HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 July 2007

REMICADE 100 mg, soluble powder for dilution for infusion purposes
Pack of 1 (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

Date of latest revision of Marketing Authorisation: 4 January 2007

Reason for request: inclusion on the list of medicines approved for use by hospitals in the new indication: **treatment of moderate to severe active ulcerative colitis in patients who have not responded adequately to conventional treatment comprising corticosteroids and azathioprine or 6-mercaptopurine, or in whom this treatment is poorly tolerated or contraindicated**.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Infliximab

1.2. Background

Infliximab is a monoclonal antibody that blocks TNF-alpha.

1.3. Indications

Ulcerative colitis:

REMICADE is indicated in the treatment of moderate to severe active ulcerative colitis in patients who have not responded adequately to conventional treatment comprising corticosteroids and azathioprine or 6-mercaptopurine, or in whom this treatment is poorly tolerated or contraindicated.

Psoriatic arthritis

Remicade is indicated in:
the treatment of active, progressive psoriatic arthritis in adults previously responding inadequately to treatment with DMARDs.
Remicade should be administered:
- In combination with methotrexate
- or alone in patients who have shown intolerance to methotrexate or for whom methotrexate is contraindicated.

Note: the amended wording of the indication for use in psoriatic arthritis will be dealt with in a subsequent opinion.

Crohn's disease

Remicade is indicated in:
- the treatment of severe, active Crohn's disease in patients who have not responded to appropriate and properly administered treatment with corticosteroids and/or immunosuppressants, or in whom the treatment is contraindicated or poorly tolerated.
- the treatment of fistulised active Crohn's disease in patients who have not responded to appropriate and properly administered treatment (comprising antibiotics, drainage and immunosuppressive therapy).

Rheumatoid arthritis

Remicade, in combination with methotrexate, is indicated for:
the reduction of signs and symptoms and also the improvement of functional abilities in:
- patients with active disease who have responded inappropriately to treatment with disease-modifying drugs, including methotrexate
- patients with severe, progressive, active disease not previously treated with methotrexate or other DMARDs.

A slowing of joint destruction as measured by radiography has been demonstrated in these patient populations.

Ankylosing spondylitis

Remicade is indicated in the treatment of ankylosing spondylitis in patients who have severe axial signs and high levels of serological markers for inflammatory activity, and who have not responded adequately to conventional treatment.

Psoriasis
Remicade is indicated in the treatment of moderate to severe adult plaque psoriasis in cases of failure or contraindication of, or intolerance to, other systemic treatments, including ciclosporin, methotrexate or PUVA treatment.

1.4. Dosage (see SPC)

REMICADE is indicated for intravenous use in adults (≥ 18 years of age) in all its approved indications.
REMICADE is not recommended for use in young people ≤ 17 years of age since its efficacy has not been established for this age group.

Ulcerative colitis:
5 mg/kg administered by intravenous infusion over 2 hours followed by further 5 mg/kg infusions in weeks 2 and 6 after the first infusion, and then every 8 weeks. The available data suggest that a clinical response is usually achieved within 14 weeks of treatment, i.e. after 3 doses. Continuation of this treatment should be carefully reconsidered in patients for whom no therapeutic benefit has been demonstrated during this period.

Readministration for ulcerative colitis:
The safety and efficacy of readministration, other than every 8 weeks, have not been established.

Rheumatoid arthritis:
In patients not previously treated with Remicade: 3 mg/kg administered by intravenous infusion over 2 hours followed by further 3 mg/kg infusions in weeks 2 and 6 after the first infusion, and then every 8 weeks.

In certain carefully selected rheumatoid arthritis patients who have tolerated the first three 2-hour infusions of Remicade, consideration may be given to the administration of subsequent infusions over a period of not less than 1 hour. Shorter infusions at doses > 6 mg/kg have not been investigated.

Remicade must be administered in combination with methotrexate.

