70
Median	4.0
Min - Max	0 - 19
Assessment of pain by parents (VAS, mm)	
Mean ± SD	46.1 ± 25.73
Median	51.0
Min - Max	0 - 83
Overall assessment of disease by parents (VAS, mm)	
Mean ± SD	47.6 ± 25.91
Median	51.5
Min - Max	0 - 90
PGA (Physician Global Assessment) assessment of pain by doctor	
Mean ± SD	55.3 ± 19.70
Median	60.5
Min - Max	9 - 84
DICHAQ (Disability Index of Childhood Health Assessment Questionnaire) assessment of child's disability questionnaire by parents	
Mean ± SD	1.2 ± 0.66
Median	1.3
Min - Max	0 – 2.9
CRP (mg/dl)* C Reactive Protein	
Mean ± SD	1.6 ± 2.43
Median	0.4
Min - Max	0.4- 12.8
Normal (<0.9 mg/dl), n (%)	19 (61.3)
Abnormal (≥0.9 mg/dl), n (%)	12 (38.7)
Missing data	1

**N=31*

- **Associated treatments taken before inclusion and during the study**

Before inclusion:

78.1% of patients had already received treatment with methotrexate to treat their JIA; 68.8% used systemic corticosteroids and 37.5% NSAIDs. No patients had received a biological treatment.

On inclusion:

71.9% of patients received treatment with methotrexate, 43.8% with systemic corticosteroids and 31.3% with NSAIDs.

The associated treatments taken before and at the time of inclusion are presented in Table 3.

Table 3: Associated treatments

Substances	Before inclusion, n (%)	At inclusion, n (%)
Synthetic DMARD*		
Methotrexate	25 (78.1)	23 (71.9)
Systemic corticosteroids	22 (68.8)	14 (43.8)
Systemic NSAIDs	12 (37.5)	10 (31.3)
Biological medication	0	0

**Disease-modifying anti-rheumatic drugs*

- **Results for the secondary efficacy endpoints (primary endpoint being a safety endpoint (see section 09.2.1))**

Paediatric ACR response rate

The percentage of patients achieving a paediatric ACR 30 response was 93.5% at Week 12 and 90% at Week 24 (ITT population).
The paediatric ACR 50/70/90 response rates were 90.3%/61.3%/38.7% at Week 12 and 83.3%/73.3%/36.7% at Week 24 (ITT population).

Note: the results were similar when calculated using the LOCF statistical method, however not quite as good with the NRI method.

The percentage of patients achieving a paediatric ACR 30/50/70/90 response was 85.7%/78.6%/71.4%/64.3% at Week 48. It should be noted that the number of patients followed-up reduced considerably after Week 48.

Table 4: paediatric ACR response rate at Weeks 12 to 96

		HUMIRA 24 mg/m^2 every other week			
Visit	**Analysis method**	**PedACR30 n/N1 (%)**	**PedACR50 n/N1 (%)**	**PedACR70 n/N1 (%)**	**PedACR90 n/N1 (%)**
Week 12	Observed	29/31 (93.5)	28/31 (90.3)	19/31 (61.3)	12/31 (38.7)
	NRI	29/32 (90.6)	28/32 (87.5)	19/32 (59.4)	12/32 (37.5)
	LOCF	29/31 (93.5)	28/31 (90.3)	19/31 (61.3)	12/31 (38.7)
Week 24	Observed	27/30 (90.0)	25/30 (83.3)	22/30 (73.3)	11/30 (36.7)
	NRI	27/32 (84.4)	25/32 (78.1)	22/32 (68.8)	11/32 (34.4)
	LOCF	28/31 (90.3)	26/31 (83.9)	23/31 (74.2)	11/31 (35.5)
Week 36	Observed	18/20 (90.0)	17/20 (85.0)	13/20 (65.0)	11/20 (55.0)
Week 48	Observed	12/14 (85.7)	11/14 (78.6)	10/14 (71.4)	9/14 (64.3)
Week 60	Observed	4/5 (80.0)	3/5 (60.0)	3/5 (60.0)	2/5 (40.0)
Week 72	Observed	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
Week 84	Observed	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
Week 96	Observed	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)

LOCF: Last Observation Carried Forward, NRI: Non Responders Imputation
n: number of responder patients
N1: number of patients with no missing data

Evaluation of joints

At Weeks 12 and 24, the observed data regarding the condition of the joints showed a reduction in all the assessment scores compared with baseline values (Table 5).

