



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

**TRANSPARENCY COMMITTEE**

OPINION

04 March 2009

**REMICADE 100 mg, powder for concentrate for solution for infusion**  
**Pack of 1 vial (CIP: 562 070-1)**

**Applicant: SCHERING-PLOUGH**

Infliximab  
ATC code: L04AA12

List I

Medicinal product for hospital use only

Date of Marketing Authorisation: 13 August 1999 (centralised Marketing Authorisation)

Date of Marketing Authorisation amendment concerning extension of indication to Crohn's disease in children: 30 May 2007

Reason for request: inclusion on the list of medicines approved for use by hospitals in the new indication (Crohn's disease in children).

## 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

Infliximab

### 1.2. Novel aspects

First TNF-alpha inhibitor to have a Marketing Authorisation in paediatric Crohn's disease.

### 1.3. Indications

#### **"Paediatric Crohn's disease:**

**Remicade is indicated for treatment of severe, active Crohn's disease, in paediatric patients aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies.**

**Remicade has been studied only in combination with conventional immunosuppressive therapy."**

#### **"Adult Crohn's disease:**

Remicade is indicated for:

- treatment of severe, active Crohn's disease, in 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.
- treatment of fistulising, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

#### **Ulcerative colitis:**

Remicade is indicated for:

treatment of moderately to severely active ulcerative colitis in 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.

#### **Rheumatoid arthritis:**

Remicade, in combination with methotrexate, is indicated for:

the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated.

#### **Ankylosing spondylitis:**

Remicade is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis:

Remicade is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.

Remicade should be administered

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Remicade has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Psoriasis:

Remicade is indicated for:

treatment of moderate to severe 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."

NB:

*The changes made to the SPC concerning the indications for Crohn's disease in adults, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis will be the subject of a separate opinion.*

**1.4. Dosage**

Crohn's disease (6 to 17 years)

5 m/kg given as an intravenous infusion over a 2-hour period followed by additional 5 g/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Available data do not support further infliximab treatment in paediatric patients not responding within the first 10 weeks of treatment.

For other indications: see SPC.

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC classification (2009)

L:	Antineoplastics and immunomodulating agents
L04:	Immunosuppressants
L04A:	Immunosuppressants
L04AA:	Selective immunosuppressants
L04AA12:	Infliximab

### 2.2. Medicinal products in the same therapeutic category

No other TNF-alpha inhibitors have a Marketing Authorisation for the treatment of paediatric Crohn's disease

#### Medicinal products with the same therapeutic aim

#### Medicines with a Marketing Authorisation for the treatment of paediatric Crohn's disease:

- 5 ASA (mesalazine, sulfasalazine)
- corticosteroids
- azathioprine (AZA)

Medicines used off-label in the treatment of paediatric Crohn's disease:

- methotrexate (MTX)
- 6-mercaptopurine (6-MP)

Nutrition therapy

## 3 ANALYSIS OF AVAILABLE DATA

### 3.1. Efficacy

The evaluation of the efficacy of infliximab (Remicade) in the treatment of active and severe Crohn's disease in children aged 6 to 17 years is based on:

- one pivotal study, REACH,
- one study by the *Groupe Francophone d'Hépatologie, Gastroentérologie et Nutrition Pédiatrique [French Hepatology, Gastroenterology and Paediatric Nutrition Group] (GFHGNP)*, and
- three observational studies.

There were no placebo-controlled studies. Two pharmacokinetic studies were supplied but will not be described.

#### REACH study<sup>1</sup> (pivotal study for the Marketing Authorisation)

The primary endpoint of the study was to evaluate the efficacy and tolerance of infliximab as induction therapy in 112 patients aged 6–17 years (median age = 13 years) with moderate-to-severe Crohn's disease (PCDAI score<sup>2</sup> >30). One of the secondary endpoints was to compare two Remicade administration regimens in maintenance therapy to maintain response and clinical remission.

The diagnosis of Crohn's disease was confirmed by biopsy and by endoscopy. For inclusion in the study, patients had to have been treated with immunosuppressants (6-MP, AZA or MTX) for at least 8 weeks before inclusion and had to have been on a stable dose of 6-MP, AZA or MTX for at least two weeks (35% were also taking corticosteroids at inclusion). These existing therapies were continued at a stable dose throughout the study.

