HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 May 2008

HUMIRA 40 mg, solution for injection in pre-filled syringe
Pack of 2 x 0.8 ml glass syringes with two alcohol pads (CIP: 362 230-5)

HUMIRA 40 mg, solution for injection in pre-filled pen
Pack of 2 x 0.8 ml pens with 2 alcohol pads (CIP: 378 014-5)

ABBOTT

adalimumab

List I

Medicinal product for initial annual hospital prescription.
Prescription restricted to specialists in rheumatology, internal medicine, gastroenterology, digestive surgery or dermatology.

Date of marketing authorisation: 08 September 2003 (centralised procedure)
Date of latest revision of Marketing Authorisation: 19 December 2007 (extension of indication to psoriasis)

Exception drug status

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “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”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

adalimumab

1.2. Indications

Indications prior to the application:

"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.

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.

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.
For induction treatment, HUMIRA should be given in combination with corticosteroids.
HUMIRA can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate."

New indication applied for:

"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".

1.3. Dosage

"HUMIRA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or **psoriasis**. Patients treated with HUMIRA should be given the special alert card.
After proper training in injection technique, patients may self-inject with HUMIRA if their physician determines that it is appropriate and with medical follow-up as necessary.
During treatment with Humira, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Adults

Psoriasis

The recommended dose of Humira for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.
Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Elderly patients

No dose adjustment is required.

Children and adolescents

There has been no experience in children.

Impaired renal and/or hepatic function

HUMIRA has not been studied in these patient populations. No dose recommendations can be made.

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

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

L	: Antineoplastic and immunomodulating agents
L04	: Immunosuppressants
L04A	: Immunosuppressants
L04AB	: Tumor necrosis factor alpha (TNF-α) inhibitors
L04AB04	: Adalimumab

2.2. Medicines in the same therapeutic category

These are biotherapies indicated in the treatment of moderate to severe psoriasis after failure of other systemic therapies (including MTX, cyclosporine, PUVA):

- REMICADE (infliximab), a TNFα antagonist
- ENBREL (etanercept), a TNFα antagonist
- RAPTIVA (efalizumab), a monoclonal antibody targeting T-cell surface protein (LFA-1).

2.3. Medicines with a similar therapeutic aim

Local treatments:

These are medicinal products indicated for the topical treatment of psoriasis: keratolytics (including salicylic acid), highly active dermocorticosteroids, vitamin D analogues and vitamin A derivatives.

Systemic treatments:
SORIATANE (acitretin), NEORAL and SANDIMMUN (ciclosporin), NOVATREX 2.5 mg tablets, METHOTREXATE BELLON, METOJECT (methotrexate)

Other forms of treatment:
UVA photochemotherapy (in combination with photosensitising agents)
UVB phototherapy.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy of HUMIRA in the treatment of moderate to severe plaque psoriasis was evaluated in two clinical studies: the REVEAL study (M03-656) versus placebo and the CHAMPION study (M04-716) versus methotrexate (MTX) and placebo.
The extension study M03-658, which included patients from the previous studies with the aim of evaluating the long-term (120 weeks) efficacy and safety of HUMIRA, will not be discussed in detail since the results are not yet all available (study in progress).

The two studies submitted used mainly the following evaluation criteria:

- PASI (Psoriasis Area and Severity Index) is a composite index based on measurement of erythema, induration, desquamation and body surface area affected. It ranges from 0 (no psoriasis) to 72 (maximum severity). This score, however, is only valid where at least 3% of the body's skin area is affected and erythema, induration and area are evaluated in combination. A PASI 75 response means at least a 75% reduction on the initial PASI score. A PASI 100 response corresponds to complete remission.
- PGA (Physician Global Assessment) represents the dermatologist's overall assessment of the severity of the disease on a 6-point scale from "clear" or "almost clear" to "severe".
- DLQI (Dermatology Life Quality Index): this quality of life score evaluates the impact of the skin condition on psychosocial, social and sexual function and the performance of daily activities. The DLQI score ranges from 0 to 30 – the higher the score, the worse the quality of life. A 5-point change in the total DLQI score is the smallest change that is clinically significant in evaluating quality of life.

