HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

05 May 2010

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

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

Applicant: ABBOTT FRANCE

adalimumab

ATC code: L04AB04

List I

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

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

Date of latest revision of Marketing Authorisation: 25 August 2008 (extension for the indication idiopathic juvenile rheumatoid arthritis)

Exception drug status.

Reason for the request: renewal of inclusion on the list of medicines reimbursed by National Health Insurance (+ request for reassessment of the wording of the improvement in actual benefit (IAB) in psoriasis, following the submission of new data).

Medical, Economic, and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
adalimumab

1.2. Indications
Rheumatoid arthritis
HUMIRA in combination with methotrexate is indicated for:
- treatment of moderate to severe active rheumatoid arthritis in adults responding inadequately to disease-modifying treatments, including methotrexate.
- treatment of severe, active, progressive rheumatoid arthritis in adults not previously treated with methotrexate.

HUMIRA may be given as monotherapy in cases of methotrexate intolerance or where continued treatment with methotrexate is inappropriate.

It has been shown that HUMIRA, when administered in combination with methotrexate, slows the progression of radiographically measured structural joint damage and improves functional capabilities.

Polyarticular juvenile idiopathic arthritis
HUMIRA®, combined with methotrexate, is indicated for the treatment of progressive polyarticular juvenile idiopathic arthritis in adolescents aged 13 to 17 years who have not had a satisfactory response to one or more disease-modifying treatments.
HUMIRA® may be given as monotherapy in cases of methotrexate intolerance or where continued treatment with methotrexate is inappropriate.

Psoriatic arthritis
HUMIRA is indicated for the treatment of active, progressive psoriatic arthritis in adults previously responding inadequately to disease-modifying treatment. It has been shown that HUMIRA slows the progression of radiographically measured structural damage of peripheral joints in patients with symmetrical polyarticular forms of the disease and improves functional capabilities.

Ankylosing spondylitis
HUMIRA is indicated for the treatment of severe, active ankylosing spondylitis in adults responding inadequately to conventional treatment.

Crohn's disease
HUMIRA is indicated for the treatment of severe, active Crohn's disease in patients who have not responded to treatment with corticosteroids and/or immunosuppressants, even though it was suitable and administered properly, or in those for whom the treatment is contraindicated or who find difficulty tolerating it.
In the case of induction treatment, HUMIRA must be administered in combination with corticosteroids. HUMIRA may be given as monotherapy in cases of corticosteroid intolerance or where continued treatment with corticosteroids is inappropriate.

Psoriasis
HUMIRA is indicated in the treatment of moderate to severe plaque psoriasis in adults who have not responded to other systemic treatments, including ciclosporin, methotrexate or PUVA treatment, or in whom these treatments are contraindicated or poorly tolerated.

1.3. Dosage

Treatment with HUMIRA must be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or psoriasis. Patients being treated with HUMIRA will be given a special alert card.
After proper training in the injection technique, patients may self-inject with HUMIRA if their physician considers it feasible, subject to appropriate medical monitoring.
During treatment with HUMIRA, other concomitant treatments (such as corticosteroids and/or immunomodulators) should be optimised.

Adults

Rheumatoid arthritis
The recommended dosage of HUMIRA® in adults with rheumatoid arthritis is a single 40 mg subcutaneous injection of adalimumab every two weeks.
Methotrexate should continue to be administered during HUMIRA® treatment.
Use of glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs and analgesics may be continued during treatment with HUMIRA®. In monotherapy, some patients in whom a decrease in response to HUMIRA® has been observed may benefit from having the dose increased to 40 mg adalimumab every week.

Psoriatic rheumatism and ankylosing spondylitis
The recommended dosage of HUMIRA® in patients with psoriatic arthritis or ankylosing spondylitis is a single 40 mg subcutaneous injection of adalimumab every two weeks.
For all the above indications, the available data support the assumption that a clinical response is usually obtained within 12 weeks of treatment. Continued therapy must be carefully reconsidered in patients who have not responded to the treatment within these time limits.