#### Treatment

The study was carried out in two phases:

- an initial noncomparative phase during which all patients received infliximab 5 mg/kg during weeks 0, 2 and 6.
- a maintenance phase comparing two dosage regimens for infliximab. During this phase, patients showing a response by week 10 were randomised to receive maintenance therapy, either infliximab 5 mg/kg every 8 weeks (2 months) or infliximab 5 mg/kg every 12 weeks (3 months). If the response was lost during maintenance therapy, patients were allowed to increase the dose (10 mg/kg) and/or to take the dose at shorter intervals (every 8 weeks).

#### Endpoints:

The primary efficacy endpoint was the percentage of responders at week 10, defined as a reduction of at least 15 points in the PCDAI score and a PCDAI score ≤ 30.

The secondary endpoints for the study included response and clinical remission by week 54 (1 year). Clinical remission was defined as a reduction of at least 10 points in the PCDAI.

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1 Hyams J, Crandall W, Kugathasan S et al. Induction and Maintenance Infliximab Therapy for the Treatment of Moderate-to-severe Crohn's Disease in Children. *Gastroenterology* 2007; 132: 863-873.

2 PCDAI: Pediatric Crohn's Disease Activity Index, a validated score to evaluate Crohn's disease severity in children (Hyams et al. *J Pediatr Gastroenterol Nutr.* 2005 Oct;41(4):416-21). It is accepted that a PCDAI score ≥ 30 indicates moderate to severe activity and that a reduction of 12.5 points in the CDAl under treatment reflects a clinical response regarded as significant. Unlike the CDAl (Crohn's Disease Activity Index used in adults), the PCDAI takes account of linear growth and places less emphasis on subjective reporting of symptoms and more on laboratory markers of intestinal inflammation.

## Results:

Table1: Patient characteristics at inclusion

	Subjects not randomised at W10	Subjects randomised at W10			
		Infliximab 5mg/kg q8 wks	Infliximab 5mg/kg q12 wks	Total infliximab	Total no. of patients enrolled
<b>Duration of Crohn's disease (year)</b>					
N	9	52	51	103	112
mean ± standard deviation	2.4 ± 1.6	2.3 ± 1.5	1.6 ± 1.3	1.9 ± .4	2.0 ± 1.4
<b>Duration of symptoms (months)</b>					
N	8	47	48	95	103
mean ± standard deviation	4.6 ± 2.9	6.6 ± 7.9	8.2 ± 9.6	7.4 ± 8.8	7.2 ± 8.5
<b>Linear growth and weight gain</b>					
Weight (kg) mean ± standard deviation	47.9 ± 13.2	45.0 ± 17.3	41.9 ± 11.5	43.5 ± 14.7	43.8 ± 14.6
Height (cm) mean ± standard deviation	153.7 ± 18.0	153.1 ± 15.2	153.0 ± 14.6	153.1 ± 14.8	153.1 ± 15.0
<b>Disease severity</b>					
PCDAI score mean ± standard deviation	41.7 ± 10.2	42.1 ± 9.2	40.1 ± 6.8	41.1 ± 8.1	41.2 ± 8.3
ESR (mm/h) mean ± standard deviation	30.6 ± 22.4	37.3 ± 18.7	41.9 ± 26.8	39.6 ± 23.1	38.9 ± 23.1
<b>Concomitant medication</b>					
Subjects taking more than 1 concomitant medicine	9 (100.0%)	52 (100.0%)	50 (98.0%)	102 (99.0%)	111 (99.1%)
Corticosteroids	3 (33.3%)	24 (46.2%)	12 (23.5%)	36 (35.0%)	39 (34.8%)
✓ Prednisone equivalent ≤ 1 mg/kg	2 (22.2%)	23 (44.2%)	10 (19.6%)	33 (32.0%)	35 (31.3%)
✓ Prednisone equivalent > 1 mg/kg	1 (11.1%)	1 (1.9%)	2 (3.9%)	3 (2.9%)	4 (3.6%)
Immunomodulating agents	9 (100.0%)	52 (100.0%)	49 (96.1%)	101 (98.1%)	110 (98.2%)
✓ 6-mercaptopurine/azathioprine	7 (77.8%)	46 (88.5%)	47 (92.2%)	93 (90.3%)	100 (89.3%)
✓ Methotrexate	2 (22.2%)	7 (13.5%)	2 (3.9%)	9 (8.7%)	11 (9.8%)
✓ Aminosalicylates	3 (33.3%)	31 (59.6%)	25 (49.0%)	56 (54.4%)	59 (52.7%)

