HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

3 October 2012

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 code: 362 230-5)

HUMIRA 40 mg, solution for injection in pre-filled pen
B/2 x 0.8 ml pens with 2 alcohol wipes (CIP code: 378 014-5)

Applicant: ABBOTT FRANCE

adalimumab
ATC code: L04AB04 (TNF inhibitor)

List I

Medicine for initial annual hospital prescription only.
Prescription restricted to specialists in rheumatology, gastroenterology, gastrointestinal surgery**,** dermatology, paediatrics and internal medicine.

Exception drug status

Date of initial Marketing Authorisation: 08 September 2003 (centralised procedure)

Date of latest revision of the Marketing Authorisation: 04 April 2012 (extension of the indication for ulcerative colitis)

Reason for the request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the new indication (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).

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

adalimumab

1.2. Indication

New indication forming the subject of the application

Ulcerative Colitis (UC):
"HUMIRA 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."

Note: wording is identical to that of REMICADE

Indications prior to application (not included in this evaluation):

"Rheumatoid arthritis
HUMIRA in combination with methotrexate is indicated for:

- the treatment of moderate to severe active rheumatoid arthritis in adults responding inadequately to disease-modifying treatments, including methotrexate.

- the treatment of severe, active, 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.

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

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

Crohn's Disease
HUMIRA 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.

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.

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 (for the efficacy in monotherapy see SPC). HUMIRA has not been studied in children aged less than 4 years."

1.3. Dosage

"HUMIRA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which HUMIRA is indicated. Patients treated with HUMIRA will be given a special alert card.
After proper training in the injection technique, patients may self-inject with HUMIRA if their doctor considers it feasible, subject to appropriate medical follow-up.
During treatment with HUMIRA, other concomitant therapies (e.g. corticosteroids and/or immunomodulators) should be optimised.

Dosage relating to the new indication (UC):
The recommended HUMIRA induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection.
During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.
Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg HUMIRA every week.
Available data suggest that clinical response is usually achieved within 2 to 8 weeks of treatment. **HUMIRA therapy should not be continued in patients failing to respond within this time period**."

Note:
The idea of stopping treatment in situations where there is an absence of response "in 2 to 8 weeks is specific to the SPC indication, and was motivated by clinical trial data."

For other indications already evaluated by the Committee, refer to the SPC.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

L : Antineoplastic and immunomodulating agents
L04 : Immunosuppressants
L04A : Immunosuppressants
L04AB : Inhibitors of tumour necrosis factor alpha (TNF alpha)
L04AB04 : adalimumab

2.2. Medicines in the same therapeutic category

This is REMICADE (infliximab), another TNF inhibitor, which is administered via IV infusion (substantial AB, IAB II - Opinion of 18 July 2007; this opinion resulted in the following notice: “the Committee will be re-evaluating REMICADE when the results from the GETAID study, the aim of which is to compare infliximab with cyclosporine in the treatment of UC flares after failure of corticosteroids, are available”).

Note: at the time of publishing this document, this study (CYSIF) was still in progress.

2.3. Medicines with a similar therapeutic aim

In the treatment of UC inadequately responding to corticosteroids and immunosuppressants (azathioprine and 6-mercaptopurine), or who are intolerant to or have medical contraindications for such therapies, cyclosporine can be used without Marketing Authorisation on the advice of a specialised expert.[1,2]

1 Long-term disease Guide 2008 (update expected in September 2012 with removal of medicinal products without Marketing Authorisation from the list).
2 Travis et al. European evidence-based Consensus on the management of ulcerative colitis: Current management Journal of Crohn's and Colitis 2008; 24–62.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy of adalimumab (HUMIRA) in the treatment of ulcerative colitis (UC) was evaluated in two placebo-controlled trials: ULTRA 1 and ULTRA 2, which started in 2006 (ULTRA 1: 1st patient/1st appointment on 13 November 2006. ULTRA 2: 1st patient/1st appointment on 20 November 2006). The comparison with REMICADE (which obtained Marketing Authorisation on 04 January 2007 for UC) was not possible. An open-label follow-up study of patients from these two trials, M10-223, was also included in this dossier.

ULTRA 1 Study – M06-826 (carried out between November 2006 and March 2010)[3]

Aim:
To evaluate the efficacy and safety of two administration regimens of adalimumab **in the induction** of clinical remission in TNF inhibitor-naive patients with active, moderate to severe UC.

Methodology:
This randomised, double-blind trial over 8 weeks, followed by an open-label phase up to the 52nd week, included 576 biotherapy naive patients with moderate to severe UC activity (Mayo[4] score 6 to 12 points and an endoscopic sub-score of 2 to 3 despite concomitant treatment with corticosteroids and/or immunosuppressants).

Treatments:
The initial study protocol planned for two treatment groups: one placebo group and one HUMIRA 160, 80 then 40 mg group, but at the request of EMA in August 2007, following the granting of the Marketing Authorisation for HUMIRA for Crohn's disease, the protocol was changed (amendment 3) in order to evaluate the 160/80/40 mg and 80/40/40 mg regimens (addition of a treatment group) in particular and to reduce the double-blind period from 12 to 8 weeks.
Thus, patients included were randomised to receive during the 8 week double-blind phase, either:

- placebo in weeks 0, 2, 4 and 6 then 40 mg adalimumab in Week 8
- adalimumab 160 mg in Week 0 then 80 mg in Week 2, then 40 mg every 2 weeks
- adalimumab 80 mg in Week 0, 40 mg in Week 2, then 40 mg every 2 weeks.

