HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
19 February 2014

SIMPONI 50 mg, solution for injection in pre-filled pen
Pre-filled B/1 pen - 0.5 ml (CIP: 34009 397 307 45)

SIMPONI 50 mg, solution for injection in pre-filled syringe
Pre-filled B/1 syringe - 0.5 ml (CIP: 34009 397 309 74)

Applicant MSD FRANCE

INN	golimumab
ATC Code (2013):	L04AB06 (TNF inhibitors)
Reason for the review	**Extension of indication**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6 mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies."**

AB	**Substantial**
IAB	**"In view of:** - **the efficacy and safety data versus placebo,** - **the absence of direct comparative data versus other anti-ANF agents, particularly infliximab,** **the Transparency Committee considers that SIMPONI (golimumab) does not provide any improvement in actual benefit (IAB V, non-existent) in the treatment of moderately to severely active UC which is resistant to conventional therapies."**
Therapeutic use	**SIMPONI is a new alternative for the treatment of patients with UC requiring anti-TNF treatment.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	01/10/2009 (centralised): Marketing Authorisation in the rheumatology indications 19/09/2013: Indication extension for UC
Prescribing and dispensing conditions/special status	List I Medicine for initial annual hospital prescription Initial prescription and renewal restricted to specialists in rheumatology, internal medicines or gastroenterology and hepatology. Exception drug status

ATC Classification	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AB	Tumour necrosis factor alpha (TNF-α) inhibitors
	L04AB06	golimumab

02 BACKGROUND

SIMPONI (golimumab) is an anti-TNF agent included in the list of medicines refundable in retail pharmacies and reimbursed in hospitals since August 2012 in its rheumatology indications (rheumatoid arthritis, psoriatic rheumatism and ankylosing spondylitis).

In September 2013, it obtained an indication extension in gastroenterology in the treatment of ulcerative colitis (UC).

This evaluation aims to review the application for extension of the drug's reimbursement in this new indication.

Two other anti-TNF agents are currently reimbursed: REMICADE given as an IV infusion every 8 weeks* and HUMIRA given as a SC injection every 2 weeks.* Regarding SIMPONI, it is administered subcutaneously every 4 weeks.*

A new strength of golimumab (100 mg) is also available and is part of a separate opinion as a line extension. This dosage has been specifically developed by the company for the treatment of patients with UC considering the dosage described in the Marketing Authorisation for the induction phase and the maintenance phase of patients weighing 80 kg and more.

03 THERAPEUTIC INDICATIONS

Indication forming the subject of the application:

"SIMPONI is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies."
Previous indications not related to the application:

* frequency of maintenance treatment.

"Rheumatoid arthritis (RA)
SIMPONI, in combination with methotrexate (MTX), is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate;
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

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

Psoriatic arthritis (PsA)
SIMPONI, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti rheumatic drug (DMARD) therapy has been inadequate. SIMPONI has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Ankylosing spondylitis (AS)
SIMPONI is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy."

04 DOSAGE

"Ulcerative colitis
Patients with body weight less than 80 kg
SIMPONI is given as an initial dose of 200 mg, followed by 100 mg at week 2, then 50 mg every 4 weeks thereafter.

Patients with body weight greater than or equal to 80 kg
SIMPONI is given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks thereafter.
During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.
Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period."

To be reminded of the dosage in the rheumatological indications see SPC.

05 THERAPEUTIC NEED

The aim of UC treatment is to obtain prolonged clinical remission without corticosteroids and endoscopic and histological healing of the lesions.
According to the European consensus conference ECCO[1] and the chronic conditions guide[2] edited by HAS, the treatment of UC is progressive, defined as escalating and is based on different lines of treatment with a combination of topical or oral conventional treatments which are the 5 aminosalicylates, the corticosteroids and the immunosuppressants. After the failure of or intolerance to these conventional treatments, the anti-TNF agents represent an alternative drug treatment.

The anti-TNF agents currently refundable in this indication are REMICADE (infliximab, administered intravenously) and HUMIRA (adalimumab, administered subcutaneously). They must be restricted to the treatment of UC in patients who have an inadequate response to conventional therapy including corticosteroids and azathioprine or 6 mercaptopurine, or who are intolerant to or have medical contraindications for such therapies.

For these patients, the alternatives to these anti-TNF agents are ciclosporin (off-label and restricted to specialised centres) and surgery for the severe corticosteroid resistant and corticosteroid-dependent forms.