Crohn's disease
In adult patients with severe Crohn's disease, the recommended dosage regimen for induction is 80 mg HUMIRA® in week 0, followed by 40 mg in week 2. If it is necessary to achieve a more rapid response to treatment, it is possible to use a regimen of 160 mg in week 0 (the dose can be administered as 4 injections per day or as 2 injections per day on two consecutive days), 80 mg in week 2, in the knowledge that the risk of adverse events will therefore be higher during this induction phase.
After the induction treatment, the recommended dosage is a dose of 40 mg administered by subcutaneous injection every two weeks. If a patient has discontinued treatment with HUMIRA® and the signs and symptoms of the disease reappear, HUMIRA may be administered again. Experience of readministering treatment more than 8 weeks after the previous dose is limited.
During maintenance treatment, corticosteroids can be gradually reduced in keeping with clinical practice guidelines.
Some patients, in whom a reduction in the response to the treatment has been observed, may benefit from having the HUMIRA dosage increased to 40 mg every week.
Some patients who have not responded to treatment by week 4 can continue the maintenance treatment until week 12. Continuation of treatment should be carefully reconsidered if a patient does not respond within this period.

Psoriasis
The recommended dose of HUMIRA® in adults 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.
Continuation of treatment after 16 weeks must be carefully reconsidered in patients who have not responded within this period.

Elderly patients
No dose adjustment is necessary.

Children and adolescents (aged 13 to 17 years):

Polyarticular juvenile idiopathic arthritis
The recommended dosage in patients aged 13 years or older with polyarticular juvenile idiopathic arthritis is a single 40 mg subcutaneous injection of adalimumab every other week. The available data permit the assumption that a clinical response is usually achieved within 12 weeks of treatment. Continuation of treatment must be carefully reconsidered in patients who have not responded to the treatment within this period.

Patients with kidney or liver failure
The use of HUMIRA® has not been studied in these patient populations. No dosage can be recommended.

See the SPC**.**

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

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

2.2. Medicines in the same therapeutic category

Other anti-TNF alpha agents entered into the list of reimbursable medicines; their indications are not identical (see table below).

Anti-TNF alpha indications	HUMIRA	REMICADE	ENBREL	CIMZIA
RA	Combined with MTX: - RA with failure of classic DMT including MTX - Naive for MTX Monotherapy possible in cases of intolerance or when continuation of MTX treatment is inappropriate Structural effect demonstrated in combination with MTX	Combined with MTX: - RA with failure of classic DMT including MTX - Naive for MTX and other classic DMT No monotherapy Structural effect demonstrated	Combined with MTX: RA with failure of classic DMT including MTX Monotherapy possible in cases of intolerance or when continuation of MTX treatment is inappropriate Naive for MTX Structural effect of ENBREL demonstrated *only in combination with MTX*	Combined with MTX: RA with failure of classic DMT including MTX Monotherapy possible in cases of intolerance or when continuation of MTX treatment is inappropriate Structural effect demonstrated in combination with MTX
JIA	In combination with MTX, adolescents aged 13 to 17 years in cases of insufficient response to one or more disease-modifying treatments Monotherapy possible in cases of intolerance or when continuation of MTX treatment is inappropriate	*No MA*	Children and adolescents aged 4 to 17 years in cases of an inadequate response or tolerance to MTX	*No MA*
RA in adults	Previous failure of disease-modifying treatment Structural effect demonstrated	Failure of a classic DMT in combination with MTX or alone in the case of CI or intolerance to MTX Structural effect demonstrated	Previous failure of disease-modifying treatment Structural effect demonstrated	*No MA*
AS in adults	Failure of conventional treatment	Failure of conventional treatment	Failure of conventional treatment	*No MA*

Anti-TNF alpha indications	HUMIRA	REMICADE	ENBREL	CIMZIA
CD in adults	Severe active CD in the case of failure, CI or intolerance to corticosteroids and/or immunosuppressants	Severe active CD in the case of failure, CI or intolerance to corticosteroids and/or immunosuppressants Active CD with fistula in cases of failure of conventional treatment	*No MA*	*No MA*
CD in children	*No MA*	Severe active CD in children aged 6-17 years in cases of failure, CI or intolerance to conventional treatments including corticosteroids, immunomodulators and dietary treatments	*No MA*	*No MA*
HRC in adults	*No MA*	Moderate to severe active HRC in cases of inadequate response, CI or intolerance to conventional treatment including corticosteroids, 6-MP or AZA	*No MA*	*No MA*
Plaque Pso in adults	Failure, CI or intolerance to systemic treatment, including ciclosporin, MTX or PUVA therapy	Failure, CI or intolerance to systemic treatment, including ciclosporin, MTX or PUVA therapy	Failure, CI or intolerance to systemic treatment, including ciclosporin, MTX or PUVA therapy	*No MA*
Plaque Pso in children	*No MA*	*No MA*	In cases of inadequate control or intolerance to systemic treatments or phototherapy	*No MA*

RA: rheumatoid arthritis, JIA: juvenile idiopathic arthritis, PR: psoriatic rheumatism, AS: ankylosing spondylitis, MTX: methotrexate, classic DMT: classic disease-modifying treatments, CI: contraindications, CD: Crohn's disease, HRC: haemorrhagic rectocolitis, Pso: psoriasis.