The available data suggest that a clinical response is usually achieved within 12 weeks of treatment. If a patient responds inadequately or does not respond any more after this period, a dose increase by steps of approximately 1.5 mg/kg may be considered, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be envisaged. If an adequate response is obtained, the selected dose or frequency of administration should be maintained. Continuation of this treatment should be carefully reconsidered in patients for whom no therapeutic benefit has been demonstrated during the first 12 weeks of treatment or after a dose adjustment.

Severe, active Crohn's disease:
5 mg/kg administered by intravenous infusion over a period of 2 hours. The available data do not allow for a continuation of infliximab treatment in patients who do not respond in the 2 weeks following the initial infusion. In responding patients, the alternative strategies for continuing treatment are:

- maintenance therapy: additional 5 mg/kg infusions in weeks 2 and 6 after the initial dose, followed by infusions every 8 weeks, or
- readministration: a 5 mg/kg infusion if the signs and symptoms of the disease reappear.

Fistulised, active Crohn's disease:
An initial 5 mg/kg infusion over 2 hours should be followed by further 5 mg/kg infusions in weeks 2 and 6 after the first infusion. If the patient does not respond after these 3 doses, no further infliximab treatment should be administered.

In responding patients, the strategies for continuing treatment are:

- further 5 mg/kg infusions every 8 weeks, or
- readministration if the signs and symptoms of the disease reappear, followed by 5 mg/kg infusions every 8 weeks.

In Crohn's disease, there is limited experience of readministration following reappearance of the signs and symptoms of the disease, and there are insufficient data on the benefit/risk ratio of the alternative strategies for continuing treatment.

Readministration for Crohn's disease and rheumatoid arthritis:
If the signs and symptoms of the disease reappear, Remicade may be readministered in the 16 weeks following the last infusion. In the clinical studies, delayed hypersensitivity reactions were uncommon and occurred after intervals without treatment of less than 1 year (see Special warnings and special precautions for use, and adverse events: delayed hypersensitivity). The safety and efficacy of readministration after an interval without treatment of more than 16 weeks have not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

Ankylosing spondylitis:
5 mg/kg administered by intravenous infusion over 2 hours followed by further 5 mg/kg infusions in weeks 2 and 6 after the first infusion, and then every 6 to 8 weeks. If a patient has not responded by week 6 (i.e. after 2 doses), no further infliximab treatment should be administered.

Readministration for ankylosing spondylitis: the safety and efficacy of readministration, other than every 6 to 8 weeks, have not been established.

Psoriatic arthritis:
5 mg/kg administered by intravenous infusion over 2 hours followed by further 5 mg/kg infusions in weeks 2 and 6 after the first infusion, and then every 8 weeks. Efficacy and tolerance have been demonstrated in combination with methotrexate.
Readministration for psoriatic arthritis: the safety and efficacy of readministration, other than in the dosage schedule of every 8 weeks, have not been established.

Psoriasis:
5 mg/kg administered by intravenous infusion over 2 hours followed by further 5 mg/kg infusions in weeks 2 and 6 after the first infusion, and then every 8 weeks. If a patient has not responded by week 14 (i.e. after 4 doses), no further infliximab treatment should be administered.

Readministration for psoriasis: limited experience of retreatment of psoriasis with a single dose of infliximab after an interval of 20 weeks suggests that efficacy is reduced and there is a higher incidence of slight to moderate infusion reactions in comparison with the initial induction regime.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

L	:	Antineoplastic and immunomodulating agents
04	:	Immunosuppressants
A	:	Immunosuppressants
A	:	Selective immunosuppressants
12	:	Infliximab

2.2. Medicines in the same therapeutic category

Comparator medicines
No other anti-TNFα has a Marketing Authorisation (MA) for ulcerative colitis (UC).