Stable concomitant doses of oral aminosalicylates, corticosteroids, and/or immunosuppressants (azathioprine or 6-mercaptopurine) were permitted.

Endpoints:
The primary efficacy endpoint was clinical remission at Week 8, defined as a Mayo score ≤ 2 and the absence of individual sub-score > 1.

3 Reinisch W. et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial, GUT, 2010

4The Mayo activity score for UC takes into account:

- Frequency of stools - 0 (normal) to 3 (1 = 1-2, 2 = 3-4, 3 = 5 or more)
- Rectal bleeding - 0 (absent) to 3 (discharge of pure blood)
- Rectal sigmoidoscopy - 0 (normal) to 3 (severe abnormalities)
- Overall assessment by the doctor - 0 (normal) to 3 (severe illness)

The score therefore ranges from 0 to 12.
Colitis is considered as inactive if the Mayo score ≤ 2 points.
Low activity: Mayo score 3-5 points, Moderate activity: 6-10 points, Severe activity: 11-12 points

Secondary endpoints evaluated at Week 8 were:

- clinical response, defined by a reduction in Mayo score ≥ 3 compared with the score at inclusion and a reduction in Mayo score ≥ 30% compared with the score at inclusion and a reduction in rectal bleeding sub-score ≥1 compared with the score at inclusion or a sub-score of 0 or 1
- mucosal healing (endoscopic sub-score of 0 or 1)
- rectal bleeding sub-score (≤ 1) indicating a milder stage of the disease
- doctor's assessment sub-score (≤ 1) indicating a milder stage of the disease (PGA)
- stools frequency sub-score (≤ 1) indicating a milder stage of the disease
- response in IBDQ[5] quality of life score

Results:

Analysis population:
Several analysis populations were considered after the amendments to the protocol:

- The "intention to treat" analysis population for the primary endpoint during the double-blind period included 390 patients randomised after amendment 3, who received at least one dose of induction treatment with at least one efficacy evaluation (ITT-A3). This population represents 68% of the overall randomised population. *According to the applicant, this should ensure that the analyses are carried out on a homogeneous population.* In the analysis of results relating to this population, missing or incomplete data were considered as "non responses".

- Analysis of safety included all patients randomised (n = 576).
- During the open-label follow-up period, analysis of efficacy was based on 575 patients (ITT-E); one randomised patient who did not have UC, but instead had Crohn's disease, was not included in the analysis population.

According to the calculation of the number of patients required, the minimum number was 125 patients per group, i.e. a minimum of 375 patients to detect a 15% difference between the groups.

Patient characteristics: see Table 1
The demographic and medical characteristics of the 390 patients for the primary efficacy endpoint analysis were comparable between the groups. On inclusion, patients had been treated and were being treated with conventional treatments (corticosteroids and/or immunosuppressants).

5 IBDQ (Inflammatory Bowel Disease Questionnaire): this is a quality of life index, specific to CIBD, including 32 questions completed by the patients and covering four areas: gastrointestinal symptoms (10 questions), general signs (5 questions), emotional state (12 questions) and impact on social life (5 questions).
Each point is measured using the Likert technique. Questions are randomly split into the various areas, and for each question there are seven possible answers. As a result, by adding up the individual scores, it is possible to arrive at a numerical value.
The score ranges from 32 to 224; the higher the score, the better the quality of life. Patients in remission generally have a score above 170.

Table 1. Demographic and medical characteristics of patients included in the ITT-A3 population

	Placebo N = 130	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 **= Marketing Authorisation dosage** N = 130
Mean age	38.9 ± 12.68	41.6 ± 13.99	38.2±13.46
Mean duration of UC (years)	7.48 ± 7.16	8.57 ± 7.51	8.11 ± 7.25
Mean Mayo score	8.7 ± 1.56	9.0 ± 1.62	8.8 ± 1.61
History of treatment for UC over the last 5 years	114 (87.7%)	120 (92.3%)	120 (92.3%)
corticosteroids	110 (84.6%)	115 (88.5%)	116 (89.2%)
azathioprine	49 (37.7%)	54 (41.5%)	49 (37.7%)
6-MP	8 (6.2%)	13 (10.0%)	10 (7.7%)
Treatment for condition at inclusion	125 (96.2%)	124 (95.4%)	121 (93.1%)
corticosteroids	89 (68.5%)	74 (56.9%)	71 (54.6%)
azathioprine	48 (36.9%)	44 (33.8%)	46 (35.4%)
mercaptopurine	4 (3.1%)	7 (5.4%)	5 (3.8%)
aminosalicylates	98 (75.4%)	99 (76.2%)	105 (80.8%)

The demographic characteristics of the 576 patients in the overall population ITT-E were on the whole similar to those of the ITT-A3 population. The mean age of patients was 39.9 years versus 39.6 in the ITT-A3 population, the mean duration of UC was 8.29 years versus 8.06 years in the ITT-A3 population and the mean Mayo score, defining disease activity, was 8.9 versus 8.8 in the ITT-A3 population (moderate activity).

Patients were divided, based on the severity of the disease, as follows:

- 49.56% of the ITT-E population versus 51.3% of patients from the ITT-A3 population had an endoscopic sub-score equal to 2, relating to moderate disease activity and 50.1% of the ITT-E population versus 48.43% of patients from the ITT-A3 population had a sub-score equal to 3, which relates to severe disease activity;
- 47.13% of the ITT-E population versus 47.67% of patients from the ITT-A3 population had a rectal bleeding sub-score equal to 2, relating to moderate disease activity and 14.83% of the ITT-E population versus 14.1% of patients from the ITT-A3 population had a sub-score equal to 3, which relates to severe disease activity.
- 61% of the ITT-E population versus 63.1% of patients from the ITT-A3 population had an overall doctor's evaluation sub-score indicating a moderate form of the disease
- 59.8% of the ITT-E population versus 59.23% of patients from the ITT-A3 population had stool frequency sub-score indicating a severe form of the disease.