Ciclosporin is quickly effective in the corticosteroid-resistant patients, but its long-term safety is poor (nephrotoxicity, risk of induced tumour) and cannot be considered as a basic treatment. In practice, it is only used for a short period (3 months) to induce remission pending the efficacy of another background treatment introduced concomitantly.

The results of an open-label study published[3] in 2012 which compared infliximab with ciclosporin in 115 patients with severe acute colitis resistant to IV corticosteroids did not show any evidence of superiority of ciclosporin over infliximab. However, given the methodology of the study and the number of patients, these results do not allow for the prioritisation of these two drugs in the treatment of these severe forms. Indeed, according to the authors of the publication, in clinical practice the choice between the two treatments should be guided by the experience of the doctor or reference centre.

Surgery is necessary in around 25 to 45% of patients in the absence of any improvement in symptoms or occurrence of complications of the disease.
The choice of surgery will be dependent on age, the period since the UC was first diagnosed, the extension of the colon's lesions, the desire to get pregnant, the condition of the rectum, the risk factors for colon cancer. Indeed, total coloproctectomy with ileal pouch-anal anastomosis is a major surgical procedure requiring two or three surgeries. Mortality is low (less than or equal to 1%) but the morbidity is high (30-40%: occlusions, pelvic sepsis, etc.). In addition, it significantly reduces fertility in females.

[1] Dignass A, et al. Second European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Current management. J Crohns Colitis. 2012; 6: 991-1030.
[2] Guide ALD 24, rectocolite hémorragique évolutive, HAS, mai 2008 [chronic conditions guide 24, Progressive ulcerative colitis, HAS, May 2008]
[3] This study will be analysed by the Committee in an opinion which is separate from the REMICADE re-assessment.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators are the other anti-TNF agents indicated in the treatment of UC:

- administered subcutaneously: HUMIRA (adalimumab)
- administered intravenously: REMICADE (infliximab)

For a reminder of the indication wording and their levels of AB and IAB, please refer to Table 1 below.

06.2 Other health technologies

Surgery is necessary in around 25% to 45% of patients in the absence of any improvement in symptoms or case of any complications of the disease.

◗ Conclusion

The comparators listed are all clinically relevant.

Table 1. Reminder of the indication wording, the AB and IAB, and the comparators in UC

INN Proprietary Medicinal product	Company	Indication	Dosage	Date of TC opinion	AB	IAB (Wording)	Reimbursed Yes/No
Infliximab REMICADE 100 mg powder for concentrate for solution for infusion	MSD France	Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6 mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.	The dosage is 5 mg/kg given as an intravenous infusion at W0, W2 and W6, then every 8 weeks.	18/07/2007	**Substantial**	**II** (Based on the current state of available data, the Transparency Committee considers that REMICADE provides a substantial IAB level II for patients with UC who have had an inadequate response to conventional therapy including corticosteroids and azathioprine or 6-mercaptopurine, or who are intolerant to or have medical contraindications for such therapies.)	Yes
Adalimumab HUMIRA 40 mg solution for injection in a pre-filled syringe and pre filled pen	AbbVie		Induction: 160 mg at Week 0 and 80 mg at Week 2. Maintenance: 40 mg every other week. Some patients who experience decrease in their response to treatment may benefit from an increase in dosing frequency to 40 mg Humira every week.	03/10/2012		**V** (HUMIRA does not provide any IAB in the treatment of moderately to severely active UC for patients who have had an inadequate response to or been intolerant to conventional therapies: corticosteroids, azathioprine or 6 mercaptopurine).	

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

At the time of writing this document, the proprietary medicinal product SIMPONI was reimbursed in the indication extension for UC in seven countries in the EU:

Country	Status of UC reimbursement	Additional information on the reimbursement
AUSTRIA	No	-
BELGIUM	No	-
BULGARIA	No	-
CROATIA	No	-
CYPRUS	No	-
CZECH REPUBLIC	No	-
DENMARK	Yes at 100%	Hospital
ESTONIA	No	-
FINLAND	No	-
FRANCE	No	-
GERMANY	Yes at 100%	National
GREECE	No	-
HOLLAND	Yes at 100%	Hospital
HUNGARY	No	-
ICELAND	No	-
IRELAND	Yes at 100%	National
ITALY	No	-
LUXEMBOURG	No	-
MALTA	No	-
NORWAY	Yes at 100%	National
POLAND	No	-
PORTUGAL	Yes at 100%	Hospital
ROMANIA	No	-
SLOVAKIA	No	-
SLOVENIA	No	-
SPAIN	No	-
SWEDEN	Yes at 100%	National
SWITZERLAND	No	-
UNITED KINGDOM	No	-