2.3. Medicines with a similar therapeutic aim

Other disease-modifying medicines with the same indications.

3. REMINDER OF THE TRANSPARENCY COMMITTEE'S OPINION

Indication / dates of TC reports	AB:	Reminder of wording of IAB given by the TC
Rheumatoid arthritis 16 June 2004, 15 Sept 2004, 2 Nov 2005	Substantial	When combined with MTX, HUMIRA shares the level **II IAB of ENBREL** with respect to clinical efficacy and slowing the progression of structural damage to the joints. In monotherapy, HUMIRA was not shown to be superior to MTX alone in patients who are naïve for MTX.
Psoriatic arthritis (2 Nov 2005)	Substantial	HUMIRA shares the substantial improvement in actual benefit (IAB, **level II**) of ENBREL in patients with active and progressive psoriatic rheumatism in whom the response to previous disease-modifying treatment has been inadequate
Ankylosing spondylitis (18 Oct 2006)	Substantial	The Transparency Committee considers that HUMIRA provides **the same improvement in actual benefit (IABII) as the other TNF antagonists** (etanercept and infliximab) in the treatment of severe, active ankylosing spondylitis in adults responding inadequately to conventional treatment.
Crohn's disease in adults (24 Oct 2007)	Substantial	HUMIRA (adalimumab) does not provide any improvement in actual benefit (IAB) compared to REMICADE (infliximab) (**level V**) in the treatment of severe and active Crohn's disease in patients who have not responded to appropriate treatment administered properly using corticosteroids and immunosuppressants or in those for whom this treatment is contraindicated or poorly tolerated.
Psoriasis (28 May 2008)	Substantial in the case of chronic severe psoriasis with failure of at least 2 systemic treatments out of photo-therapy, MTX and ciclosporin. Insufficient for other patients	In adult patients with chronic severe plaque psoriasis with failure of at least 2 systemic treatments out of phototherapy, MTX and ciclosporin, for whom alternatives are very restricted or non-existent, HUMIRA does not provide an IAB (**level V**) with respect to efficacy in comparison to other anti-TNF alpha agents (REMICADE and ENBREL)
Polyarticular juvenile idiopathic arthritis (24 June 2009)	Substantial	In the treatment of progressive polyarticular juvenile idiopathic arthritis in adolescents aged 13 to 17 years in cases of an inadequate response to one or more disease-modifying treatments, HUMIRA does not provide an IAB (**level V**) in the therapeutic strategy

4. UPDATE OF CLINICAL DATA

4.1. Efficacy

4.1.1. Rheumatoid arthritis

For the indication RA with failure of classic disease-modifying treatments including MTX, the company has supplied results from the following studies:

- open-label 4-year extension of the 24-week DE009-ARMADA study, which had been a double-blind comparison of adalimumab + MTX versus MTX[1]
- open-label 5-year extension of the 52-week (unpublished) DE019 study, which had been a double-blind comparison of adalimumab + MTX versus MTX[2]
- non-comparative REACT[3] study in 6,610 patients with active RA, in whom conventional disease-modifying treatment had failed or who had previously been treated with anti-TNF (13.6% of the total).

For the indication RA not treated previously with MTX, the company has not supplied any new clinical data. As a reminder, in this population the ACR 20 response rate at 52 weeks was greater with MTX than with HUMIRA in the DE013-PREMIER study.

The results of 3 meta-analyses and of a literature review evaluating the efficacy of anti-TNF alpha in RA have been supplied. The results of three meta-analyses by Alonso-Ruiz[4] (13 studies, of which 5 evaluated adalimumab), Lee[5] (3 studies, of which 1 evaluated adalimumab) and Venkateshan[6] (26 studies, of which 6 evaluated adalimumab) confirmed the efficacy of anti-TNF alpha, including adalimumab, in the treatment of RA.
A systematic review of the literature performed by NICE and published in 2006 (Chen et al[7]) also showed that anti-TNF alpha agents (adalimumab, etanercept and infliximab) were effective in comparison to placebo in the treatment of RA with failure of classic DMT. The results also showed that monotherapy with adalimumab was less effective than MTX in patients who were naive for MTX.