Table 5: Mean variation in joint condition assessment scores at Weeks 0, 12 and 24.

	Mean variation in the various scores compared with baseline ± SD			
Visit	**TJC75**	**SJC66**	**POM75**	**LOM69**
Week 0 (mean) n/N = (32/32)	3.8 ± 5.02	8.9 ± 7.37	5.1 ± 4.70	8.5 ± 7.70
Week 12 (change) n/N = (31/32)	-2.7 ± 5.09	-6.2 ± 4.24	-4.7 ± 4.63	-5.6 ± 4.84
Week 24 (change) n/N = (30/32)	-3.00 ± 5.54	-6.3 ± 5.83	-3.9 ± 7.32	-5.6 ± 5.56

Evaluation of health and quality of life

An improvement in the parameters based on health and quality of life of children evaluated was noted with HUMIRA compared with baseline values after 12 weeks and after 24 weeks of treatment (Table 6).

Table 6: Mean change compared with baseline for health and quality of life of patients at Weeks 0, 12 and 24.

Mean change compared with baseline ± SD				
Visit	**Overall assessment of the severity of the disease by parents**	**Assessment of pain by parents**	**Overall assessment of the disease by parents**	**DICHAQ**
Week 0 (mean) n/N = (32/32)	47.6 ± 25.91	46.1 ± 25.73	55.3 ± 19.70	1.2 ± 0.66
Week 12 (change) n/N = (31/32)	-28.1 ± 29.91	-27.2 ± 25.36	-41.4 ± 21.20	-0.5 ± 0. 64
Week 24 (change) n/N = (30/32)	-32.2 ± 29.74	-29.5 ± 28.28	-45.3 ± 21.32	-0.5 ± 0. 69

09.2 Safety/Adverse effects

09.2.1 Safety data from the clinical study

The main aim of study M10-444 was to determine the safety profile of HUMIRA for children aged from 2 to under 4 years and above 4 years weighing less than 15 kg, with moderately to severely active polyarticular juvenile idiopathic arthritis.

The mean duration of exposure to treatment was 299.1 days (SD = 129.84; median = 266.0) with a total exposure of 26.2 patient-years (PY). All patients were exposed to HUMIRA for a minimum duration of 57 days, with a maximum exposure of 679 days.

At the interim date, across the whole study, 27 patients (84.4%) had presented with adverse events (Table 7). No cases of death were reported.

Table 7: Summary of all the adverse effects between 24 March 2009 and 9 September 2011

	HUMIRA	
Patients with	**N (%) N = 32**	**Events (Events/100 PY*) PY = 26.2**
Adverse event (AE)	27 (84.4)	133 (507.6)
AE at least possibly treatment-related	8 (25.0)	14 (53.4)
Severe AE	4 (12.5)	4 (15.3)
Serious AE	5 (15.6)	5 (19.1)
"Infection" AE	22 (68.8)	57 (217.6)
Serious "infection" AE	3 (9.4)	3 (11.5)
"reaction at injection site" AE	2 (6.3)	2 (7.6)
Death	0	0

**PY: patient-year*

A total of 8 patients (25.0%) presented with an AE considered as being at least possibly (5 AE: laryngitis, viral pharyngitis, upper respiratory tract infection, fever) or probably (4 AE: reaction at injection site, pain at injection site, cystitis, skin rash) treatment-related.
The majority of AEs were mild to moderate in intensity, however 4 patients (12.5%) had severe adverse events (uveitis, otitis media, diabetes mellitus and arthritis).

Table 8 presents the most commonly reported adverse events.