08 ANALYSIS OF AVAILABLE DATA

The efficacy of golimumab (SIMPONI) subcutaneously administered as an induction and maintenance treatment for ulcerative colitis (UC) is based on two controlled studies versus placebo:

- "PURSUIT INDUCTION study C0524T17 via the subcutaneous route" in which efficacy in the induction treatment was evaluated and
- "PURSUIT MAINTENANCE study C0524T18 via the subcutaneous route" in which efficacy in the maintenance treatment was evaluated in patients selected as responders to golimumab.

These studies included patients with an moderately to severely active form (defined by the Mayo score[4]), resistant to conventional therapies (including 5-ASA, corticosteroids or immunomodulating agents 6-mercaptopurine or azathioprine), or patients who are intolerant to or have medical contraindications for such therapies.

The choice of placebo as a comparator in these studies may seem questionable.
Indeed, the recruitment of patients to the golimumab induction study started on 18 July 2007. On this date, infliximab had a Marketing Authorisation for UC (04 January 2007) the Marketing Authorisation for adalimumab is, more recent (04 April 2012, studies started in 2006).
Given the different administration routes - the intravenous (IV) route for infliximab and the subcutaneous (SC) route for golimumab - a double-placebo would have been necessary to compare these two treatments.

In addition to as the two studies versus placebo and to compensate for the absence of a direct comparison with existing alternatives, the company provided the results of a network meta-analysis for an indirect comparison of the effect of anti-TNF agents (adalimumab, infliximab and golimumab) for UC.

Finally, the company provided the results of a study which evaluated the efficacy of golimumab as an IV induction treatment (PURSUIT INDUCTION study C0524T16 via the IV route). These results will not be described as this form does not have a Marketing Authorisation.

[4] The Mayo score for UC activity takes the following into account:
- Stool frequency - 0 (normal) to 3 (1 = 1-2, 2 = 3-4, 3 = 5 or more)
- Rectal bleeding - 0 (absent) to 3 (evacuation of pure blood)
- Rectosigmoidoscopy - 0 (normal) to 3 (severe abnormalities)
- Overall assessment by the doctor - 0 (normal) to 3 (severe disease)

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

08.1 Efficacy

PURSUIT INDUCTION study C0524T17 via the SC route (performed between July 2007 and November 2010)[5]

This randomised, double-blind study comprised two phases:

- a dose-ranging study (phase IIb) which involved the first 169 patients included. Its aim was to identify the ideal dosing scheme for the golimumab treatment induction;
- a "dose confirmation" phase (phase III) which started from the inclusion of the 170th patient and involved 896 patients. Its aim was to ensure the efficacy and safety of the dosing schemes selected at the end of the 1st phase.

There was no interruption in the inclusion of patients between the two study phases.

Inclusion criteria:

- patients aged 18 and over with moderately to severely active UC (Mayo score between 6 and 12 points at baseline with an endoscopic Mayo sub-score ≥ 2), confirmed by a biopsy;
- patients for whom a treatment conducted adequately with 5-ASA, corticosteroids via the oral route or immunomodulating agents (6-MP or AZA) did not result in a sufficient therapeutic response or patients who showed intolerance to these treatments or corticosteroid dependency.

Patients who had already been treated with infliximab or other anti-TNF agents and those with an imminent risk of colectomy were not included.

Treatments:

During the 1st part of the study (dose-ranging), the first 169 patients included in the study were randomised to receive:

- placebo at W0 and W2 (n=42)
- golimumab 100 mg at W0 and golimumab 50 mg at W2 (n=42)
- golimumab 200 mg at W0 and golimumab 100 mg at W2 (n=42)
- golimumab 400 mg at W0 and 200 mg at W2 (n=43)

The patients were followed up for 6 weeks. During this period, one randomised patient was not treated.

The 2nd part of the study started in parallel with the end of the first part, from the inclusion of the 170th patient. The first patients of this 2nd part of the study (n=122) were randomised to one of the four groups of the first part of the study.