2.3. Medicines with a similar therapeutic aim

In the treatment of UC for which treatment with corticosteroids and immunosuppressants (azathioprine and 6-mercaptopurine) has failed, or where these treatments are poorly tolerated or contraindicated, two medicinal products are used in practice and mentioned by the SNFGE (French National Society for Gastroenterology) in their French guidelines, but they have no specific MA for use in UC:

- ciclosporin
- methotrexate (the efficacy of which in UC has not been demonstrated).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy of infliximab (REMICADE) in the treatment of UC has been demonstrated in two placebo-controlled studies: ACT 1 and ACT 2.[1] As the methodology of these studies was similar (population studied, inclusion criteria, efficacy endpoints, etc.), the data from the two studies have been pooled.

Methodology:
These two randomised, double-blind studies each included 364 patients who had:

- moderate to severe active UC (Mayo score[2] between 6 and 12 with an endoscopy subscore ≥ 2), and
- an inadequate response to conventional treatments (corticosteroids and/or azathioprine and/or 6-mercaptopurine).

Some patients who had an inadequate response to aminosalicylates were included in the ACT 2 study.

Treatments:
The patients enrolled were randomised to receive either placebo (n = 244), or infliximab 5 mg/kg (n = 242), or infliximab 10 mg/kg (n = 242) in weeks 0, 2 and 6 and then every 8 weeks (until the 22nd week in the ACT 2 study and until the 46th week in the ACT 1 study.
Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were authorised.
A reduction in corticosteroids was permitted after the 8th week of treatment.

Patients were followed-up until week 30 in the ACT 2 study and until week 54 in the ACT 1 study.

Endpoints:
The primary endpoint was the clinical response after 8 weeks. It was defined by a decrease of at least 3 points and at least 30% in the Mayo score compared with the baseline score, with a reduction in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 to 1.

[1] Rutgeerts et al. Infliximab for induction and Maintenance therapy for ulcerative colitis. N. Engl J Med 2005; 353: 2462-76.
[2] The Mayo UC activity score consists of:
- Stool frequency - 0 (normal) to 3 (1 = 1-2, 2 = 3-4, 3 = 5 or more)
- Rectal bleeding - 0 (no blood seen) to 3 (blood alone passes)
- Proctosigmoidoscopy - 0 (normal) to 3 (severe disease)
- Physician's global assessment - 0 (normal) to 3 (severe disease)

The total score therefore ranges from 0 to 12
Colitis is considered inactive if the Mayo score ≤ 2 points
Mild disease: Mayo score of 3-5 points
Moderate disease: Mayo score of 6-10 points
Severe disease: Mayo score of 11-12 points

The secondary endpoints common to both studies were:

- Clinical response at week 30.
- Clinical remission assessed at weeks 8 and 30, defined by a Mayo score below or equal to 2 points, with no individual subscore greater than 1.
- Endoscopic mucosal healing at weeks 8 and 30 was defined by an absolute endoscopy subscore of 0 or 1.

Quality of life (assessed by the IBDQ score[3] and the SF36 scale), number of hospital admissions, and corticosteroid withdrawal were also studied.

Results:

Baseline patient characteristics in the ACT 1 and ACT 2 studies were as follows:
Patient characteristics in the 3 treatment groups were similar in both studies. 11% of patients had severe UC (Mayo score = 11 or 12) and 88% had moderate UC (Mayo score 6–10) on enrolment.