Table 8: Most commonly reported adverse effects

	HUMIRA N=32 N (%)
Adverse event (AE)	**27 (84.4)**
Fever	7 (21.9)
Rhinopharyngitis	6 (18.8)
Upper respiratory tract infections	5 (15.6)
Cough	5 (15.6)
Vomiting	4 (12.5)
Rhinorrhoea	4 (12.5)
Rash	4 (12.5)
Gastroenteritis	4 (12.5)
Bronchitis	4 (12.5)
Otitis media	3 (9.4)
Diarrhoea	3 (9.4)
Cystitis	2 (6.3)
Ear infections	2 (6.3)
Rhinitis	2 (6.3)
Elevated liver enzymes	2 (6.3)
Juvenile arthritis	2 (6.3)
Headaches	2 (6.3)
Reaction at injection site	2 (6.3)

Serious adverse events

Five patients (15.6%) presented with a serious adverse event (SAE), all considered by the investigator as not or probably not related to HUMIRA. It should be noted that for one patient the serious adverse event, which was diabetes mellitus in a child with no personal history of the disease, however the father has type II diabetes, required admission to hospital.
No patient discontinued the study prematurely due to an SAE.

Adverse events of particular interest

Regarding the adverse events of particular interest for the TNF inhibitor class of products, only infections and reactions at the injection site were reported.

- **Infections**

In total, 68.8% of patients presented with an infection; mainly rhinopharyngitis, upper respiratory tract infections, bronchitis and gastroenteritis.
The majority of infections were of mild to moderate intensity. Only one patient had a severe infection (otitis media).
A total of three patients had an infection considered by the investigator as possibly (cystitis) or probably (ear infection, laryngitis, pneumonia and viral pharyngitis) being related to HUMIRA.

- **Serious infections**

Three patients had serious infections (caries, rotavirus and chickenpox) considered by the investigator as not being related to HUMIRA and of mild to moderate intensity.

- **Reactions at the injection site**

Two patients presented with reactions and pain at the injection site, considered by the investigator as probably being related to HUMIRA and of mild intensity. In both cases, the events were resolved and the patients continued with the study.

09.2.2 Safety data from the PSURs

The last PSUR available (No.15) covering the period from 1 January 2010 to 31 December 2010, reports a worldwide estimation of the distribution by age and gender of patients treated with HUMIRA extrapolated from usage data for HUMIRA in the USA.
According to this estimation, over the period from 1 January 2010 to 31 December 2010, 1.8% of patients exposed to HUMIRA were patients aged between 0 and 18 years, which represents 16,835 patients (which is 6,854 patient-years).

Table 9 compares the most commonly reported adverse effects between 1 January 2010 and 31 December 2010, combined in the first 5 system organ classes, for paediatric and elderly patients, in comparison with the general population.

Table 9: The most commonly reported adverse effects (1 January 2010 - 31 December 2010) combined in the first 5 SOC* for paediatric and elderly patients in comparison with the general population

Notifications for children n = 215 (303 AE)		Notifications for the elderly n = 1,842 (8,304 AE)		General population n = 10,990 (27,380 AE)	
SOC	%	SOC	%	SOC	%
General disorders and administration site conditions	26.7	Infections and infestations	14.4	General disorders and administration site conditions	32.1
Gastrointestinal disorders	18.6	General disorders and administration site conditions	13.8	Infections and infestations	25.5
Infections and infestations	9.5	Respiratory and mediastinal disorders	8.9	Skin and subcutaneous tissue disorders	21.3
Skin and subcutaneous tissue disorders	9.1	Skin and subcutaneous tissue disorders	8.7	Musculoskeletal and connective tissue disorders	13.3
Nervous system disorders	7	Musculoskeletal and connective tissue disorders	8.1	Gastrointestinal disorders	12.7

** SOC: System Organ Class*

In the paediatric population, the majority of medically confirmed cases concern patients treated in 50% of cases for Crohn's disease (AE occurred essentially during clinical studies) and in 19% for polyarticular juvenile idiopathic arthritis.
The median age of these patients was 15 years.
For the effects included in the first 5 SOCs (System organ class):
- General disorders are mainly represented by reactions at the injection site.
- Gastrointestinal disorders are on the whole the same as with Crohn's disease.
- Infections are represented by herpes virus or ENT infections (rhinopharyngitis, sinusitis).
- Skin disorders are represented by rash, urticaria, pruritus and psoriasis.
- Neurological disorders are mainly represented by headaches and vertigo.