➢ Efficacy compared with placebo: REVEAL study (M03-656)

Objective: Evaluation of the efficacy and safety of HUMIRA in the treatment of moderate to severe psoriasis.

Methodology: Placebo-controlled, randomised trial, double blind during periods A and C and open-label in period B.

The study comprised 3 periods:
- period A: patients were randomised to the HUMIRA or placebo groups for 16 weeks. The aim of this period was to evaluate the short-term efficacy of HUMIRA.
- period B: patients who achieved at least a PASI 75 response by Week 16 continued the study until Week 33. They were all treated with open-label HUMIRA. The aim of this period was to evaluate the maintenance of efficacy until Week 33.

- period C: patients whose response remained higher than PASI 75 at Week 33 were re-randomised to a HUMIRA group or a placebo group. The aim of this period was to evaluate loss of adequate response by Week 52.

Patients randomised to the HUMIRA group received a loading dose of 80 mg at Week 0 followed by 40 mg every other week starting in Week 1, in accordance with the dosage given in the marketing authorisation.

Main inclusion criteria:
- Patients with psoriasis for at least 6 months
- BSA (Body Surface Area) ≥ 10% and PASI ≥ 12

Primary efficacy endpoints:
- Period A: percentage of patients achieving a PASI 75 response (proportion of subjects whose PASI score fell by at least 75%) at Week 16.
- Period C: percentage of patients with a loss of adequate response at Week 52 (6-point increase in PASI score relative to Week 33 or response poorer than PASI 50 relative to baseline).

Secondary endpoints included:
- PASI 75/100 for periods A and B
- PGA (Physician Global Assesment)
- DLQI (Dermatology Life Quality Index) for period A

Results:

A total of 1212 patients was randomised in this study. The main patient characteristics were: a mean baseline PASI score of 18.9, a PGA score that was “moderate” (53%), “severe” (41%) or “very severe” (6%), and a mean BSA score of 26%.

Most patients had received prior topical or systemic treatment for psoriasis, but not all of them had failed to respond to that treatment.

Table 1: Prior treatment (in the 12 months prior to commencement of the study)

	Topical treatment n (%)	Phototherapy n (%)	Non-biological systemic treatment n (%)	Biological systemic treatment n (%)	Laser n (%)
Placebo (n =398)	290 (72.9)	59 (14.8)	88 (22.1)	53 (13.3)	0
HUMIRA (n = 814)	618 (75.9)	138 (17.0)	188 (23.1)	97 (11.9)	1 (0.1)

The results for period A were analysed on the ITT population.

Of the 814 patients treated by HUMIRA in period A, 31 (3.8%) discontinued the study (10 of them stopped following adverse events, 6 withdrew consent, 6 were lost to follow-up, 2 had an inadequate response and 7 discontinued for various reasons). Of the 398 patients randomised to the placebo group, 43 (10.8%) discontinued the study (4 of them stopped following adverse events, 9 withdrew consent, 8 were lost to follow-up, 17 had an inadequate response and 5 discontinued for various reasons).

Results for the efficacy endpoints:
The results for period A were as follows:

Table 2: Efficacy results at Week 16 (ITT)

	Placebo N = 398	HUMIRA N = 814	p	Difference (%) (95% CI)
Primary endpoint				
PASI 75 n (%)	26 (6.5)	578 (70.9)	<0.001	64.4 (58.4 ;70.4)
Secondary endpoints				
PASI 100 n (%)	3 (0.8)	163 (20.0)	<0.001	-
PGA "clear" or "minimal" n (%)	17 (4.3)	506 (62.2)	<0.001	-
Mean change in DLQI[1] (points)	-1.7	-8.2	<0.001	-

For the primary endpoint at Week 16, the observed results for PASI 75 were significantly higher in the HUMIRA group than in the placebo group (Δ= 64.4%, 95% CI [58.4;70.4]).
For the secondary endpoints, the observed results were significantly higher in the HUMIRA group than in the placebo group for both PASI 100 (complete remission) and PGA.
In addition, a significant improvement in quality of life (DLQI) was observed with HUMIRA (-8.2 points versus -1.7 for the placebo).