Table 1 Summary of patient characteristics in the ACT 1 and ACT 2 studies

	ACT 1			ACT 2		
	Placebo n = 121	Infliximab 5 mg/kg n = 121	Infliximab 10 mg/kg n = 122	Placebo n = 123	Infliximab 5 mg/kg n = 121	Infliximab 10 mg/kg n = 120
Age (years)	41.4 ± 13.7	42.4 ± 14.3	41.8 ± 14.9	39.3 ± 13.5	40.5 ± 13.1	40.3 ± 13.3
Disease duration (years)	6.2 ± 5.9	5.9 ± 5.4	8.4 ± 8.1	6.5 ± 6.7	6.7 ± 5.3	6.5 ± 5.8
Mayo score	8.4 ± 1.8	8.5 ± 1.7	8.4 ± 1.4	8.5 ± 1.5	8.3 ± 1.5	8.3 ± 1.6
Concomitant medication (n, (%))						
Corticosteroids	79 (65.03)	70 (57.9)	73 (59.8)	60 (48.8)	60 (49.6)	66 (55.0)
≥ 20 mg/day	54 (44.6)	45 (37.2)	46 (37.7)	43 (35)	40 (33.1)	47 (39.2)
5-aminosalicylates	85 (70.2)	82 (67.8)	86 (70.5)	89 (72.4)	92 (76.0)	91 (75.8)
Immunosuppressants	53 (43.8)	66 (54.5)	59 (48.4)	54 (43.9)	52 (43.0)	50 (41.7)
azathioprine	36 (29.8)	45 (37.2)	44 (36.1)	35 (28.5)	41 (33.9)	37 (30.8)
6-mercaptopurine	17 (14)	21 (17.4)	15 (12.3)	19 (15.4)	11 (9.1)	13 (10.8)

[3] IBDQ (Inflammatory Bowel Disease Questionnaire). This IBD-specific quality of life index comprises 32 questions filled out by the patient and covering 4 domains: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items) and social function (5 items).
Each item is measured on a Likert scale. The questions are ordered at random in each domain, and a choice is made out of 7 possible answers to each question. A total score may be calculated by adding the individual marks. The total score may range from 32 to 224, the higher the score the better the quality of life. Patients in remission generally have scores above 170.

Table 2: Clinical response (n, %) at week 8 (primary endpoint)

	placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg
ACT 1	45/121 (37.2)	84/121 (69.4)	75 /122 (61.5)
ACT 2	36/123 (29.3)	78/121 (64.5)	83/120 (69.2)
Pooled data	81/244 (33.2)	162/242 (66.9)	158/242 (65.3)
p compared with placebo	-	<0.001	<0.001

A statistically significant difference ($p < 0.001$) was found in favour of infliximab (5 mg/kg and 10 mg/kg) compared with placebo for clinical response at week 8 (primary endpoint).

Table 3: Pooled data (n, %) for the secondary endpoints (clinical response at week 30, and clinical remission and mucosal healing at weeks 8 and 30)

Secondary endpoints	placebo (n = 244)	Infliximab 5 mg/kg (n = 242)	Infliximab 10 mg/kg (n = 242)
% of patients who had a clinical response at week 30	27.9	49.6	55.4
% of patients in clinical remission at week 8	10.2	36.4	29.8
% of patients in clinical remission at week 30	13.1	29.8	36.4
% of patients with mucosal healing at week 8	32.4	61.2	60.3
% of patients with mucosal healing at week 30	27.5	48.3	52.9

Source: SPC and EPAR

A significant difference ($p < 0.001$) was found in favour of infliximab (5 mg/kg and 10 mg/kg) compared with placebo for all these secondary endpoints.

Quality of life:
Quality of life assessed by means of SF36 and IBDQ was significantly improved in the infliximab groups compared with the placebo group.

Number of hospital admissions:
The number of hospital admissions per 100 patients was lower with infliximab (both doses combined) than with placebo (9 compared with 18 per 100 patients, $p < 0.005$).

Corticosteroid withdrawal:
A significant difference was found between infliximab (both doses combined) and placebo in the proportion of patients able to stop taking corticosteroids while remaining in clinical remission at week 30 (22.3% compared with 7.2%, $p < 0.001$).

Follow-up data

The week-54 efficacy data for infliximab came from the ACT 1 study.

At week 54, a significant difference ($p < 0.001$) was found in favour of infliximab (both doses combined) compared with placebo for the following endpoints: clinical response, clinical remission and mucosal healing.

A statistically significant difference was found for corticoid withdrawal at week 54 compared with placebo only with the 5 mg/kg dosage of infliximab.