09.3 Summary & discussion

Efficacy and safety data in support of the extension of the indication for juvenile idiopathic arthritis (JIA) to children from 2 to 4 years is based on an interim analysis (to 9 September 2011) of results from study M10-444, a non-comparative trial that started in March 2009, and included 32 children of whom 28 were aged between 2 and 4 years, with moderately to severely active polyarticular JIA. The main aim of the study was to analyse safety.
On inclusion, 71.9% of patients were receiving methotrexate, 43.8% systemic corticosteroids and 31.3% NSAIDs.
Four patients discontinued the study prematurely, for reasons other than the occurrence of an adverse event.
The duration of exposure to HUMIRA was between 57 and 679 days (mean of 299.1 days; SD = 129.84; median = 266.0).

On the interim date, across the whole study, 27 patients (84.4%) had had adverse events (AEs), including:
- 8 had had AEs considered by the investigator as possibly being (laryngitis, viral pharyngitis, upper respiratory tract infection, fever) or probably being (reaction at injection site, pain at injection site, cystitis, skin rash) treatment-related.
- 5 had had serious AEs, including a single case (diabetes mellitus) that required admission to hospital.
- 4 had had severe AE (uveitis, otitis media, diabetes mellitus and arthritis).
- 25 had had infections (mainly rhinopharyngitis, upper respiratory tract infections, bronchitis and gastroenteritis), most of which were mild to moderate in intensity. Three children had had infections considered by the investigator as possibly being (cystitis) or probably being (ear infection, laryngitis, pneumonia and viral pharyngitis) related to HUMIRA.
- 2 had had reactions and pain at the injection site.

Safety data in this population of children corresponds to the known profile for HUMIRA.

The results suggest an efficacy for HUMIRA in terms of paediatric ACR response (ITT population):
- at Week 12, ACR 30/50/70/90 of 93.5%, 90.3%, 61.3%, 38.7% respectively,
- at Week 24, ACR 30/50/70/90 of 90%, 83.3%, 73.3%, 36.7% respectively,
- at Week 48, ACR 30/50/70/90 of 85.7%, 78.6%, 71.4%, 64.3% respectively.

Improvements in the various scores for joints, health and quality of life were observed at Week 12 and Week 24 compared with baseline.

010 THERAPEUTIC USE

Therapeutic use for juvenile idiopathic arthritis
The aim of juvenile idiopathic arthritis (JIA) treatment is to combat inflammation, relieve pain and stiffness and prevent or slow down the progression of articular lesions. It uses fast-acting symptomatic treatments (NSAIDs, corticosteroids) and sometimes disease-modifying treatments, depending on the form of JIA (whether it is systemic, oligio or polyarticular).

NSAIDs are used as first-line treatments, but they are not always effective. If required, they can be combined with intra-articular infiltrations of corticosteroids.

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

Leflunomide, hydroxychloroquine, sulfasalazine, azathioprine and cyclosporine are sometimes used (off-list) as alternatives to methotrexate, but their efficacy in polyarticular JIA in children is less well documented.

Two TNF inhibitors, adalimumab and etanercept, have Marketing Authorisation for children from the age of 2 years in the treatment of polyarticular JIA in cases of failure of first-line disease-modifying treatments.

For patients who have had an unsatisfactory response to a TNF inhibitor (adalimumab or etanercept), the alternatives are:
- the addition of a non-biological disease-modifying treatment, in particular MTX if the TNF inhibitor has been used as monotherapy,
- treatment with a 2nd TNF inhibitor that has not already been used before,
- treatment with abatacept (ORENCIA) (indicated in children over the age of 6 years).