Table 2. Demographic and medical characteristics of patients included in the ITT-E population

	Placebo N = 222	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 223
Mean age	39.7 ± 12.72	41.6 ± 13.99	38.5±13.06
Mean duration of UC (years)	7.89 ± 7.52	8.57 ± 7.51	8.41 ± 7.28
Mean Mayo score	8.8 ± 1.58	9.0 ± 1.62	8.9 ± 1.65
Treatment for condition at inclusion **corticosteroids** **azathioprine** **mercaptopurine** **aminosalicylates**	209 (94.1%) 138 (62.2%) 73 (32.9%) 12 (5.4%) 165 (74.3%)	124 (95.4%) 74 (56.9%) 44 (33.8%) 7 (5.4%) 99 (76.2%)	211 (94.6%) 133 (59.6%) 75 (33.6%) 9 (4%) 180 (80.7%)

Source: EPAR

Discontinuation of treatment:
Of the 576 patients included in the ULTRA 1 study (186 before the amendment and 390 after), 90.6% (521) completed the 8 week double-blind phase. The main reasons for discontinuing treatment were adverse effects (5.4%), lack of efficacy (3.3%) and withdrawal of consent (2.1%).
During the double-blind phase and the extension phase, 33.6% (193) stopped treatment prematurely (35.9% in the adalimumab 160/80/40 group and 31.1% in the placebo group). The main reasons for discontinuing treatment were a lack of efficacy (17% in the adalimumab 160/80/40 group and 19.8% in the placebo group) and adverse effects (14.8% in the adalimumab 160/80/40 group and 17.6% in the placebo group).

Results for the primary efficacy endpoint – clinical remission

- Analysis of the ITT-A3 population (n = 390)

The proportion of patients who achieved clinical remission at Week 8 was statistically greater in the adalimumab 160/80/40 mg group (18.5%) than in the placebo group (9.2%), p = 0.031, which is an absolute benefit of 9.3% [0.9; 17.6].
No difference was highlighted between the administration regimen that included lower doses of adalimumab (80/40 mg) and placebo; clinical remission was achieved by 10% of patients treated with adalimumab 80/40 versus 9.2% of those in the placebo group.

- Analysis of the overall study population, ITT-E (n = 575)

During the analysis on the overall population (ITT-E), comparable results were highlighted: the proportion of patients who achieved clinical remission at Week 8 was statistically greater in the adalimumab 160/80/40 mg group (15.7%) than in the placebo group (7.2%), p = 0.005.
No statistical difference was highlighted between adalimumab 80/40 mg and placebo: 10% of patients in clinical remission with adalimumab 80/40 mg versus 7.2% with placebo.

Results for the secondary endpoints (see Table 3):
Superiority of adalimumab 160/80/40 mg over placebo was only highlighted for two of the six secondary endpoints, which were the proportion of patients with a rectal bleeding sub-score < 1 and the favourable doctor's evaluation. Superiority was not highlighted for clinical response at 8 weeks, nor was improvement in quality of life evaluated by the IBDQ score.

Table 3. Results for the secondary endpoints in the ULTRA 1 study – ITT-A3 population

	Placebo N = 130	Adalimumab 160/80/40 N = 130 **Marketing Authorisation dose**	p	Adalimumab 80/40 N = 130	p
Clinical response	58 (44.6)	71 (54.6)	NS	67 (51.5)	NS
Mucosal healing	54 (41.5)	61 (46.9)	NS	49 (37.7)	NS
Rectal bleeding ≤ 1	86 (66.2)	101 (77.7)	**0.038**	91 (70.0)	NS
PGA ≤ 1	61 (46.9)	78 (60.0)	**0.035**	70 (53.8)	NS
Frequency of stools ≤ 1	49 (37.7)	63 (48.5)	NS	47 (36.2)	NS
Response in IBDQ score	75 (57.7)	79 (60.8)	NS	70 (53.8)	NS

Analysis of the results for the ITT-E population (n=575) showed similar results.

Follow-up data

Data from the open-label follow-up period at 52 weeks for the ITT-E population (n=575) showed that the proportion of patients in clinical remission was 26.1% in the placebo group, 20% in the adalimumab 80/40 group, and 24.7% in the adalimumab 160/80/40 mg group.

Discussion of results from the ULTRA 1 trial:
- The EMA considers that the level of effect versus placebo was modest (difference of less than 10%);
- Results were not conclusive versus placebo for the majority of the secondary endpoints, including some that were pertinent, and in particular clinical response;
- It is possible to question the “ITT” population used, especially as the characteristics of patients from the overall randomised population were similar. However, the results from the analyses of these two populations are comparable.

ULTRA 2 Study – M06-827 (carried out between November 2006 and March 2010)[6]

Aim:

To evaluate the efficacy and safety of adalimumab in **inducing and maintaining** clinical remission in patients with active, moderate to severe UC.