During the open-label period B (N=580), the PASI 75, PASI 100 and PGA clear or minimal responses remained stable until Week 33 for those patients that had achieved a PASI 75 response at the end of period A.

In period C, the patients treated with HUMIRA in period B who still showed PASI 75 response at Week 33 were re-randomised either to the HUMIRA group (N=250) or to the placebo group (N=240).
For the primary endpoint at Week 52, 4.9% of the patients treated with HUMIRA showed a loss of adequate response[2] compared with 28.4% of the patients in the placebo group (Δ= -23.5%, 95% CI [-30.2; -16.9]).

- **Efficacy versus active comparator, methotrexate: CHAMPION study (M04-716)**

Objective: To compare the efficacy and safety of HUMIRA versus a standard of care treatment, methotrexate, in patients with moderate to severe psoriasis.

Methodology: This was a randomised, double-blind, comparative study versus methotrexate and placebo.
This study had been designed to reveal Humira's non-inferiority, and possibly superiority, to methotrexate (MTX), if the non-inferiority of Humira compared with MTX was demonstrated.

[1] The smallest significant individual change for a psoriasis patient is 5 points.
[2] A loss of adequate response was defined as a 6-point increase in PASI score relative to Week 33 or response poorer than PASI 50 relative to baseline.

Limit of non-inferiority:
For the comparison with MTX, non-inferiority was demonstrated if the lower limit of the 95% confidence interval for the difference between the PASI 75 responder rates (HUMIRA – MTX) was greater than -20%. If the lower limit of the confidence interval was positive, the HUMIRA group should be considered superior to the MTX group.

Treatments:
Patients randomised to the HUMIRA group received a loading dose of 80 mg at Week 0 followed by 40 mg every other week starting in Week 1.
All patients randomised to the MTX group received increasing doses of oral MTX up to 15 mg/week at Week 4. At Week 8, patients who had achieved a response greater than or equal to PASI 50 were kept at the dose of 15 mg/week. If the patients' response was less than PASI 50, the dose of MTX was increased to 20 mg/week, and then to 25 mg/week at Week 12 if they still had not achieved a PASI 50 response.

Main inclusion criteria:
- Patients with psoriasis for at least 1 year
- BSA (Body Surface Area) ≥ 10% and PASI ≥ 10
- TNFα antagonists and MTX naïve patients

Primary efficacy endpoint:
- PASI 75 at Week16

Secondary endpoints included:
- PASI 100 (complete remission)
- PGA (Physician Global Assesment)
- DLQI (Dermatology Life Quality Index)

Results:
The study included 271 patients who had had psoriasis for an average of 18.5 years; their mean PASI score was 19.7 and their mean BSA was 32.1%.
Between 82.2% and 90.4% of patients had previously received phototherapy and/or systemic treatment, but not all of them had failed to respond to that treatment.
Of the patients randomised to the MTX group, 94% received doses greater than 15 mg/week.

Of the 108 patients included in the HUMIRA group, 4 (3.7%) discontinued the study (1 stopped following an adverse event, 2 withdrew consent and 1 discontinued for various reasons); 6 of the 110 patients (5.5%) in the MTX group discontinued the study (all due to adverse events); and 5 of the 53 patients (9.4%) in the placebo group discontinued the study (1 due to an adverse event and 4 due to a lack of efficacy).