The therapeutic use of HUMIRA
For active polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 to 17 years, HUMIRA is a second-line treatment for those who have not had a satisfactory response to one or more disease-modifying treatments. HUMIRA should preferably be used in combination with methotrexate, however it may be given as monotherapy, in cases of methotrexate intolerance or where continued treatment with methotrexate is inappropriate.
The Committee would like to note that for children and adolescents, it is recommended if possible, that all vaccinations comply with the vaccine guidelines in force before treatment with HUMIRA is started. Furthermore, before starting treatment with HUMIRA, all patients should be screened for active or non-active (latent) tuberculosis.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

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

011.1 Actual benefit

◗ 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. These are serious and debilitating chronic conditions.

◗ These medicinal products are intended as symptomatic treatments.

◗ The efficacy / adverse effects ratio for these medicinal products is high.

◗ There is a treatment alternative.

◗ These proprietary medicinal products are second-line therapies.

◗ 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).
Improvement of the management of this orphan disease is an established public health priority (National rare disease plan 2005-2008, Regulation of paediatric medicines).
In view of the available data for patients aged from 2 to 4 years, it is expected that HUMIRA will have, at best, a small impact on morbidity and quality of life of patients being treated.
Consequently, in the current state of knowledge and in view of the restricted size of the population concerned, it is not expected that HUMIRA will benefit public health in this indication.

Consequently, the Committee considers that the actual benefit of HUMIRA is substantial in the extension of the indication for the treatment of active polyarticular juvenile idiopathic arthritis when combined with methotrexate (or as monotherapy, in cases of intolerance to methotrexate) for children from 2 years who have not had a satisfactory response to one or more disease-modifying treatments.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and 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%**

011.2 Improvement in actual benefit (IAB)

In the absence of clinical data versus the only clinically relevant comparator, etanercept, HUMIRA does not provide an improvement in actual benefit (IAB V, non-existent) compared with ENBREL when combined with methotrexate in the treatment of active polyarticular juvenile idiopathic arthritis (or as monotherapy in cases of intolerance to methotrexate) in children from 2 years who have not had a satisfactory response to one or more disease-modifying treatments.

011.3 Target population

In view of the extension of the indication in JIA to children from 2 years, the additional target population is represented by patients aged from 2 to 4 years with active polyarticular JIA who have had an inadequate response to one or more disease-modifying treatments.

The prevalence of JIA in France is estimated as being approximately 2 to 3/10,000 children. According to INSEE data, on 1 January 2013, there would be 1.6 million children aged between 2 and 4 years in France. The population of patients aged between 2 and 4 years with juvenile idiopathic arthritis would therefore be between 320 and 480 children. Of these patients, approximately 30% would require a methotrexate type disease-modifying treatment and approximately 30% would have an unsatisfactory response or proven intolerance to methotrexate (source: expert opinion.[2])

Estimation/conclusion
Based on this, the target population for HUMIRA in juvenile idiopathic arthritis for children aged from 2 to 4 years would be **a maximum of 44 children**.

It should be noted that the assessed target population for children aged from 4 to 12 years was a maximum of 180 children[3] and that for adolescents aged from 13 to 17 years was a maximum of 100 children[4].

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescription conditions according to the indication, the dosage and the treatment duration.

◗ Specific requests inherent to reimbursement
Exception drug status.

◗ Request for data
As stated in previous Opinions, the Transparency Committee would like to receive the results of the everyday clinical practice study, with a follow-up period lasting 10 years, requested by EMA in the context of the Risk Management Plan (RMP) on patients with JIA aged 13 to 17 years (STRIVE register), then extended to children from 4 to 12 years, then to children aged over 2 years.

According to the November 2012 version of the RMP, this study is in progress and 318 patients have been included.

The Transparency Committee wishes to receive the results of the everyday clinical practice study, for patients with JIA aged from 2 to 17 years, when it next reviews the continued inclusion of HUMIRA.

[2] Haute Autorité de Santé. Transparency Committee Opinion. ENBREL. 11 April 2012.
[3] Haute Autorité de Santé. Transparency Committee Opinion. HUMIRA. 21 September 2011.
[4] Haute Autorité de Santé. Transparency Committee Opinion. HUMIRA. 24 June 2009.