Table 4: Week-54 data (ACT 1)

Parameters	placebo (n = 121)	Infliximab 5 mg/kg (n = 121)	Infliximab 10 mg/kg (n = 122)
N (%) of patients who had a clinical response	24 (19.8)	55 (45.5)	54 (44.3)
N (%) of patients in clinical remission	20 (16.5)	42 (34.7)	42 (34.4)
N (%) of patients with mucosal healing	22 (18.2)	55 (45.5)	57 (46.7)
N (%) of patients able to stop taking corticosteroids while remaining in clinical remission	7/79 (8.9)	18/70 (25.7)	12/73 (16.4)

3.2. Adverse effects

Safety data for infliximab (REMICADE) in UC came from the two studies ACT 1 and ACT 2. Patients were followed-up for 30 to 54 weeks and received 7.3 infliximab infusions, i.e. a mean cumulative dose of 36.5–73 mg/kg.

Infliximab was relatively well tolerated and no new adverse event was identified. The safety profile of infliximab in UC appears to be similar to that observed in its other indications, particularly Crohn's disease. One case of tuberculosis was observed in a patient treated with infliximab 10 mg/kg.

Anti-infliximab antibodies were detected in approximately 5% of patients treated with infliximab.

3.3. Conclusion

The efficacy of infliximab (REMICADE) 5 mg/kg and 10 mg/kg in the treatment of UC was demonstrated in comparison with placebo in 728 patients responding inadequately to or intolerant of conventional treatments: corticosteroids and/or azathioprine and/or 6-mercaptopurine (ACT 1 and ACT 2 studies).

Infliximab was superior to placebo in the proportion of patients who had a clinical response at week 8 (primary endpoint): 66.9% on 5 mg/kg, 65.3% on 10 mg/kg, compared with 33.2% on placebo, $p < 0.001$.

A significant difference was found in favour of infliximab (5 mg/kg and 10 mg/kg) compared with placebo for all the secondary endpoints: clinical response at week 30, clinical remission, mucosal healing, corticosteroid withdrawal, hospital admissions and quality of life.

Very few data are available on the efficacy of infliximab in severe patients.

No new adverse event was identified. The safety profile of infliximab in UC was similar to that known in its other indications, particularly Crohn's disease.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Ulcerative colitis is an inflammatory bowel disease (IBD) which manifestations are severe, chronic, bloody diarrhoea and episodically progression. It causes a marked deterioration in quality of life and exposes patients to serious complications, such as acute colitis, dysplasia and bowel cancer.
REMICADE may be classed as a symptomatic treatment.

Public health benefit:
The public health burden represented by ulcerative colitis is moderate. The burden corresponding to the more restricted population defined by the indication (patients with a moderate to severe form of the disease who have tolerated conventional treatment poorly or responded poorly to it) is low.
The improved management of ulcerative colitis is a public health need that falls within the scope of identified priorities (GTNDO,[4] National Rare Diseases Plan).
The clinical data available do not provide any information on the effect of REMICADE on the need for surgery and/or on mortality. REMICADE is, however, expected to have an impact on morbidity and patients' quality of life. Since there is no guarantee that the clinical trial results can be transposed into practice, because of uncertainty regarding the stability of the therapeutic effect, doubts concerning the long-term safety of REMICADE and fact that the profile of the patients treated in real practice may differ from that of the trial patients, this impact is likely to be low.
Consequently, REMICADE is expected to provide some public health benefit in this indication. This benefit is low

The efficacy/ adverse effects ratio of REMICADE is high.
REMICADE is a medicinal product intended for second-line therapy.
There is no alternative medicinal product with an MA validating its use at this stage of the disease. The only alternative treatment is colectomy.
The actual benefit of this product is substantial.

4.2. Improvement in actual benefit

Based on the data currently available, the Transparency Committee considers that REMICADE provides an important (level II) improvement in actual benefit for ulcerative colitis patients who have not responded adequately to conventional treatment comprising corticosteroids and azathioprine or 6-mercaptopurine or in whom such treatment is poorly tolerated or contraindicated.
The Committee will reassess REMICADE when the results of the GETAID[5] study – the objective of which is to compare infliximab with ciclosporin in the treatment of UC attacks after failure of corticosteroids – are available.