Methodology:
A randomised, double-blind study up to Week 52, followed by an open-label follow-up period up to Week 62.
The patients included could (as opposed to those in the ULTRA 1 study) have been treated with a TNF inhibitor if this treatment was stopped due to a lack of response (lack of improvement or deterioration in symptoms) or intolerance (acute reaction in the 24 hours following the injection or delayed reaction between 24 h and 14 days after the injection). However, patients should not have been treated with infliximab or any other TNF inhibitor in the 56 days prior to their inclusion in the study.

According to the calculation of the number of patients required for the study, a minimum of 500 patients should be included.

Treatments:
Patients included (n = 518) were stratified based on their previous exposure to infliximab and/or any other TNF inhibitor, and randomised to receive:
- 160 mg adalimumab in Week 0, 80 mg in Week 2 then 40 mg every 2 weeks (n = 248) or
- a placebo (n = 246 patients)

Endpoints:
The joint primary efficacy endpoints were:
- clinical remission (defined by a Mayo score ≤ 2 and the absence of an individual sub-score > 1) at Week 8
- clinical remission at Week 52

Secondary endpoints included:

- clinical response[7] at Week 8 and Week 52
- mucosal healing at Week 8 and Week 52
- rectal bleeding sub-score (≤ 1) indicating a milder stage of the disease at Week 8
- a PGA sub-score (≤ 1) indicating a milder stage of the disease at Week 8
- a stools frequency sub-score (≤ 1) indicating a milder stage of the disease at Week 8
- response in IBDQ quality of life score at Week 8 and Week 52
- clinical remission at Week 52 and discontinuation of corticosteroids before Week 52

Results:
Analysis of the results for the primary endpoint was carried out on the "ITT" population, defined in the study as randomised patients with confirmed UC and who have had at least one injection.

Of the 518 patients randomised, 24 patients (14 from the adalimumab group and 10 from the placebo group) from 3 investigative sites (out of 120 sites in total) were excluded form the "ITT analysis" due to non-compliance with the protocol requirements before the blinding was lifted. Analysis was therefore carried out on 494 patients, which is 95% of the randomised population.

Patient characteristics at inclusion in the ULTRA 2 study, see Table 4

6 Sandborn W. et al. Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe Ulcerative Colitis, Gastroenterology 2012; 142: 257–265.

7 Defined at Week 8 and Week 52 as a reduction in total Mayo score of 3 points and by at least 30% and reduction in the endoscopic Mayo sub-score of at least 1 point and reduction in "rectal bleeding" score to 0 or 1

Demographic and medical characteristics of the “ITT population” were comparable in the two groups. The mean age of patients was 40 years, the disease had been progressing for over 8 years, and had been confirmed by biopsy. They had been previously treated with corticosteroids, azathioprine and 6 mercaptopurine and 75% of them were still taking these treatments at the time of their inclusion in the study. In addition, 41% of patients had also been treated with a TNF inhibitor, and in general this was infliximab.

Table 4. Demographic and medical characteristics of patients in the ULTRA 2 study, “ITT population”

	Placebo **N = 246**	**Adalimumab** **N = 248**	**Total** **N = 494**
Mean age	41.3 ± 13.22	39.6 ± 12.47	40.4 ± 12.86
Mean duration of UC (years)	8.5 ± 7.37	8.1 ± 7.09	8.3 ± 7.23
Mayo score N Mean (SD)	245 8.9 (1.75)	246 8.9 (1.50)	491 8.9 (1.63)
History of treatment for UC	230 (93.5)	232 (93.5)	462 (93.5)
Corticosteroids	217 (88.2)	219 (88.3)	436 (88.3)
Azathioprine	122 (49.6)	113 (45.6)	235 (47.6)
Mercaptopurine	36 (14.6)	34 (13.7)	70 (14.2)
Any TNF inhibitor	101 (41.1)	98 (39.5)	199 (40.3)
Infliximab	101 (41.1)	97 (39.1)	198 (40.1)
Golimumab	0	2 (0.8)	2 (0.4)
Certolizumab	0	1 (0.4)	1 (0.2)
Any treatment for UC used at inclusion	218 (88.6)	224 (90.3)	442 (89.5)
Corticosteroids	140 (56.9)	150 (60.5)	290 (58.7)
Azathioprine	64 (26.0)	76 (30.6)	140 (28.3)
Mercaptopurine	16 (6.5)	17 (6.9)	33 (6.7)
Aminosalicylates	155 (63.0)	146 (58.9)	301 (60.9)

Discontinuation of treatment:

Of the 518 patients randomised, 517 were treated and 209 (42.3%) discontinued treatment prematurely (46.7% in the placebo group and 37.9% in the adalimumab group), primarily due to:

- a lack of efficacy (28.5% in the placebo group versus 25.4% in the adalimumab group)
- adverse events (10.2% in the placebo group versus 4.8% in the adalimumab group)

Among the 494 patients from the “ITT population” defined in the study, 11.9% of patients discontinued the study during the 8 weeks of evaluation for the primary endpoint (14.6% in the placebo group and 9.3% in the adalimumab group), primarily due to a lack of efficacy and adverse events.

Results for the primary efficacy endpoints – analysis of the "ITT" population:

The proportion of patients in clinical remission at Week 8 and Week 52 was significantly greater in the adalimumab group than in the placebo group:

- at Week 8, 41/248 (16.5%) with adalimumab versus 23/246 (9.3%) with placebo, which is an absolute difference of 7.2% 95% CI [1.2; 12.9], p = 0.019.
- at Week 52, 43/248 (17.3%) with adalimumab versus 21/246 (8.5%) with placebo, which is an absolute difference of 8.8% 95% CI [2.8; 14.5], p = 0.004.