Then, on the basis of pharmacokinetic, efficacy (intermediate analysis) and safety data, two dosing schemes were selected (200 mg at W0 then 100 mg at W2 and 400 mg at W0 then 200 mg at W2); the new patients included (n=774) were therefore randomised to one of the following three groups:

- placebo at W0 and W2 (n=258)
- golimumab 200 mg at W0 and golimumab 100 mg at W2 (n=258)
- golimumab 400 mg at W0 and golimumab 200 mg at W2 (n=258)

All the patients that were treated (whenever they were included), i.e. 1064 patients, were eligible for inclusion in the PURSUIT MAINTENANCE study C0524T18.

Endpoints:

The primary efficacy endpoint was clinical response at Week 6 defined by:

- a reduction in the total Mayo score ≥ 30 % and ≥ 3 points compared with the baseline score
- combined with a reduction in the rectal bleeding sub-score ≥ 1 or a sub-score of 0 or 1 compared with the inclusion score.

[5] Sandborn WJ, Feagan BG, Marano C et al. Subcutaneous Golimumab Induces Clinical Response and Remission in Patients with Moderate-To-Severe Ulcerative Colitis. Gastroenterology 2013; 146: 85-95

Statistical analyses:
The main efficacy analysis was performed as ITT on patients randomised to the second part of the study (phase III, dose confirmation) after the selection of doses (based on the interim analysis of data from the first part of the study) excluding three patients randomised in a centre[6] which had mis-filled patient informed consent forms and the Mayo scores.

Results:

- Demographic and clinical patient characteristics

The characteristics of 774 patients randomised to the 2nd part of the study after selection of the doses were as follows:

- median age 38 years, median weight 71 kg
- male sex at 54.8%
- median duration of UC of 4.3 years
- median Mayo score of 8
- 92.1% of patients received concomitant treatments for their UC (corticosteroids, budesonide, aminosalicylates, immunomodulating agents),
- 100% had already been treated for their UC (99.5% had used aminosalicylates, 91.7% corticosteroids (apart from budesonide), 55.4% immunomodulating agents and 33.3% antibiotics)
- 100% had had an inadequate response or intolerance to at least one conventional therapy (68.9% had had an inadequate response or were intolerant to corticosteroids or were corticosteroid-dependent; 49.6% had had an inadequate response or were intolerant to 6-MP/AZA; 95.7% had had an inadequate response or were intolerant to 5-ASA) and
- 100% were biotherapy-naïve patients.

- Treatment drop-outs:

Of the 774 randomised patients, 18 patients (2.3%) discontinued treatment before 6 weeks: 6 (2.3%) patients in the placebo group and 12 (2.3%) patients in the golimumab group.
The main reasons for discontinuing treatment were the withdrawal of consent (0.6%), lost to follow-up (0.1%), other reasons including: worsening of the UC, adverse effect, non-compliant patient, insufficient efficacy and investigator decision (1.6%).

- Results of the primary endpoint – clinical response

The main analysis of the efficacy results focussed on 771 patients (774 randomised patients minus 3 patients).
The proportion of patients who obtained clinical response at W6 was statistically greater:

- in the golimumab 400/200 mg (55%) group than in the placebo group (29.7%), $p<0.0001$, i.e. an absolute benefit of 25.3%.
- in the golimumab 200/100 mg (51.8%) group than in the placebo group (29.7%), $p<0.0001$, i.e. an absolute benefit of 22.1%.

Sensitivity analyses were conducted and confirmed the robustness of the result of the analysis in terms of primary endpoint.

The superiority of golimumab over the placebo was shown for all of the secondary endpoints, particularly:

- clinical remission at Week 6 (difference of 11.5% in favour of golimumab 400/200 mg and 12.4% in favour of golimumab 200/100 mg over the placebo, $p<0.0001$),

[6] This is a centre located in Poland. Given the doubts of the auditors on compliance with best practice and rules in terms of managing patient files, the data from this centre were not included in the efficacy analyses. Sensitivity analises were performed (no statistical impact was shown due to the non-consideration of data from this centre).

- proportion of patients with mucosal healing at Week 6 (difference of 16.8% in favour of golimumab 400/200 mg, p<0.0001 and 14.7% in favour of golimumab 200/100 mg over the placebo, p=0.0005),
- quality of life (IBDQ score), difference of 12.4% in favour of golimumab 400/200 mg and 12.8% in favour of golimumab 200/100 mg over the placebo, p<0.0001.