The company has supplied a set of observational data from various European registers concerning data on the use of anti-TNFα including HUMIRA :

1 Weinbaltt ME, Keystone EC, Furst DE, et al. Long term efficacy and tolerance of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis 2006;65:753-759.
2 Internal report of the company
3 Burmester GR, Ferraccioli G, Flipo RM et al. Clinical Remission and/or Minimal Disease Activity in Patients Receiving Adalimumab Treatment in a Multinational, Open-Label, Twelve-Week Study. Art & Rheum 2008;59:32-41.
4 Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor α drugs in rheumatoid arthritis: systematic review and meta-analysis of efficacy and safety. BMC Musculoskeletal Disorders 2008; 9(52).
5 Y H Lee, J H Woo, Y H Rho et al. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatol int 2008;28:553-559.
6 Venkateshan SP, Sidhu S, Malhotra S et al. Efficacy of Biologicals in the treatment of Rheumatoid Arthritis. Pharmacology 2009;83:1-9
7 Chen YF, Jobanputra P, Barton P et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technology Assessment 2006; 10(42). IL MANQUE LES PAGES

Swiss register[8]

Since 1998, this register has included 70 to 80% of Swiss patients with RA who are treated with anti-TNFα. A total of 1198 patients was followed up until September 2004 (etanercept n=519, infliximab n=362 and adalimumab n=317), with a mean follow-up of 23.7 months for etanercept, 18.8 months for infliximab and 10.7 months for adalimumab.
The median period of maintenance on treatment was 38.52 months, without any significant differences between the three medicines.
A second analysis of this register was published in May 2009[9]. For the cohort as a whole: the median period of maintenance on treatment was 37 months.

Dutch DREAM register[10]
Between February 2003 and August 2007, 916 patients were included into this register. On the day of analysis, 707 patients had been treated with anti-TNF for at least 1 year, of whom 267 had received adalimumab. Of the patients treated with adalimumab, 87% were treated concomitantly with a disease-modifying treatment, primarily MTX, 22% stopped treatment after 1 year. The reasons for stopping treatment were the occurrence of adverse effects (48%) and lack of efficacy (33%).

British national register of the BSRBR[11]
The aim of this publication was to analyse the reasons for the first switch to a second anti-TNF alpha in a British prospective observational study.
A total of 6739 patients naive for anti-TNFα was included and followed up. The patients were treated with adalimumab (876, 13%), etanercept (2,826, 42%) and infliximab (3,037, 45%). The mean follow-up of patients was 11 months for adalimumab, 13 months for etanercept and 18 months for infliximab. The first anti-TNFα was stopped by 841 patients (12%) due to inefficacy and by 1023 (15%) due to an adverse event. Of these patients, 503 stopping treatment due to inefficacy and 353 stopping treatment due to intolerance switched to a second anti-TNF alpha.
At the end of follow-up (April 2005), 73% of patients continued to be treated with the second anti-TNF alpha. The percentage of those who stopped the second anti-TNF was similar to that for discontinuation of the first anti-TNF: 13% due to inefficacy and 14% due to adverse effects. An analysis showed that the risk of stopping the second anti-TNF treatment due to inefficacy is even greater than the risk of the first anti-TNF treatment being stopped for the same reason: HR = 2.7 (CI 95%: 2.1-3.4). The same applies to the risk for stopping the second anti-TNF treatment due to an adverse event: HR = 2.3 (CI 95%: 1.9-2.9).

8 Finckh A, Simard JF, Gabay C et al. Evidence for differential acquired drug resistance to anti-tumor necrosis factor agents in rheumatoid arthritis. Ann Rheum 2006; 65:746-752.

9 SM Du Pan et al. Comparison of Drug Retention Rates and Causes of Drug Discontinuation Between Anti-Tumor Necrosis Factor Agents in Rheumatoid Arthritis & Rheumatism. Arthritis Care & Research 2009; 61(5):560-568.

10 W. Kievit, PCLM Van Riel et al. The effectiveness and medication costs of three anti-TNF α agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Ann Rheum Dis 2008.