Results for the efficacy endpoints:

Table 3: Number of patients achieving a PASI 75 response at Week 16

	Placebo n (%)	**MTX n (%)**	**HUMIRA n (%)**
ITT population	***N = 53***	***N = 110***	***N = 108***
PASI 75	10 (18.9)	39 (35.5)	86 (79.6)
Difference (%) (95% CI)	60.5 (44.5; 76.6)	44.1 (30.8; 56.7)	-
p	<0.001	<0.001	-
PP population	***N = 48***	***N = 99***	***N = 93***
PASI 75	9 (18.8)	36 (36.4)	75 (80.6)
Difference (%) (95% CI)	61.5 (44.5; 78.4)	43.6 (29.9; 57.3)	-
p	<0.001	<0.001	-

For the primary endpoint at Week 16, the observed results for PASI 75 were significantly higher in the HUMIRA group than in the placebo group (Δ= 60.5%, 95% CI [44.5; 76.4]).
The results of the PP and ITT analyses show that HUMIRA was non-inferior to MTX on PASI 75 (hypothesis of non-inferiority: CI 95% for the difference [30.8%; 56.7%]; threshold δ = -20%).
There is a significant difference in favour of HUMIRA compared with MTX (p<0.001).
The results of the comparison with MTX must be interpreted with caution, however, because of the slow increase in MTX dose until Week 12, which means that there is no guarantee that MTX had reached its optimum efficacy by Week 16.

Table 4: Results for secondary endpoints at Week 16 (ITT):

	Placebo N = 53	**MTX N = 110**	**HUMIRA N = 108**
PASI 100 n (%)	1 (1.9)	8 (7.3)	18 (16.7)
PGA "clear" or "minimal" n (%)	6 (11.3)	33 (30.0)	79 (73.1)
Mean change in DLQI[3] (points)	-3.1	-5.4	-9.0

For the secondary endpoints, HUMIRA was superior to placebo and non-inferior to MTX for both PASI 100 (complete remission) and PGA.
An improvement in quality of life (DLQI) was observed with HUMIRA.

[3] The smallest significant individual change for a psoriasis patient is 5 points.

- **Indirect comparison of efficacy for Humira versus Remicade, Enbrel and Raptiva**

The company has put forward an indirect comparison:

Table 5: Indirect comparison of PASI 75 results

Product Studies	Patient characteristics	Treatment dose*	Weeks	Treatment group	Placebo group
Raptiva GORDON / MENTER	Duration of psoriasis = 19 years PASI score = 19 BSA = 28%	1 mg/kg/week	12	26.6%	4.3%
Enbrel (etanercept) LEONARDI	Duration of psoriasis = 18.7 years PASI score = 18.4 BSA = 28.7%	25 mg x2/week	12	33.9%	3.6%
		50 mg x2/week		49.4%	
Remicade EXPRESS I	Duration of psoriasis = 18.7 years PASI score = 22.9 BSA = 34%	5 mg/kg	10	80.4%	2.6%
Remicade EXPRESS II	Duration of psoriasis = 17.8-19.1 yrs PASI score = 19,8-20.4 BSA = 28%	5 mg/kg	10	70.3%	1.9%
Humira REVEAL	Duration of psoriasis = 18.7 years PASI score = 18.9 BSA = 26%	40mg/2 weeks	16	70.9%	6.5%
Humira vs MTX CHAMPION	Duration of psoriasis = 18.5 years PASI score = 19.9 BSA = 32.1%	HUMIRA 40mg/2 weeks	16	79.6%	18.9%
		MTX 15-25 mg		35.5%	

* Off-label treatment doses have not been included in this table.

It cannot be concluded from this comparison that there is superiority in terms of efficacy compared with the other biotherapies, since:

- although the PASI score is a criterion validated by EMEA and the FDA for evaluating the efficacy of psoriasis treatments, its relevance in clinical practice is debatable[4]
- no heterogeneity test was performed to ensure that the populations were comparable
- the follow-up times differed from one study to another
- the thoroughness of the studies considered in this indirect comparison has not been established.

3.2. Safety

During the clinical studies, 1696 patients were exposed to treatment with HUMIRA.
The safety profile was similar to that observed in the other indications.
The infection risk was significantly higher in the HUMIRA group (293/966 (30.3%)) than in the placebo group (120/503 (23.9%)).
Of all the subjects treated with HUMIRA in clinical studies, 12 had skin cancer other than melanoma. Of these 12 subjects, 6 had a history of keratoacanthoma or skin cancer other than melanoma, and 8 had been treated with phototherapy.