PURSUIT MAINTENANCE study C0524T18 (performed between September 2007 and October 2011)[7,8]
This phase III, controlled versus placebo, randomised, double blind study aimed to evaluate the efficacy and safety of golimumab for the maintenance treatment for moderate to severe UC.
It included patients identified as responders to golimumab at W6 in the induction studies (PURSUIT Induction SC: C0524T17 or PURSUIT Induction IV: C0524T16). Patients who are responders and non-responders to the placebo and patients who are non-responders to golimumab could also be included in the maintenance study only for evaluation of the safety; they were not considered in the efficacy analyses.

After inclusion, the patients were randomised to three groups to be treated every 4 weeks until Week 52 (placebo, golimumab 50 mg or 100 mg). They were authorised to continue their previous treatment with 5-ASA and immunomodulating agents at a stable dose.
If the disease activity was not improved at Week 16, the patients had to discontinue their treatment. Patients with loss of response over 52 weeks could benefit from a dose adjustment:
- those in the placebo group received golimumab 100 mg every 4 weeks
- those in the golimumab 50 mg group re-randomised to golimumab 50 mg or 100 mg every 4 weeks
- those in the golimumab 100 mg group were, before amendment no. 3 of the protocol, re-randomised to golimumab 100 mg or golimumab 200 mg every 4 weeks. After amendment no. 3 of the protocol, the patients continued golimumab 100 mg every 4 weeks. Those who were re-randomised to the golimumab 200 mg group before amendment no. 3 received again a dose regimen of golimumab 100 mg every 4 weeks.

Endpoints:
The primary efficacy endpoint was the maintenance of the clinical response until Week 54. Clinical response was defined by:
- a reduction in the total Mayo score ≥ 30 % and ≥ 3 points
- with a reduction in the rectal bleeding sub-score ≥ 1 or a rectal bleeding sub-score of 0 or 1 compared with the inclusion Mayo score in one of the two induction studies.

Clinical response was evaluated every 4 weeks by a partial Mayo score to ensure the maintenance of clinical response over time; at Weeks 0, 30 and 54 by a full Mayo score.

In patients with loss of response, an endoscopy (total Mayo score) was performed for confirmation. If loss of response was confirmed, the patient was considered as a non-responder for the rest of the study.

Results:
Overall, 464 patients were randomised including 308 patients in the golimumab groups (154 in the 50 mg group and 154 in the 100 mg group) and 156 patients in the placebo group.

- Demographic and clinical patient characteristics

7 Sandborn et al. Subcutaneous Golimumab Maintains Clinical Response in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology 2014; 146: 96-109.
8 Sandborn et al. Subcutaneous Golimumab Induces Clinical Response and Remission in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology 2014; 146: 85-95.

These patients had the following characteristics and the distribution was comparable between the treatment groups:
- majority are male (51.9%)
- median age was 39 years
- median weight was 71.95 kg
- median duration of UC of 4.55 years
- mean Mayo score of 8.3
- 93.8% of patients had received concomitant treatments for their UC (51.5% with corticosteroids (apart from budesonide), 31.7% immunomodulating agents and 80.2% aminosalicylates).
- all the patients had had an inadequate response or were intolerant to at least one conventional therapy and/or had a proven corticosteroid dependency (75.4% had had an inadequate response or were intolerant to corticosteroids or were corticosteroid-dependent; 50.4% had had an inadequate response or were intolerant to 6-MP/AZA; 94.5% had had an inadequate response or were intolerant to 5-ASA)
- all the patients had been treated for their UC (99.6% with 5-ASA, 93.3% with corticosteroids apart from budesonide, 58.6% with immunomodulating agents and 41.2% with antibiotics).

- Premature treatment drop-outs:

Of 464 randomised patients, 131 patients (28.2%) discontinued the treatment prematurely (27.6% in the placebo group and 28.6% in the golimumab groups).

The reasons for discontinuation were:
In the placebo group:
- unsatisfactory efficacy: 19 patients (12.2%),
- adverse events: 17 patients (10.9%),
- "other" reasons: Six patients (3.8%) including four who withdrew their consent, one who underwent bariatric (weight loss) surgery, and for one, decision by the principal investigator.

In all the golimumab groups
- unsatisfactory efficacy: 39 patients (12.7%),
- adverse events: 24 patients (7.8%),
- "other" reasons: 22 patients (7.1%, 15 of whom withdrew their consent and 1 patient for each of the following reasons: the decision of the sponsor, closed site, planned pregnancy, non-compliance to treatment, patient's decision, family reasons, principal investigator's decision.