11 Kimme L. Hyrich, Mark L et al. For the British Society for Rheumatology Biologics Register. Outcomes After Switching From One Anti-Tumor Necrosis Factor Agent to a Second Anti-Tumor Necrosis Factor Agent in Patients With Rheumatoid Arthritis. Results from a Large UK National Cohort Study. Art & Rheum 2007; 56 (1):13-20.

BIOBADASER Spanish national register[12]
The rates for maintenance on anti-TNF alpha treatment of patients with chronic inflammatory rheumatic diseases who had switched between anti-TNFα preparations were analysed. Between February 2000 and September 2004, 4706 patients were included into this register, of whom 68% had rheumatic arthritis, 11% ankylosing spondylitis, 10% psoriatic rheumatism and 11% other forms of chronic arthritis.
According to the authors, the rates for maintenance on anti-TNF were 83% for 1 year and 75% for 2 years. 488 patients were treated with more than one anti-TNF. In this situation, the rates for maintenance on the second anti-TNF alpha treatment were smaller: 68% for 1 year and 60% for 2 years.

Conclusion regarding efficacy data for RA:
The data supplied by the company for the indication RA deriving from open-label extension phases of studies which have already been examined by the Transparency Committee and from published meta-analyses and the data from European registers confirm the efficacy of HUMIRA in RA in patients with an inadequate response to MTX. No new clinical data was submitted to challenge the results of the PREMIER study concerning the superiority of MTX monotherapy over adalimumab monotherapy in the treatment of RA in patients naive for MTX. No study involving a direct comparison of adalimumab with other anti-TNF alpha agents was presented by the company.

4.1.2. Juvenile idiopathic arthritis
Since the extension of the indication in this study was recent (MA in August 2008 and TC opinion in June 2009), no new clinical data have been supplied.

12 Juan J Gomez-Reino, Loreto Carmona and the BIOBADASER Group**.** Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Research & Therapy* 2006, **8**:R29

4.1.3 Psoriatic arthritis

During the listing of adalimumab for this indication, the Transparency Committee noted the demonstration of efficacy of adalimumab in peripheral forms and regretted the absence of a direct comparison with MTX and with other anti-TNF alpha agents.

During the renewal of the listing, the company presented the results of:

- an unpublished open-label extension[13] of two studies, ADEPT and M02-570, which have already been evaluated by the Transparency Committee;
- an unpublished non-comparative study, STEREO[14]
- an analysis[15] based on the British BSRBR register, which evaluated the rates of maintenance on treatment after the first and second anti-TNF. The mean age of patients was 45.7 years, 53% were women, the mean duration of the disease was 12.4 years. The data on persistence with treatment were available for 422 patients followed up for 1 year. The rate of maintenance on the first anti-TNF alpha treatment was 75.5% at 1 year, while that for the second anti-TNF alpha treatment was 74%.
- the SAAD 2008[16] meta-analysis, which confirmed the superiority of anti-TNF agents over placebo in the treatment of PR. It included 6 studies, of which 2 were performed with adalimumab (these studies have already been evaluated by the Transparency Committee).

In conclusion, the data presented for the indication psoriatic arthritis do not provide information on the efficacy of adalimumab compared to that of MTX or other anti-TNF alpha agents.

4.1.4. Ankylosing spondylitis

The company presented the results of the analysis of some secondary endpoints, the results of analyses of subgroups and the open-label extension phase as well as combined analyses from two placebo-controlled studies that were already evaluated by the Transparency Committee during the listing process.

The results of a new non-comparative study (RHAPSODY – M05-760)[17] as well as those of a review of the literature[18], evaluating efficacy and the cost-efficacy ratio of anti-TNF alpha agents (including 9 studies already evaluated by the Transparency Committee, of which 2 were with adalimumab) were also presented.

No study comparing adalimumab with other anti-TNF alpha agents was presented.

13 Internal report of the company.

14 Internal report of the company.

15 Saad Amr A, Ashcroft Darren M, Watson Kath D et al. Persistence with anti-tumor necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Research & Therapy 2009. IL MANQUE LA REFERENCE

16 Saad Amr A., Symmons Deborah P.M., Noyce Peter R. et al. Risks and Benefits of Tumor Necrosis Factor α Inhibitors in the Management of Psoriatic Arthritis: Systematic Review and Meta-analysis of Randomized Controlled Trials. J Rheumatol 2008;35:883–890.