No analysis based on all patients randomised has been provided.

Secondary endpoints:

With the exception of the PGA endpoint and clinical remission at Week 32 with discontinuation of corticosteroid treatment, a statistical difference in favour of adalimumab was highlighted for the secondary endpoints, see Table 5.

Table 5. Results for the secondary endpoints for the ULTRA 2 study

Secondary endpoints	Number (%) of patients		
	Placebo N = 246	Adalimumab N = 248	P value
Clinical response at Week 8	85 (34.6)	125 (50.4)	≤ 0.001
Clinical response at Week 52	45 (18.3)	75 (30.2)	0.002
Mucosal healing at Week 8	78 (31.7)	102 (41.1)	0.032
Mucosal healing at Week 52	38 (15.4)	62 (25.0)	0.009
Stools frequency sub-score ≤ 1 at Week 8	70 (28.5)	94 (37.9)	0.028
Rectal bleeding sub-score ≤ 1 at Week 8	143 (58.1)	174 (70.2)	0.006
Clinical remission at Week 32 with discontinuation of corticosteroids	10/140 (7.1)	21/150 (14.0)	NS
Clinical remission at Week 52 with discontinuation of corticosteroids	8/140 (5.7)	20/150 (13.3)	0.035
Response in IBDQ score at Week 8	112 (45.5)	144 (58.1)	0.006
Response in IBDQ score at Week 52	40 (16.3)	65 (26.2)	0.007
PGA sub-score < 1 at Week 8	92 (37.4)	114 (46.0)	NS

Supplementary analyses of results:

- based on previous treatment with a TNF inhibitor

In TNF inhibitor treatment-naïve patients, clinical remission was achieved at Week 8 in a greater proportion of patients in the adalimumab group (21.3%) than in the placebo group (11%), which is an absolute difference of 10.3%, p = 0.017. At Week 52, superiority of adalimumab compared with placebo was also demonstrated, with an absolute difference of 9.6%, p = 0.029, see Table 6.

In patients previously treated with a TNF inhibitor, no statistical difference was highlighted in the proportion of patients in remission at Week 8, but a difference in favour of adalimumab was shown at Week 52 (difference of 7.2%).

Table 6. Efficacy results based on whether patients were naive or non-naive to TNF inhibitor treatment

	TNF inhibitor-naive			Previous use of TNF inhibitor		
	Number (%) of patients			Number (%) of patients		
Efficacy endpoint	Placebo N = 145	Ada N = 150	p	Placebo N = 101	Ada N = 98	p
Remission at Week 8	16 (11.0)	32 (21.3)	0.017	7 (6.9)	9 (9.2)	NS
Remission at Week 52	18 (12.4)	33 (22.0)	0.029	3 (3.0)	10 (10.2)	0.039

Discussion of results from the ULTRA 2 study:

- Although the superiority of adalimumab compared with placebo has been demonstrated, the CHMP considered (see EPAR) that the proportion of patients achieving clinical remission with adalimumab compared with placebo was modest (below 10%), 7.2% [1.2; 12.9] for inducing remission at Week 8 and 8.8% [2.8; 14.5] for maintaining remission at Week 52.
- By analysing the proportion of patients who initially achieved clinical remission at Week 8 and maintained this remission at Week 52, the results are even more modest: 21/248 (8.5%) with adalimumab versus 10/246 (4,1%) with placebo, p = 0.047, i.e. a difference of 4.4% [0.1; 8.6], suggesting a minimal level of effect.
- Supplementary exploratory analyses showed that in comparison to the overall population a greater proportion of patients who achieved an "early" clinical response, i.e. between weeks 2 and 8 were still in clinical remission at Week 52; Thus,
  - among the 39% who achieved clinical response[8] at Week 2, 32% were in clinical remission and 47.4% had a clinical response at Week 52;
  - among the 46% who achieved clinical response[8] at Week 4, 29.2% were in clinical remission and 46% had a clinical response at Week 52;
  - among the 50.4% who achieved clinical response[7] at Week 8, 28.8% were in clinical remission and 47.2% had a clinical response at Week 52.

  Given these results, the SPC for HUMIRA states that “treatment with adalimumab **should not be continued** in patients failing to respond within 2 to 8 weeks”. This recommendation is not included in the SPC for REMICADE.[9]

M10-223 (November 2007, in progress)

The aim of this open-label follow-up study was to evaluate the maintained clinical response and the safety of taking repeated doses of adalimumab as a maintenance treatment in 498 patients with active, moderate to severe UC from the ULTRA 1 and 2 studies. Patients received a sub-cutaneous injection of 40 mg of adalimumab every 2 weeks or every week up to the 240th week. The results presented are from an interim analysis at Week 60 (31 December 2009) and are therefore only exploratory.

Change in partial Mayo activity score[10] up to Week 60

	Adalimumab 40 mg, N=498		
	n	Mean ± SD	Median
Week 0 (inclusion)	493	2.5 ± 1.99	2.0
Week 2	466	2.3 ± 2.06	2.0
Week 4	460	2.4 ± 2.06	2.0
Week 8	441	2.3 ± 2.04	2.0
Week 12	416	2.3 ± 2.09	2.0
Week 24	348	2.3 ± 2.0	2.0
Week 36	281	2.3 ± 2.15	2.0
Week 48	183	2.3 ± 2.26	2.0
Week 60	130	2.5 ± 2.50	2.0

8 Defined at Week 2 and Week 4 as a reduction in partial Mayo score of at least 2 points and by at least 30% and reduction in endoscopic Mayo sub-score of at least 1 point and reduction in “rectal bleeding” score by at least 1 compared with at inclusion or a sub-score from 0 to 1.