- Results of the primary endpoint

The proportion of patients with clinical response maintained until Week 54 was:
- 50.6% in the golimumab 100 mg group ($p < 0.001$ versus placebo, absolute difference of 19.2%)
- 47.1% in the golimumab 50 mg group ($p = 0.010$ versus placebo, absolute difference of 15.7%)
- 31.4% in the placebo group.

Overall, 172 patients (37% of the patients) had a dose adjustment of the treatment during the study due to a loss of efficacy, the proportions were 49% in the placebo group, 28% in the golimumab 100 mg group and 34% in the 50 mg group. Among the patients meeting the criteria of "loss of response", an endoscopy was performed to confirm the loss of response. If loss of response was confirmed, the patient was considered as a non-responder for the rest of the study.

A statistically significant difference in favour of golimumab over the placebo was also shown in terms of the principal secondary endpoints, including clinical remission and mucosal healing.

Indirect comparison:
The network meta-analysis proposed by the company compared golimumab with adalimumab and infliximab in terms of efficacy and safety in patients with moderate to severe UC, not previously treated with anti-TNF agents.

Four efficacy endpoints were considered (clinical remission, clinical response, level of mucosal healing, IBDQ quality of life) and only the treatment drop-outs were considered for evaluating the safety.
Six clinical studies which evaluated the drug versus placebo were used for comparison.

The results of this meta-analysis suggest the absence of a statistically significant difference between golimumab (whatever the dosage) and infliximab 5 mg in terms of the evaluated endpoints, apart from the level of mucosal healing, greater than induction treatment with infliximab.
Golimumab and infliximab seem more effective than adalimumab in terms of induction and maintenance of the remission and clinical response. However, no statistically significant difference was shown between the three treatments in terms of the mucosal healing levels, the IBDQ score and the adverse effects causing the treatment discontinuation.

Overall, these indirect comparisons remain purely exploratory insofar as the studies used to achieve them had not been designed to compare active treatments with each other but to compare them with the placebo. It is indeed impossible to guarantee in this context that the strength of these indirect comparisons would be enough to detect any difference between the two treatments and this is particularly true for the comparisons in terms of safety which were not the main aim of the studies versus placebo included in the meta analysis.

In conclusion, the results of this meta-analysis do not allow any conclusions to be drawn regarding the comparable efficacy of golimumab versus infliximab and therefore no prioritization of these medicines in the treatment of UC can be achieved.

08.2 Safety/adverse effects

- Data from clinical studies

Induction phase:
During the course of the 6-week follow-up, at least one adverse event (AE) was reported in 38.2% of patients in the placebo groups, 37.5% in the golimumab 200/100 mg group and 38.9% in the golimumab 400/200 mg group.
The AEs most commonly reported by organ system were "infections/infestations"[9] (12.0% in the placebo group and 10.9% in the golimumab groups, 2 dosages combined), as well as gastrointestinal disorders (10.5% in the placebo group and 12.4% in the golimumab groups).
One patient from the golimumab 400 mg/200 mg group died following an ischiorectal abscess 10 weeks after the last injection of golimumab.

Maintenance phase:
During the course of the maintenance phase, at least one adverse event (AE) was reported in 66% of patients in the placebo group, 72.7% in the golimumab 50 mg group and 73.4% in the golimumab 100 mg group. The incidence of AEs based on 100 patient-years of follow-up was 211.22 in the placebo group, 187.16 in the golimumab 50 mg group and 172.68 in the golimumab 100 mg group.

The most commonly reported AEs were:
- gastrointestinal disorders (including ulcerative colitis) 32.1% in the placebo group, 32.5% in the golimumab 50 mg group and 37.0% in the 100 mg group and
- infections and infestations (25.6% in the placebo group, 37% in the golimumab 50 mg group and 39.6% in the golimumab 100 mg group).

One death occurred in the golimumab 100 mg group. This patient had heart failure and a history of thrombosis. Five cases of cancer were reported during the clinical studies in patients treated with golimumab, i.e. an incidence of 0.46 per 100 patient-years. Among these five cases, three were diagnosed before golimumab was administered.

[9] Terminology of the MedRA classification for the system organ classes.

Overall, no new sign of safety was identified compared with safety information available on the use of golimumab in the rheumatological indications.

- PSUR data

Not relevant as the PSURs provided only cover the rhemumatological indications. For information, since the marketing of SIMPONI (4 years), the global exposure has been estimated to be 147,900 patients worldwide and no pharmacovigilance signal has been observed.