[4] GTNDO (National Technical Group for Defining Public Health Objectives), 2003
[5] GETAID: Inflammatory Bowel Disease Treatment Study Group.

4.3. Therapeutic use[6]

The aim of treatment for UC is to achieve prolonged clinical remission without corticosteroids as well as endoscopic and histological healing of the lesions.
According to the wording of the indication, REMICADE (infliximab) should be reserved for the treatment of UC in patients who have not responded adequately to conventional treatment comprising corticosteroids and azathioprine or 6-mercaptopurine or in whom this treatment is poorly tolerated or contraindicated.
Alternatives to REMICADE in such patients are ciclosporin and surgery for severe corticosteroid-resistant forms, and methotrexate (MTX) and surgery for corticosteroid-dependent forms. However, ciclosporin and MTX do not have an MA for use in UC.
The efficacy of MTX has not been demonstrated in UC. GETAID is to conduct a study to compare MTX with placebo in corticosteroid-dependent forms of UC.
Ciclosporin is rapidly effective in corticosteroid-resistant patients, but its long-term safety is mediocre (nephrotoxicity and risk of induced tumour), so that it cannot be considered a disease-modifying drug. In practice it is only used for a short period (3 months) to induce remission while waiting for another disease-modifying drug introduced at the same time to take effect.
At present, no study has compared infliximab with ciclosporin in corticosteroid-resistant UC. A study with this objective is currently being conducted by GETAID.
The choice between REMICADE and colectomy will depend on the patient's age, duration of the UC, extent of the disease in the colon, desire for pregnancy, state of the rectum, bowel cancer risk factors, etc.
Total coloproctectomy with an ileoanal anastomosis and pouch is in fact a substantial surgical intervention requiring an operation in 2 or 3 stages. Mortality is low (less than or equal to 1%) and morbidity high (30–40%: occlusions, pelvic sepsis, etc.). In addition, it significantly reduces female fertility.

REMICADE is an alternative of interest in active forms of UC that are refractory to conventional treatment. However, its safety has only been assessed in the short term. The long-term profile of disease progression in patients with UC treated with REMICADE for long periods is unknown, particularly in terms of bowel cancer.

4.4. Target population

The prevalence of UC is estimated to be 1 in 1000, or approximately 60,000 patients in France.
The population most likely to benefit from REMICADE treatment is difficult to quantify. It consists of UC patients who have not responded adequately to conventional treatment comprising corticosteroids and azathioprine or 6-mercaptopurine, or in whom this treatment is poorly tolerated or contraindicated.
Given the results of an American cohort study in 2001:[7]

- roughly 30% of UC patients are treated with corticosteroids
- one year after corticosteroid therapy, 49% of patients have a prolonged response, 22% are corticosteroid-dependent and 29% have colectomy,

Based on expert opinion, it may be estimated that 15% of UC patients will be treated with REMICADE, i.e. a target population of less than 10,000 patients.

[6] Marteau et al. Recommandations pour la pratique clinique dans le traitement de la rectocolite ulcéro-hémorragique. Gastroenterol clin biol 2004;28: 955-960.
[7] Faubion et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001; 121: 255-60.

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 posology in the marketing authorisation.

The Transparency Committee would like to see a long-term follow-up study on patients with ulcerative colitis treated with REMICADE. The purpose of this study is to document the following parameters in a real treatment situation:

- The characteristics of the patients being treated: sex, age, history, clinical profile (frequency and severity of the attacks, extent of the lesions, disease activity level on the Mayo scale, existence of dysplasia, complications due to infection, etc.)

- The conditions for using this medicinal product, especially the conditions for initiating the treatment: previous medical or surgical treatments and associated treatments

- Maintenance of the benefit of this treatment in the medium and long terms, including in terms of quality of life and impact on the need for surgery (total coloproctectomy)

- The long-term safety of this medicinal product.

If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, cannot answer all the questions raised by the Transparency Committee, a specific study must be conducted.

The duration of the study must be justified by an independent scientific committee.