9 The SPC for REMICADE states that "Available data suggest that the clinical response is usually achieved within 12 weeks of treatment, i.e. after three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this period of time”

10 The partial Mayo score does not include the rectal sigmoidoscopy sub-score. It is thus an overall composite score ranging from 0 to 9 and combining three sub-scores, each one between 0 and 3.

At Week 60, 67 patients (or 13.5%) had stopped treatment, the most common reasons being a lack of efficacy (4.6%), adverse events (3.4%) or withdrawal of consent (2.8%).

3.2. Adverse effects

Safety data are taken from the two controlled trials and the follow-up study described above. A total of 1,093 patients were included in these studies, and received either adalimumab or the placebo. The mean duration of treatment with adalimumab was 382 days and the mean total number of injections was 35.6 (on average 3 injections per month).

During the 8 week induction period, between 54.9 and 58.4% of patients reported an adverse event. Reactions at the injection site were significantly more common in patients treated with adalimumab (6.3%) than those given the placebo (3.1%); p = 0.022. Cases of UC flares were significantly less common in patients treated with adalimumab (7.3%) than those on placebo (12.2%); p = 0.012. No difference was highlighted for other types of adverse events.
During the clinical remission maintenance period (up to 52 weeks), the proportion of patients who reported at least one adverse event was 73.5% in the adalimumab groups and 68.2% with placebo. A greater proportion of patients reported adverse effects in the adalimumab group (30.8%) compared with the placebo group (21.5%), p = 0.026, in particular reactions at the injection site (6.8% with adalimumab versus 1.3% with placebo; p = 0.004). There were no other significant differences observed.

The overall analysis of safety in patients treated with adalimumab (all doses and administration regimens included) during these trials showed that 81% of patients had an adverse event, 16.6% of patients discontinued treatment due to an adverse event with worsening of UC being the most commonly reported serious adverse event (8.2%). One death due to cardiorespiratory failure (9 days after the last injection of adalimumab in a male aged 34 years) was reported during the study and was considered by the clinical investigator to be possibly linked to treatment with adalimumab.
Serious infections affected 40 patients treated with adalimumab (4%). The most common infections included: appendicitis (n=6), pneumonia (n=4) and abdominal abscess (n=3). An opportunistic infection (but no cases of tuberculosis) was reported in 21 patients (2.1%) treated with adalimumab.
Ten patients treated with adalimumab developed tumours: three cases of B-cell lymphoma (evaluated as linked to treatment but with coincidental factors), two cases of breast cancer, one case of stomach cancer (evaluated as not linked to treatment), one case of small-cell carcinoma, one case of squamous-cell carcinoma, one case of basal-cell carcinoma (evaluated as not linked to treatment), and one case of malignant melanoma. No cases of colon cancer were reported.

Among the other adverse effects reported with adalimumab during the clinical trials, it was noted that there were:

- four cases of heart failure, including two considered as not linked to treatment.
- one case of leukoencephalopathy possibly linked to treatment.
- hepatic toxicity reported in 43 patients (4.3%). In three patients, the cases were serious, however not linked to treatment.
- cases of allergic reaction, including four cases of hypersensitivity (one case linked to another treatment and three cases linked to adalimumab) in 13 patients (1.3%).
- two cases of pseudo-lupus syndrome probably linked to treatment, and which led to premature discontinuation of treatment.
- haematological events were reported in 20 patients (2%). These included leucopoenia in 16 patients, neutropenia in three patients, and thrombocytopenia in one patient. One case was serious and six cases were possibly linked to treatment.

- cases of diverticulitis not linked or probably not linked to treatment reported in 3 patients (0.3%).
- cases of intestinal perforation were reported in four patients.
- one case of pancreatitis which was not linked to treatment and was not serious was reported in one patient in the adalimumab group.

No new adverse effects were identified for adalimumab during these studies. The most common adverse effect and the one which most frequently led to discontinuation of treatment with adalimumab was worsening of UC.

Within the scope of the RMP (Risk Management Plan), a register with the aim of evaluating the long-term safety and efficacy of treatment with adalimumab in patients with UC will be set up.

3.3. Conclusion

Adalimumab (HUMIRA) for moderate to severe UC (Mayo score of 6 to 12 and an endoscopic sub-score of 2 to 3 points), despite treatment with corticosteroids and/or immunosuppressants, was evaluated in two randomised, double-blind trials versus placebo, (ULTRA 1 and ULTRA 2) and in an open-label study (M10-223), an extension to the previous studies, but with only interim results available. The comparison with infliximab, another TNF inhibitor indicated in UC, is not possible, as it only obtained its Marketing Authorisation for UC in January 2007, when the ULTRA 1 and 2 trials started in 2006.

In the ULTRA 1 trial on 576 patients, two dose regimens for adalimumab (160 in Week 0 then 80 in Week 2 then 40 mg every 2 weeks, and 80/40 mg) were compared with placebo over 8 weeks. The percentage of patients in clinical remission (Mayo score ≤ 2 and no individual sub-score > 1) at Week 8 was greater with adalimumab 160/80/40 mg than with placebo (18.5% vs. 9.2%; p = 0.031) but the difference of 9.3% [0.9; 17.6] is modest. No difference was highlighted between the placebo and the 80/40 mg regimen, for which the MA has not been retained.