[4] Stern RS. A promising step forward in psoriasis therapy. JAMA. 2003 Dec 17;290(23):3133-5.

The most frequently reported adverse effects during the REVEAL and CHAMPION studies were: nasopharyngitis, upper airway infections, headaches, joint pain, injection site reactions and sinusitis.

According to the SPC, the most commonly reported adverse events (≥ 1/100) were: upper and lower respiratory infections, viral and bacterial infections, candidiasis, headache, dizziness, neurological sensation disorders, cough, nasopharyngeal pain, diarrhoea, abdominal pain, stomatitis and mouth ulceration, nausea, hepatic enzymes increased, rash, pruritus, musculoskeletal pain, injection site reaction, pyrexia and fatigue.

A European risk management plan common to all indications has been put in place, particularly to monitor the occurrence of infections and cancers.

3.3. Conclusion

The efficacy of HUMIRA in the treatment of moderate to severe plaque psoriasis was evaluated in two clinical studies: the comparative REVEAL study versus placebo and the CHAMPION study versus methotrexate and placebo.
The patients included in these two studies had mostly received prior systematic treatment, but not all of them had failed to respond to that treatment.
After 16 weeks of treatment, the proportion of patients achieving a PASI 75 response was significantly greater in the HUMIRA group than in the placebo group in both the REVEAL study (70.9% against 6.5%) and the CHAMPION study (79.6% against 18.9%).
In addition, HUMIRA was superior to MTX for PASI 75 (CHAMPION study). The comparison with MTX should, however, be interpreted with caution. In fact, the slow increase in MTX dose until Week 12 means that there is no guarantee that MTX had reached its optimum efficacy by Week 16.
With regard to the secondary endpoints (PASI 100, PGA and DLQI), HUMIRA was observed to be superior to placebo.
The safety profile was similar to that observed in the other indications.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Psoriasis is a chronic and usually benign inflammatory dermatosis, which in some of its forms may have a significant impact on quality of life.
In the patient population included in the trials (PASI>10; BSA>10%), the short-term efficacy/safety ratio of adalimumab is substantial. The therapeutic improvement at 16 weeks varied from 60.5% to 64.4% depending on the study.
The Committee has no definitive, long-term data on psoriasis patients who have previously received several courses of systemic treatment.
HUMIRA has a delaying effect on symptoms and is a fall-back treatment.
There are alternative treatments.

Public health benefit

Psoriasis causes a substantial public health burden. The burden resulting from the minority population liable to benefit from the treatment is moderate.

In view of the rare but serious cases of psoriasis in which other systemic treatments cannot be used, and the cumulative toxicity of these systemic treatments which restricts their use, there is an unmet therapeutic need that in public health terms may be regarded as substantial, because of the serious condition of the patients who can benefit.

As with other TNF antagonists, HUMIRA is expected to have a low impact on morbidity and quality of life in the short term. The product is not expected to have an impact in the long term either, because of:

- doubt as to its safety, particularly in relation to cancer
- uncertainty as to whether the results of studies conducted over relatively short periods of time and involving a very small quantity of data can be transposed to the restricted population of patients who have actually failed to respond to any other treatment.

Consequently, in the current state of knowledge and as with the other TNF antagonists available (ENBREL and REMICADE), HUMIRA is not expected to provide any public health benefit.

The Committee believes that the actual benefit of HUMIRA is substantial for patients with serious chronic plaque psoriasis[5] who have failed to respond to or who have a contraindication to or are intolerant to at least 2 systemic treatments out of phototherapy, methotrexate and ciclosporin.
For patients not meeting these treatment criteria, the actual benefit is insufficient.

4.2. Improvement in actual benefit

For adult patients with serious chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant to at least 2 systemic treatments out of phototherapy, methotrexate and ciclosporin and who have few or no alternatives, HUMIRA does not provide any improvement in actual benefit (IAB level V) in terms of efficacy compared with other TNFα antagonists (REMICADE and ENBREL).