08.3 Summary & discussion

Golimumab (SIMPONI) as subcutaneous injection was evaluated in the induction and maintenance treatment of UC in two controlled versus placebo, randomised, double-blind studies.
The patients included had a moderate to severe form of activity (Mayo score from 6 to 12 and an endoscopic sub-score ≥ 2 points) despite treatment with corticosteroids, 5-ASA and/or immunomodulating agents, and had never been treated with biotherapies.

The first study evaluated the effect of golimumab as an induction treatment. It had a complex study design, comprising a dose-ranging phase (phase II; n=169 patients) during which three dosing schemes for golimumab (100 mg at W0 and 50 mg at W2 or 200 mg at W0 and 100 mg at W2 or 400 mg at W0 and 200 mg at W2) were compared with the placebo. In parallel to this dose-ranging phase (starting from the inclusion of the 170th patient), a confirmation phase for the doses selected was conducted (phase III). During this phase, 774 patients were randomised to receive either 400 mg of golimumab SC at Week 0 and 200 mg at Week 2, 200 mg of golimumab SC at Week 0 and 100 mg at Week 2 or a placebo SC at Weeks 0 and 2.
The main efficacy analysis focussed on 771 patients randomised to the 2nd part of the study. The superiority of golimumab over the placebo was demonstrated in terms of the proportion of patients who obtained clinical response at W6 (primary endpoint): 51.8% in the golimumab 200/100 mg group (only dosage recorded in the Marketing Authorisation) versus 29.7% in the placebo group, p<0.0001, i.e. an absolute benefit of 22.1%. The proportion of responders was 55% in the golimumab 400/200 mg group and 29.7% in the placebo group (p<0.0001, i.e. an absolute benefit of 25.3%).

The second study evaluated golimumab as a maintenance treatment. It included 464 patients who obtained clinical response after the induction treatment. These patients were randomised to receive golimumab 50 mg, 100 mg or a placebo, administered subcutaneously every 4 weeks. The proportion of patients with clinical response maintained until Week 54 was 50.6% in the golimumab 100 mg group (p < 0.001 versus placebo, an absolute difference of 19.2%), 47.1% in the golimumab 50 mg group[10] (p = 0.010 versus placebo, an absolute difference of 15.7%) and 31.4% in the placebo group.

We may question:

- the choice of placebo as a comparator in these studies. The recruitment of patients to the induction study started on 18 July 2007. On this date, REMICADE had a Marketing Authorisation for UC (04 January 2007). The Marketing Authorisation for HUMIRA is more recent (04 April 2012, studies started in 2006).
- the choice of clinical response as primary endpoint insofar as, in line with current European recommendations relating to the evaluation of treatments for UC, it is clinical remission, which should have been studied as primary endpoint (as was the case in the study evaluating adalimumab).

[10] Maintenance dosage recorded in the Marketing Authorisation.

The company provided a meta-analysis for an indirect comparison of golimumab with infliximab and adalimumab. However, this indirect comparison is purely exploratory and does not allow any conclusions about efficacy and/or safety of golimumab compared to infliximab owing to lack of guarantee of sufficient power, or consequently for the treatments prioritization.

No new sign of safety was identified for UC and the adverse events most commonly associated with golimumab were infections and gastrointestinal disorders.
However, long-term safety data were limited. Also, the EMA wanted implementation of two follow-up registries for the treated patients in this new indication.

08.4 Planned studies

The RMP for SIMPONI within the framework of the indication extension for UC provides for the establishment of two follow-up registries for the treated patients (one in Europe and one in Spain).

09 THERAPEUTIC USE

SIMPONI (golimumab) as subcutaneous injection once a month is a new alternative to HUMIRA (adalimumab) as subcutaneous injection every 2 weeks and to REMICADE as IV infusion every 8 weeks when anti-TNF treatment is considered, that is for the moderately to severely active forms resistant to conventional therapy including corticosteroids and immunosuppressants. Without a direct comparison with infliximab and adalimumab, it is not possible to define the position of golumumab in the UC management.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 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: acute colitis, dysplasia and colon cancer.

◗ SIMPONI is intended as a symptomatic treatment.

◗ Its efficacy and safety were only evaluated against placebo. The results of the indirect comparison network meta-analysis versus the other anti-TNF agents which can only be considered exploratory do not lead to any conclusions about efficacy and/or safety compared with that of other anti-TNF agents.
◗ Its efficacy/adverse effects ratio is high.