17 Rudwaleit M, Rodeland E, Holk P et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. Ann Rheum Dis. 2009;68:696-701.

18 Mc Leod C, Bagust A, Boland A, et al. Adalimumab, étanercept et infliximab for the treatment of ankylosing spondylitis : a systematic review and economic evaluation. Health Technology Assessment 2007; 11(.28).IL MANQUE LES PAGES

In conclusion, the data presented do not supply new information on the efficacy of adalimumab, especially in comparison with other anti-TNF alpha agents.

4.1.5. Crohn's disease

The laboratory presented the following results:

- analysis of secondary endpoints, post-hoc analysis and analysis of the open-label extension phase of two studies already evaluated by the Transparency Committee;
- two meta-analyses[19,20] evaluating the efficacy of anti-TNF alpha and including studies already evaluated by the Transparency Committee;
- a new non-comparative study (CARE, unpublished[21]).

In total, these data do not provide new information on the efficacy of adalimumab in the treatment of Crohn's disease. No study comparing adalimumab with infliximab for this indication has been supplied.

Note: amendments to the SPC are currently being evaluated by the EMEA and will be the subjected of an additional data submission and thus of an opinion by the Transparency Committee.

4.1.6. Psoriasis

The laboratory presented the following results**:**

- analyses of secondary endpoints of two study already evaluated by the Transparency Committee (REVEAL and CHAMPION);
- two meta-analyses[22,23] evaluating the efficacy of anti-TNF alpha;
- a new non-comparative study (BELIEVE, unpublished[24]).

Principal results of these meta-analyses

The meta-analysis by Bansback *et al* 2008 included 22 clinical studies, of which 20 compared biotherapy versus placebo and 2 versus active treatments (adalimumab vs. MTX and MTX vs. ciclosporin). The probability of achieving a PASI 75 response[25] in patients with moderate to severe psoriasis was estimated to be 81% [75-86] with infliximab 5mg/kg/week, 71% [63-79] with adalimumab 40 mg/2 weeks, 50% [43-58] with etanercept 50 mgx2/week, 42% [27-54] with MTX 15-22.5 mg/week, 33% [17-49] with ciclosporin 3 mg/kg/day.

The meta-analysis by Schmitt *et al* 2008 included 16 placebo-controlled studies. The probability of achieving a PASI 75 response during treatment was estimated to be 77% [72-81] with infliximab, 64% [61-68] with adalimumab, 44% [40-48] with etanercept 50 mg 2x/week and 33% [13-52] with ciclosporin.

19 Peyrin–Biroulet L, Pierre Deltenre, Nicolas de Suray et al. Efficacy and Safety of Tumor Necrosis Factor Antagonists in Crohn's Disease: Meta-Analysis of Placebo-Controlled Trials. Clin Gastroenterol Hepatol 2008 ; 6 :644-653

20 Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008;(1).

21 Internal report of the company

22 Schmitt J., Zhang Z., Wozel G. et al. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. British Journal of Dermatology 2008;159: 513–526

23 N Bansback et al. Efficacy of systemic treatment for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology 2009.

24 Internal report of the company

25 PASI 75 response: the PASI (Psoriasis Area Severity Index) is a composite index comprising measures of erythema, induration, desquamation and affected body area. It ranges from 0 (no psoriasis) to 72 (maximum severity). A PASI 75 response is a reduction of at least 75% in the initial PASI score.

Due to their methodology (placebo chosen as the reference comparator), these two meta-analyses only enable a comparison of each of the active treatments with placebo. They therefore do not enable the efficacy of adalimumab to be compared with that of the other treatments assessed.

In total, these data do not provide any new information concerning the efficacy of adalimumab for an indication with restricted reimbursement compared to the MA indication for severe, chronic plaque psoriasis with failure of at least 2 systemic treatments, namely phototherapy, MTX and ciclosporin. There is still no study available providing a direct comparison of adalimumab and other anti-TNF alpha agents.

4.1.7 Information concerning studies requested by the health authorities:

➢ Studies requested in the context of the risk management plan (RMP)

No definitive result is currently available from studies requested by the EMEA in the context of the RMP:

- The ReAlise study, consisting of a 5-year follow-up of patients with RA from the ReAct study* is under way. Only intermediate results for 24 months are available.
- The STRIVE study, a register of the follow-up of children treated with adalimumab for JIA is currently being set up
- The follow-up at 10 years of patients included in studies on RA and at 5 years of patients included in studies of AS is underway.
- the PYRAMID study, an international register for evaluation of the tolerance of adalimumab in CD is underway. An open-label follow-up of other CD studies is also underway.
- The ESPRIT study, an international register for evaluation of the tolerance of adalimumab after 10 years of use in psoriasis is being set up.