[5] Severity of psoriasis should be based particularly on the PASI score, extent of the lesions and psychosocial impact.

4.3. Therapeutic use

Current treatments for psoriasis are symptomatic treatments that do not cure the disease but allow the lesions to temporarily disappear, either partially or completely.

The systemic treatments for severe forms of psoriasis are phototherapy, retinoids (sometimes given in combination with phototherapy), methotrexate, ciclosporin and biological agents (etanercept, efaluzimab, infliximab and adalimumab).
Response to phototherapy is substantial, but the conditions of administration (session frequency and equipment) and the cumulative toxicity of this technique restrict access to it and limit its long-term use (risk of skin cancer).

According to specialists, methotrexate remains the standard treatment for extensive or severe cases of psoriasis, despite its serious adverse effects on the liver.

Retinoids used alone have lower efficacy, but their efficacy in synergistic combination with phototherapy is greater. This association is used particularly in diffuse forms of psoriasis.

Biotherapies (etanercept, efaluzimab, infliximab and adalimumab) should be reserved for psoriasis patients with a PASI score ≥ 10 and a DLQI > 10 who have failed to respond to or have a contraindication to or are intolerant to other systemic treatments, including ciclosporin, methotrexate and PUVA therapy.

The current treatment strategy is to “rotate” around the various alternatives. The choice of treatment should be guided by the characteristics of the patient, the disease (concomitant disease, extent of the lesions, history of treatment), and the medicinal product (adverse effects, cumulative dose).

In adult patients who have failed to respond to or who have a contraindication to or are intolerant to at least 2 systemic treatments out of phototherapy, methotrexate and ciclosporin, treatment with etanercept, efaluzimab, infliximab or adalimumab may be considered.

4.4. Target population

The target population for HUMIRA comprises adult patients with severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant to at least 2 systemic treatments, particularly phototherapy, methotrexate and ciclosporin.

The prevalence of severe plaque psoriasis may be estimated from epidemiological data, but no data have been found in the literature for the proportion of patients who are not eligible for (who have failed to respond to, are intolerant to or have a contraindication to) the available systemic treatments.

An estimate of this population may, however, be approximated by applying the current systemic treatment mean response rates to the literature data on the prevalence of the disease. The result of this estimate appears to be in the same order of magnitude as the estimates obtained in the pharmaceutical companies’ surveys of dermatologists and the estimate based on PMSI data.
On these bases, the Committee estimates that the number of patients liable to benefit from HUMIRA treatment is at least 10 000 per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services.

4.5.1 Scope of reimbursement

On the basis of the actual benefit ascribed to it, the Committee proposes that reimbursement for HUMIRA should be confined to patients with chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant to at least 2 systemic treatments out of phototherapy, methotrexate and ciclosporin.

4.5.2 Packaging: Appropriate to the prescription requirements.

4.5.3 Reimbursement rate: 65%

4.5.4 Exception drug status

4.5.5 Request for a post-listing study:

The Transparency Committee would like to see a representative cohort of patients treated in France set up in order to determine:

- an accurate profile of the populations for whom the treatment is to be prescribed: disease history, prior treatment, reasons for and objectives of prescriptions, and practical factors taken into account in order to define (1) severe psoriasis, and (2) treatment failure in an observational situation.
- evaluation of benefit over time: monitoring of the cohort for at least five years should provide a better understanding of the patient's pathway and the value of the treatments in "real life" with regard to the following four points:
  - -maintenance of the benefit after several courses of treatment and the appearance of a rebound effect
  - the treatment strategy
  - long-term toxicity (particularly with regard to cancer, including skin cancer, and risk of infection)
  - change in quality of life as perceived by the subject based on multidimensional indicators (since the consequences of treatment may affect the various areas of a patient's quality of life differently, which would not be revealed by an overall index).

The Transparency Committee asks:

- for this study to be conducted jointly for ENBREL, RAPTIVA, REMICADE and HUMIRA according to the same methodology and protocol.
- to receive the first results after one year of monitoring and yearly after that.