### Results for primary endpoint

The proportion of subjects with a clinical response at week 10 was 88.4% (99/112).

### Results for secondary endpoints

At week 54,

- a clinical response was obtained in 63.5% (33/52) of patients receiving maintenance therapy with infliximab every 8 weeks and in 33.3% (17/51) of patients receiving infliximab every 12 weeks ( $p < 0.002$ ),

- clinical remission was obtained in 55.8% (29/52) of patients receiving maintenance therapy with infliximab every 8 weeks and in 23.5% (12/51) of patients receiving infliximab every 12 weeks ( $p < 0.001$ ),

The SPC recommends the 8-week maintenance regimen.

### GFHGNP study<sup>3</sup>

The primary endpoint of the study was to evaluate the efficacy and tolerance of infliximab as induction therapy in 40 patients aged 7–17 years (mean = 13.9 ± 2.2 years, median = 14 years) with moderate to severe luminal Crohn's disease: Harvey Bradshaw Index (HBI)<sup>4</sup> ≥ 5 and erythrocyte sedimentation rate (ESR) > 20 mm/h and/or fistulising Crohn's disease, resistant to the combination of an immunosuppressant (AZA, MTX, 6-MP) and corticosteroids (> 0.3 mg/kg every other day) for at least 3 months.

One of the secondary endpoints was to compare two infliximab dosage regimens in maintenance therapy (every 8 weeks versus episodic (on-demand) treatment) for maintaining response and clinical remission.

The study was carried out in two phases:

- an initial, noncomparative phase: all patients received three infusions of 5 mg/kg infliximab as induction therapy (W0, W2 and W6).

The primary endpoint was clinical remission at W10 defined as an HBI score < 4, ESR ≤ 20 mm/h and/or complete closing of fistulae and withdrawal of corticosteroids.

- a maintenance phase, during which patients in clinical remission at week 10 were randomised to receive either infliximab 5 mg/kg every 8 weeks as maintenance therapy or infliximab 5 mg/kg as episodic therapy (only in the event of relapse defined as HBI ≥ 5 or incomplete closing or reopening of fistulae).

### Results:

At week 10, 85% of patients (34/40) were in clinical remission.

Nine out of the 40 patients included did not take part in the maintenance phase: six were not in clinical remission by W10 and three had stopped treatment because of active disease not controlled by the 5 mg/kg dose of infliximab allowed by the protocol.

In the group that received maintenance therapy every 8 weeks, 15/18 patients were in clinical remission by W60 vs. 8/13 patients in the group receiving maintenance therapy on an on-demand basis in the event of relapse.

### Other studies

The efficacy of infliximab in the treatment of Crohn's disease was also evaluated in three noncomparative observational studies (two retrospective studies and one prospective study) which enrolled small populations (21 to 88 children), with multiple evaluation endpoints, with no definition of a primary endpoint. The results of these studies are shown in Table 1.

The efficacy of Remicade has not been studied in children under the age of 6 years.