➢ Study requested by the Ministry of Health – the CORPUS study

The amendment to the agreement signed between ABBOTT and CEPS (Economic Committee for Health Products) in January 2005 mentioned this request for the study. The Transparency Committee regrets the small number of patients included into this study.

➢ Study on psoriasis requested by the Transparency Committee: PsoTEQ

This is a joint study of biotherapies in psoriasis. This study has not yet been set up.

➢ Conclusion

The Transparency Committee awaits the data from post-listing studies that are underway with respect to all the indications. More particularly, with respect to the CORPUS study on RA requested by the Ministry of Health, the Committee regrets the small number of patients included.

* Study already evaluated by the Transparency Committee.

4.2. Adverse events

From the time adalimumab was placed on the market, the estimated exposure is 877,885 patient-years. Since the previous opinion of the Transparency Committee from June 2009, the amendments concerning adverse effects have been introduced into the SPC:

- 28 August 2009: an update was made concerning the adverse events "cerebral vascular accident, psoriasis, myocardial infarction" following the submission of the last PSUR as well as an update of the comment about interruption of treatment in section 4.2;

24 July 2009: one update was made to the classification of adverse events with respect to the international MedDRA system as well as an update of the incidence of cancers, recalculated to include patients with exposure of at least 1 year.

For details of these amendments, see Appendix 1.

Data from the British BSRBR register[26] suggested that anti-TNF agents were not associated with an increased risk of severe infections compared to classic disease-modifying treatments. The incidence of tuberculosis was however smaller with etanercept (0.5 per 100 patient-years) than with infliximab (1.5 per 100 patient-years) and adalimumab (0.9 per 100 patient-years).
Data from the Italian LOHREN[27] register did not show any difference between the 3 anti-TNF agents with respect to the risk of serious infections.
Data from the Spanish BIOBADASER[28] register showed that the occurrence of new cases of tuberculosis is associated with non-compliance with the recommendations for screening and prophylaxis.
Data from American[29] and Swedish[30] registers did not show an increased risk of lymphoma in patients treated with anti-TNF alpha.
The results of the national RATIO Observatory, which are published solely as abstracts, cannot be taken into account, nor can those of the meta-analysis of Bongartz *et al* due to methodological limitations.

In conclusion, the significance of these results is limited, since they are essentially based on observational data. On the basis of these data, it was not possible to make any comparisons between the anti-TNF alpha agents with respect to their tolerance.

The combined analyses of the tolerance of adalimumab ([31,32]) performed on the basis of data from clinical studies already evaluated by the Transparency Committee were also presented, but they do not provide any new information on the efficacy/tolerance ratio.

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26 Dixon WG et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy. Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006; 54: 2368-2376.
27 Favalli EG, Desiati F, Atzeni F, et al. Serious infections during anti TNF treatment in rheumatoid arthritis patients. Autoimminity Reviews 2009 ; 266-273
28 Gomez-Reino JJ, Carmona L, et al. Risk of tuberculosis in patients treated with anti-tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection Arthritis Rheum 2007 ; 57(5) : 756-761
29 Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation.Arthritis Rheum. 2007;56:1433-9.
30 J Askling, E Baecklund, F Granth et al. Anti-tumor necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis 2009: 68; 648-653
31 Burmester GR, Mease P et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Disease 2009. IL MANQUE LE VOLUME ET LES PAGES
32. Colombel JF, William J. Sandborn, Remo Panaccione et al. Adalimumab Safety in Global Clinical Trials of Patients with Crohn's Disease. Cardoso. Inflamm Bowel Dis 2009;15:1308–1319

In addition, the company presented the results of an analysis of “paradoxical" psoriasis occurring in patients with RA who were treated with anti-TNF alpha in the British BSBR cohort[33]. The results of this analysis suggest that the incidence of “paradoxical psoriasis” is higher in patients treated with adalimumab than in those treated with etanercept or infliximab.