In the ULTRA 2 trial on 518 patients, adalimumab (160 mg in Week 0, 80 mg in Week 2 then 40 mg every 2 weeks) was compared with placebo at 8 and 52 weeks after stratification, based on previous use of a TNF inhibitor:

- The percentage of patients in clinical remission (Mayo score ≤ 2 and no individual sub-score > 1) was greater with adalimumab than with placebo:
  - at Week 8, 16.5% versus 9.3%; (p = 0.019) which is a difference of 7.2%, 95% CI [1.2; 12.9],
  - at Week 52, 17.3% versus 8.5%; (p = 0.004) which is a difference of 8.8%, 95% CI [2.8; 14.5].
- The percentage of patients who initially achieved remission at Week 8 and at Week 52, was greater with adalimumab than with placebo (8.5% versus 4.1%; p = 0.047), which is a difference of 4.4% 95% CI [0.1; 8.6].
- For TNF inhibitor treatment-naive patients (59%), the percentage of patients in clinical remission was greater with adalimumab than with placebo at Week 8 (21.3% versus 11% which is a difference of 10.3%, p = 0.017) and at Week 52 (difference 9.6%, p = 0.029). In patients previously treated with a TNF inhibitor (41%), there was no difference in the percentage of patients in clinical remission between adalimumab and placebo at Week 8 (primary endpoint).

Exploratory analyses showed that the percentage of patients in clinical remission at Week 52 was lower in patients who did not have early remission (Week 2 or Week 8). Thus, the recommendation not to continue treatment with adalimumab in patients who have not responded in Weeks 2 to 8 was added to the SPC.

The percentage of discontinuations of treatment in both trials was high:

- in the ULTRA 1 trial (double-blind and extension phases): 35.9% in the adalimumab 160/80/40 group versus 31.1% in the placebo group, the main reasons being inefficacy (17% versus 19.8%) and adverse events (14.8% versus 17.6%).
- in the ULTRA 2 trial: 37.9% versus 46.7%, the main reasons being inefficacy (25.4% versus 28.5%) and adverse events (4.8% versus 10.2%).

Serious infections affected 4% of patients treated with adalimumab and 1% developed tumours.
There were no new adverse effects associated with adalimumab identified for this new indication.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) which is manifested by severe, chronic, bloody diarrhoea and progresses episodically. It causes a marked deterioration in quality of life and exposes patients to serious complications, such as acute colitis, dysplasia and colon cancer.
HUMIRA is intended as a symptomatic treatment.

Public health benefit:
Ulcerative colitis is a serious and debilitating condition since it mainly affects young adults and because of its chronic nature. It has a high morbidity rate due to the frequency of flares, its complications (acute colitis, dysplasia and colon cancer) and surgical treatment. It is also responsible for a marked change in physical, psychological and social quality of life. The public health burden represented by ulcerative colitis may be regarded as moderate. The burden corresponding to the restricted population defined by the indication in the Marketing Authorisation (moderate to severe form intolerant or not responding to conventional treatment) is low.
Improvement in the management of ulcerative colitis is a public health need which is already an established priority (Law no. 2004-806 of 9 August 2004 on Public Health policy: objective 76 aiming to reduce the impact of CIBD on the quality of life of those effected, Plan 2007-2011 for the improvement in quality of life of patients with chronic conditions).
Based on the available data from trials carried out versus placebo, HUMIRA is expected to have a low impact on the morbidity and quality of life of patients treated (compared with placebo, 10% more patients presented with an improvement of at least 16 points in IBDQ score at Week 52 compared with at inclusion).
Moreover, the transferability of the results to clinical practice is not assured because of the absence in direct comparison with REMICADE, used since 2007 in this indication.
In addition, the available clinical data do not provide any pertinent evidence on the impact of HUMIRA on surgical treatment (colectomy).
Consequently, in the current state of knowledge, the public health benefit of HUMIRA in this indication cannot be evaluated in comparison with existing alternatives.

Its efficacy/adverse effects ratio is high.

HUMIRA is a second-line treatment in cases of failure (inadequate response, contraindication or intolerance) of conventional treatments, including corticosteroids, azathioprine and/or 6 mercaptopurine.

There is only one alternative medicinal product validated by a marketing authorisation for this stage of the disease (REMICADE – infliximab).

The actual benefit of this proprietary medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

HUMIRA does not provide any improvement in actual benefit (IAB V) in the treatment of active, moderate to severe ulcerative colitis which is intolerant or respond inadequately to conventional treatments (corticosteroids, azathioprine or 6-mercaptopurine).

4.3. Therapeutic use[11]

The aim of treatment for UC is to achieve prolonged clinical remission without the need for corticosteroids and healing of lesions, confirmed endoscopically and histologically.
According to the European ECCO consensus conference and the long-term conditions guide published by HAS,[12] the therapeutic treatment of UC is progressive, defined as increasing and based on several lines of treatment with the combination of standard topical or oral treatments, including 5 aminosalicylates, corticosteroids and immunosuppressants. After failure of or intolerance to these standard treatments, TNF inhibitors are an alternative medicinal treatment.

According to the wording of their indications, REMICADE (infliximab) and HUMIRA (adalimumab) should only be used for the treatment of UC 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.

Alternatives for such patients to these TNF inhibitors are cyclosporine (without marketing authorisation) and surgery for severe corticosteroid-resistant and corticosteroid-dependant forms.

Cyclosporine is rapidly effective in corticosteroid-resistant patients, but its long-term safety is mediocre (nephrotoxicity and risk of tumour) which means that it can not be considered as a disease-modifying treatment. In practice, it is only used over short periods (3 months) to induce remission while waiting for another disease-modifying treatment introduced at the same time to take effect.