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3 carried out by the *Groupe Francophone d'Hépatologie, Gastroentérologie et Nutrition Pédiatrique* [French Hepatology, Gastroenterology and Paediatric Nutrition group] with the support of Schering Plough

4 This is an index of disease activity which is easier to use than CDAI in everyday practice as data are collected on the day of the visit rather than over seven days as for CDAI. It is closely related to CDAI. The score measures general well-being, abdominal mass and pain, liquid stools, non-gastrointestinal signs, fistulae, anal fissure, Score < 4 = inactive disease, score 4–12 = active disease, score over 12 = very severe active disease

Table 2: Other efficacy data for Remicade in paediatric Crohn's disease

Trial	Design	Follow-up	Population	Diagnosis and inclusion criteria	Treatment (dose and route of administration)	Endpoints	Results (efficacy)
Lamireau et al <sup>5</sup> Study carried out by the GFHGNP	Retrospective study	At least 3 months	88 patients aged under 18 years (median = 14 years)	Active Crohn's disease (66% of patients, n = 58) and/or fistulising Crohn's disease (42% of patients, n = 37) resistant to corticosteroids (70% of patients) and/or to other immunosuppressants (82% of patients) and/or to parenteral nutrition (20% of patients)	1 to 17 infusions (median = 4) of Remicade® 5 mg/kg over a median period of 4 months [1-17 months]. No details were given of the method of administration of infliximab.	The following were measured at 3 months: Harvey-Bradshaw score <sup>4</sup> (HBI), ESR, CRP, fistula closure, improvement in symptoms (reduction in HBI and ESR) clinical remission (HBI ≤ 4 and ESR ≤ 20 mm, or fistula closure) relapse (increase in HBI, ESR or reopening of fistulae)	Symptom improvement (reduction in HBI and ESR) was observed in 40 patients (53%) 26 patients (34%) were in clinical remission while 10 patients (13%) relapsed.
Wynands et al <sup>6</sup> Data taken from the database of the Necker Hospital for sick children and the Robert Debré Hospital, Paris (2000–2004)	Retrospective study	At least 3 courses of infliximab and follow-up for at least 1 year after withdrawal of infliximab	38 children aged 10.7 ± 2.2 years	Active and/or fistulising Crohn's disease, corticosteroid-dependent (n = 20) or corticosteroid-resistant (n = 11) and/or resistant to other immunosuppressants (n = 30, AZA/6-MP and n = 2, MTX).	Induction therapy: 3 infusions of infliximab 5 mg/kg at W0, W2 and W6 maintenance phase: responder patients were divided into 2 groups and given either: - maintenance therapy of infliximab® 5 mg/kg every 8 weeks for 12 months (n = 20) -no treatment (n = 16)	Harvey-Bradshaw score (HBI), clinical remission (HBI < 5), fistula closure, mucosal healing (disappearance of inflammatory lesions or ulcerations).	At the end of the induction phase, 36 patients (95%) were in clinical remission.  Maintenance phase: 11 out of 20 patients receiving infliximab were in clinical remission at 12 months. 12 out of 16 patients not receiving maintenance therapy relapsed in a median time of 4 months.

5 Lamireau T. et al. Efficacy and tolerance of infliximab in Children and Adolescents with Crohn's disease .Inflamm Bowel Dis 2004;10:745-750.

6 Wynands et al. 12 month follow up after successful infliximab therapy in pediatric Crohn disease JPGN 2008;46:293-298.

Trial	Design	Follow-up	Population	Diagnosis and inclusion criteria	Treatment (dose and route of administration)	Endpoints	Results (efficacy)
<b>Study by Cezard et al<sup>6</sup></b>	Prospective study	1 year	21 children aged 15 ± 2 years	Active and/or fistulising Crohn's disease corticosteroid-dependent or -resistant and/or dependent on or resistant to other immunosuppressants and/or to parenteral nutrition.	Induction therapy: 3 infusions of infliximab 5 mg/kg at W0, W2 and W6 mean of 2–7 infusions of Remicade 5 mg/kg per patient: one patient had a single infusion	Harvey-Bradshaw score (HBI), ESR, CRP, fistula closure, reduction or withdrawal of corticosteroids, Z-score for growth.	At 3 months: reduction in HBI from 8 to 1, 19 patients were in remission (HBI < 4) 10/21 patients had stopped taking corticosteroids all fistulae had closed.  At 1 year: 90% of patients had relapsed despite administration of immunosuppressants. Supplementary infusion of infliximab was necessary in 63% of patients. Z-score for growth measured one year later had improved in 10 of the patients who had not completed puberty

<sup>6</sup> Cezard JP, Nouaili N, Talbotec C, et al. A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (Remicade) in severe pediatric Crohn's disease. *J Pediatr Gastroenterol Nutr.* 2003; 36:632-636.