◗ There are treatment alternatives (two drug alternatives at this stage of the disease are infliximab and adalimumab).

◗ Given its Marketing Authorisation, SIMPONI is a second-line therapy in the event of conventional treatment failure (inadequate response, contraindication or intolerance) including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA). Without a direct comparison with other anti-TNF agents, the position of SIMPONI compared with these medicines is difficult to define.

◗ Public health benefit
Taking into account:

- the low burden represented by the moderate to severe form, where the patients are intolerant or do not respond to conventional treatment of UC, owing to the low numbers of patients affected despite the severity of the disease;
- the identified public health need identified for IBD (inflammatory bowel disease);
- available non-comparative efficacy data versus active treatment and currently limited safety data;
- the impact - difficult to evaluate in the present state of the documentation - of the provision of one subcutaneous injection per month on the organisation of the healthcare system;

the additional public health benefit expected for the proprietary medicinal product SIMPONI over existing alternatives in this indication cannot be evaluated.

Given these elements, the Transparency Committee considers that the actual benefit of SIMPONI is <u>substantial</u> in the "treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies"

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the indication "Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-

mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies" and at the dosages in the Marketing Authorisation.

◗ Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

In view of:
- the efficacy and safety data versus placebo,
- the absence of direct comparative data versus other anti TNF agents, particularly infliximab,

the Transparency Committee considers that SIMPONI (golimumab) does not provide any improvement in actual benefit (IAB V, non-existent) in the treatment of moderately to severely active UC which is resistant to conventional therapies.

010.3 Target population

According to its Marketing Authorisation, the population likely to be treated with SIMPONI is adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy including corticosteroids and azathioprine or 6-mercaptopurine, or who are intolerant to or have medical contraindications for such therapies.

The prevalence and incidence of UC in adults can be approximated from the following sources:

- Although UC is not a rare disease, data are provided by the ORPHANET database.[11] According to this source, in Western Europe and the United States, UC has an estimated prevalence of 1 in 1500 people (40,000 patients with UC in France according to their estimation). Applying this figure to INSEE [National Institute of Statistics and Economic Studies] data relating to the French population on 1st January 2014 (65,821,000), the population with UC in France could be estimated at 44,000 people.

- According to data published in 2013[12] from the EPIMAD registry covering 9.3% of the French population, the incidence rate of UC is 4.4 per 100,000 inhabitants, which, extrapolated to the French population on 1st January 2014 (65,821,000), would represent less than 3000 new cases a year. This source provides no information on the prevalence.

- According to data from national health insurance, on 31 December 2011, 56,204 patients (average age 50 years) had a chronic condition because of UC (ulcerative colitis). Considering that the CNAMTS [National Salaried Worker's Health Insurance Fund] data cover 88% of the French population, the number of people with UC in France in 2013 could be estimated as 63,900.
  According to the experts, this figure can be used for calculating the target population.

No French epidemiological data are available to estimate the proportion of moderate to severe forms which failed to respond to corticosteroids and/or immunosuppressants. According to expert opinion, 15%[13] of cases of UC come under anti-TNF treatment.

On this basis, the population likely to benefit from SIMPONI treatment (moderately to severely active UC which failed to respond to corticosteroids and immunosuppressants) could be estimated as being between 6600 and 9600 patients, i.e. less than 10,000 patients.

11 Orphanet updated in 2011, site consulted on 24 January 2014.
12 C. Gower-Rousseau, F. Vasseur, M.Fumery et al. Epidemiology of inflammatory bowel diseases: New insights from a French population-based registry (EPIMAD). Digestive and Liver Disease 45 (2013) 89-94.
13 Transparency Committee opinion for REMICADE and HUMIRA in the case of UC

In conclusion
The target population of golimumab in moderately to severely active UC which failed to respond to corticosteroids and immunosuppressants can be estimated to be less than 10,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.
The Committee notes that a new dosage of golimumab 100 mg was specifically developed by the company for the treatment of patients with UC on account of the dosage described in the Marketing Authorisation for the induction phase and the maintenance phase of patients weighing 80 kg and more. This line extension is part of a separate opinion.

◗ Specific requests inherent to reimbursement
The Committee issues a reminder that SIMPONI has exception drug status.

◗ Request for data
The Committee would like to have the data from the registries requested as part of the RMP for this proprietary medicinal product.