Surgery is necessary in 25% to 45% of patients due to an absence of improvement in symptoms or complications of the condition.[13,14,15,16]

The decision to have surgery is based on age, how long the patient has had UC, how far the disease extends along the bowel, the desire to get pregnant, the condition of the rectum and colon cancer risk factors. Indeed, total coloprotectomy with ileoanal pouch anastomosis is a complicated surgical procedure that requires two or three operations. Mortality is low (below or equal to 1%) and morbidity is high (30-40%: blockages, pelvic sepsis, etc.). Furthermore, it significantly reduced a women's fertility.

Therapeutic use of HUMIRA

HUMIRA represents an alternative to REMICADE when treatment with a TNF inhibitor is required i.e. in active moderate to severe forms, resistant to conventional treatments including corticosteroids and immunosupressants. Given the available efficacy data, treatment with HUMIRA should not be continued in patients who have not responded in 2 to 8 weeks. Long-term safety data are limited. As with REMICADE, there is no study comparing adalimumab with cyclosporine.

As an indication:
The evaluation of HUMIRA by NICE for UC is in progress.
NICE only recommends REMICADE for UC if cyclosporine is contraindicated, due to medico-economic reasons and in the absence of satisfactory evidence of the superiority of infliximab over cyclosporine (2008).

11 Travis SP et al. J Crohns Colitis 2008; 2: 24-62.
12 Long-term Conditions Guide 24, Evolutive ulcerative colitis, HAS, May 2008.
13 Kaiser AM, Beart RW, Jr. Surgical management of ulcerative colitis. Swiss Med Wkly. Jun 162001; 131 (23-24): 323-337.
14 Hwang JM, Varma MG. Surgery for inflammatory bowel disease. World J Gastroenterol. May 7 2008; 14 (17): 2678-2690.
15 Metcalf AM. Elective and emergent operative management of ulcerative colitis. Surg Clin North Am. Jun 2007; 87 (3): 633-641.
16 Bach SP, Mortensen NJ. Ileal pouch surgery for ulcerative colitis. World J Gastroenterol. Jun 28 2007; 13 (24): 3288-3300.

4.4. Target population

According to the wording of the indication in the Marketing Authorisation, the population likely to be treated with HUMIRA includes patients with moderate to severe UC and who have had an inadequate response to conventional therapy including corticosteroids **and/or** 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

According to a national study published in 2006[17] carried out on medical insurance data relating to long-term conditions for chronic inflammatory bowel disease (CIBD) between January 2000 and December 2002, the incidence was 8.1/100,000 [8.0-8.3] for Crohn's disease and 7.1/100,000 [7.0-7.3] for UC.
According to ORPHANET data,[18] in Western Europe and the United States, the incidence of UC is approximately 6 to 8 cases in every 100,000 individuals and the estimated prevalence is approximately 70 to 150 in every 100,000 individuals.
In summary, the prevalence of UC can be estimated at 1 in every 1000, which is approximately 63,500 patients in France in 2012.[19]

There is no French epidemiological data that enables the proportion of moderate to severe forms after failure of corticosteroids **and/or** immunosuppressants to be estimated.

This proportion may be estimated based on data from the ICOMED panel, which is representative of the practice of 50% of private and hospital-based gastroenterologists in France. In 2010, according to data from this panel, 51% of UC treated by gastroenterologists was moderate to severe, which represents 32,000 patients.

The proportion of moderate to severe forms after failure of corticosteroids may be calculated based on results from a market research study (A+A) carried out by the applicant between November 2011 and January 2012, which showed that:
- 64% of patients with UC were treated with corticosteroids (i.e. 21,000 patients),
- one year after corticosteroid therapy, 51% of patients were corticosteroid-dependant, i.e. 10,000 patients.
- 76% of patients treated with immunosuppressants had an inadequate response, i.e. 8,000 patients.

In summary, the target population of HUMIRA for active, moderate to severe UC after failure of corticosteroids **and/or** immunosuppressants may be estimated as less than 10,000 patients.
This estimation is consistent with the opinions of experts, who highlighted that 15% of UC (which is less than 10,000 cases) received treatment with a TNF inhibitor.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the new indication (UC).

17 Nerich V. et al. Inflamm Bowel Dis, 2006; 12: 218–226
18 Ulcerative colitis. Orphanet 2003.
19 Evaluation of French population. INSEE Data.

4.5.1 Request for a post-marketing study:

"The Transparency Committee is requesting a long-term follow-up study in patients with ulcerative colitis and treated with HUMIRA. The aims of this study are to document, under real life treatment conditions:

- The characteristics of patients treated: sex, age, medical history, clinical profile (frequency and severity of flares, extent of lesions, level of activity on the Mayo score, existence of dysplasia, infection complications, etc.),

- Conditions of use for this proprietary medicinal product, specifically the circumstances for being put on treatment: previous medical and surgical treatments and associated care,

- Long-term maintenance of the benefits of this treatment, including quality of life and the impact on the need for surgery (total coloprotectomy).

- Long-term safety of this proprietary medicinal product.

The Committee is requesting the inclusion of patients corresponding to this new indication in this study.

If scheduled or ongoing studies, in particular within the remit of the European Risk Management Plan, fail to answer all the questions raised by the Transparency Committee, a specific study will need to be conducted. "

4.5.2 Packaging: Appropriate for the prescription conditions.

4.5.3 Reimbursement rate: 65%

4.5.4 Exception drug status