### 3.2. Adverse effects

The tolerance of Remicade in children was similar to that observed in adults. Infusion reactions and infection were the most common adverse reactions: in the REACH study, 17% of patients had an infusion reaction<sup>7</sup> and 54% had an infection, including 8% cases of severe infection requiring antibiotics.

The risk management plan included establishing a paediatric register in 3-5 European countries including France. The aim of the register was to collect data on the tolerance and efficacy of using Remicade in children. It is planned to include 2 000 patients who will be followed-up for 20 years.

### 3.3. Conclusion

The efficacy and tolerance of infliximab (Remicade) 5 mg/kg as induction and maintenance therapy in severe Crohn's disease resistant to conventional therapies (corticosteroids, immunomodulators and nutrition therapy) were evaluated in 299 children aged 6–17 years in open studies comparing doses or methods of use. Patients received infliximab as induction therapy (5 mg/kg during weeks 0, 2 and 6), followed by maintenance therapy (5 mg/kg every 8 weeks, every 12 weeks or on a demand basis).

In the REACH trial, 99 of the 112 patients enrolled (88.4%) were responders<sup>8</sup> by week 10 and received infliximab 5 mg/kg as maintenance therapy every 8 weeks or every 12 weeks. By week 54, 63.5% (33/52) of patients receiving infliximab maintenance therapy every 8 weeks had exhibited a clinical response versus 33.3% (17/51) of patients receiving infliximab maintenance therapy every 12 weeks.

In the *Groupe Francophone d'Hépatologie, Gastroentérologie et Nutrition Pédiatrique* study, 34 out of the 40 patients enrolled (85%) were in complete remission<sup>9</sup> by week 10 and received infliximab 5 mg/kg maintenance therapy every 8 weeks or episodic therapy. In the group that received maintenance therapy every 8 weeks, 15/18 patients were in clinical remission by W60 vs. 8/13 patients in the group receiving maintenance therapy on a demand basis.

The efficacy of infliximab in a real life setting was evaluated in three observational studies. Results for symptom improvement were similar to those in the two previous studies. The Transparency Committee regrets that there are no comparative data.

The tolerance of infliximab in children in the studies presented in this dossier was comparable to that observed in adults. However, no long-term data (> 1 year) are available in this paediatric population.

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7 An infusion reaction was defined as any type of ADR occurring during or within an hour of infusion. Reactions related to infusion occurring in more than 2 patients consisted of flushing (reported in 8 patients), infiltration at the injection site and dyspnoea (reported in 4 patients), sweating, urticaria, chest pain, vomiting, hypotension, paraesthesia (each symptom being reported in 2 patients)

8 Clinical response had been defined as a reduction of 15 points or more in the PCDAI<sup>2</sup>.

9 Clinical remission was defined as complete remission (HBI score < 4; ESR ≤ 20 mm/h) and/or complete closure of fistulae and withdrawal of corticosteroids.

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Crohn's disease is a very disabling chronic inflammatory intestinal disease which progresses with periods of exacerbation and remissions. In children and adolescents, the most serious factor is the risk of delayed linear growth and weight gain, often associated with delayed puberty. Remicade is a symptomatic therapy. Its efficacy/adverse effects ratio is high.

#### Public health benefit

The burden to public health represented by Crohn's disease is moderate; that of Crohn's disease in children is low, in view of the number of patients concerned.

Improvement in the management of Crohn's disease, including in children, is a public health need which is covered by established priorities (GTNDO, French national rare diseases plan, Paediatric medicines). This need is particularly important in the clinical situations in which Remicade is indicated.

The available clinical data do not provide any information on the effect of Remicade on mortality and/or on requirement for surgery.

In view of the available data (open study, noncomparative observational studies) but taking account of the absence of alternative forms of treatment, it is anticipated that Remicade will make a further contribution to reducing morbidity and mortality, with a particular impact on linear growth and weight gain, in combination with conventional immunosuppressant therapy. This impact can only be low, in view of the numbers involved.

In addition, it is not certain that study results will be transposed into everyday practice in view of the uncertainties in maintaining long-term efficacy and doubts about the tolerance of TNF inhibitors.

Remicade should be able to provide an additional response to an identified public health need. Consequently, it is anticipated that Remicade will contribute public health benefit in this indication in children, but this benefit has still to be demonstrated.

Remicade is a second-line therapy, after failure of conventional therapy consisting of a corticosteroid, an immunosuppressant and nutrition therapy. There are no alternative medicines with a marketing authorisation for this stage of the disease.

The actual benefit of Remicade is substantial in this indication.

#### **4.2. Improvement in actual benefit (IAB)**

In the treatment of active severe Crohn's disease in children aged 6–17 years who are not responding to conventional therapy consisting of a corticosteroid, an immunosuppressant (azathioprine, methotrexate, or 6-mercaptopurine) and nutrition therapy, or in whom these medicines are poorly tolerated or contraindicated, Remicade in combination with conventional immunosuppressant therapy, in the absence of treatment alternatives, provides an important actual benefit (level II) in the management strategy in this disease.

#### **4.3. Therapeutic use**

According to the consensus conference guidelines (European Crohn's and Colitis Organization - ECCO<sup>10</sup>), treatment of active Crohn's disease consists of corticosteroids.

In the event of corticosteroid-dependence, immunosuppressants such as AZA, 6-MP (off-label), or MTX (off-label) may be prescribed.

Infliximab is reserved for disease resistant to conventional therapy including corticosteroids, immunosuppressants (AZA, MTX or 6-MP) and nutrition therapy.

No other TNF alpha inhibitor currently has a Marketing Authorisation for the treatment of paediatric Crohn's disease.

Remicade is therefore a second-line therapy in paediatric Crohn's disease. In view of the available data, Remicade should preferably be prescribed in combination with an immunosuppressant.

#### **4.4. Target population**

The target population for Remicade is children aged 6–17 years with severe active Crohn's disease, who have not responded to conventional therapy consisting of a corticosteroid, an immunosuppressant and nutrition therapy.

The estimated annual incidence of paediatric Crohn's disease in France based on the EPIMAD registry is 2.3 per 100 000<sup>11</sup>.

By applying this figure to the population of children aged 6–17 years (INED data 2008, 9 387 000), the estimated population of children with Crohn's disease is 216 cases a year.

There are no available data which could be used to estimate the population of patients with severe disease not responding to conventional therapy, who are likely to be treated with Remicade.

#### **4.5. Transparency Committee recommendations**

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the new indication and at the new doses given in the Marketing Authorisation.

The Transparency Committee would like to assess the results of a long-term follow-up study in children with Crohn's disease who have been treated with Remicade. The aims of this study would be to confirm, in actual treatment situations:

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10 Stange. European evidence based consensus on the diagnosis and management of Crohn's disease: definition and diagnosis. *Gut* 2006; 55 (Suppl I): i1-i15.

11 Vernier- Massouille G, Balde M, Salleron J et al. Natural History of Pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008; 135: 1106-1113

- The characteristics of the patients treated, i.e. sex, age, history, clinical profile (frequency and severity of attacks, extent of lesions, level of activity measured from the PCDAI score, presence of fistulae, stenoses, complications in the form of infection, etc.), delayed linear growth and weight gain.
- The conditions of use of the product, and in particular the conditions under which treatment is initiated - previous medicines (notably corticosteroids and immunosuppressants) or surgery and concomitant therapies,
- The frequency of treatment discontinuations and the reasons for them.
- Maintenance of the benefit of treatment in the medium and long term, including in terms of quality of life and impact on requirement for surgery (colectomy, small intestine resection, etc.).
- Impact on linear growth, weight gain and delayed puberty, in particular related to level of corticosteroid withdrawal.
- The long-term tolerance of the medicine.

If the studies that are planned or currently in progress, notably in relation to the EU Risk Management Plan, are unable to provide answers to the questions posed by the Transparency Committee, a specific study should be carried out.

The protocol and duration of the study should be justified by an independent scientific committee.