Note: On 4 August 2009, the FDA asked for to the companies marketing anti-TNF alpha, an update of the SPC with respect to the risk of cancer. This update concerns a reference to the increased risk of cancer in children and adolescents who are receiving these treatments, particularly in the treatment of JIA and Crohn's disease. An analysis by the FDA has shown that children and adolescents treated with anti-TNF α were revealed to have an increased risk of cancer after 30 months of treatment. About half of these cancers are lymphomas. Some cases have been fatal.

4.3 Conclusion

To support its request of renewal of listing of HUMIRA (adlimumab) on the list of medicines reimbursed by NHI, the company supplied new data. These data belong to meta-analyses or reviews including clinical studies already assessed by the Transparency Committee, and new non-comparative studies and European registers data about the use of anti-TNF alpha agents. Their results confirm the efficacy of HUMIRA in all its indications.

However, as mentioned in its previous opinions, the Transparency Committee regrets the absence of comparative study with other available anti-TNF alpha agents. More particularly, with respect to the indication: “RA not previously treated with MTX”, the Transparency Committee notes the absence of a study demonstrating the superior efficacy of HUMIRA over that of MTX. With respect to the indication psoriatic arthritis, no study comparing HUMIRA with MTX was supplied. With respect to the indication psoriasis, the methodology of the meta-analyses submitted does not enable the various treatments to be ranked. As a whole, these data cannot change the assessment of the actual benefit from that given in the previous opinion of the Transparency Committee for this indication.

The Summary of Product Characteristics has been amended in order to include new tolerance information obtained since the product was placed on the market. The observational data from European and US registers have been analysed. However, the significance of the results is limited due to their observational nature. On the basis of these data, it was not possible to make any comparison between anti-TNF alpha agents with respect to their tolerance.

The Transparency Committee regrets the small number of patients included in the CORPUS study and awaits data from post-listing studies that are underway with respect to all the indications.

[33] Harrison MJ, Dixon WG, Watson KD, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor & therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2009;68:209-215

5. USAGE DATA

The company has supplied data deriving from “Panel A+A” and sales data from GERS (Groupement pour l'Elaboration et la Réalisation de Statistiques).
“Panel A+A” consists of French prescribers (304 clinical specialists, including 134 rheumatologists, 80 gastroenterologists and 89 dermatologists) and french pharmacists. Usage data from this panel have been available since 2006. The results presented below relate to 2008.

Rheumatoid arthritis
The mean age of the patients was 53 years, with 76% being women and 83% having been treated with MTX. The mean dose of adalimumab was 40 mg per administration and 90% of patients received one injection every other week. Adalimumab was prescribed in combination with MTX to 69.8% of patients and as monotherapy to 18.9%.

Psoriatic arthritis
The mean age of the patients was 53 years, with 66% having been treated with MTX. The mean dose of adalimumab was 40 mg per administration and 94% of patients received one injection every other week. Adalimumab was prescribed as monotherapy to 36.5% of patients and in combination with MTX to 53.1%.

Ankylosing spondylitis
The mean age of the patients was 43 years, with 65% being men, 32% having been treated with MTX and 82% with NSAID. The mean dose of adalimumab was 40 mg per administration and 96% of patients received one injection every other week. Prior to the current treatment, 82% of patients had already been treated with NSAID and 32% with MTX. Adalimumab was prescribed as monotherapy to 65.8% of patients and in combination with MTX to 25.6%.

Crohn's disease
The mean age of the patients was 37 years, with 56% being women, 63% having been treated with corticosteroids, 40% with azathioprine and 23% with MTX. The mean dose was 40.8 mg per administration and 89% of patients received one injection every other week. HUMIRA was prescribed as monotherapy to 54.6% of patients. Adalimumab was combined with azathioprine in 20.1% of patients and with MTX in 10.3%.

Psoriasis
The mean age of the patients was 44 years, with 55% being men, 75% having been treated with MTX and 41% with PUVA therapy. The mean dose of adalimumab was 40 mg per administration and 90% of patients received one injection every other week.

The indication “juvenile idiopathic arthritis” did not appear in this survey because adalimumab obtained a MA for this indication on 25 August 2008.

Sales data (source GERS non-hospital and hospital)
In 2008, 144,203 packs of HUMIRA were sold, approximately 97% being sold in community pharmacies.

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Reassessment of Actual Benefit

The company has supplied new data. The nature of these data cannot change the assessment of the actual benefit given in previous opinions of the Transparency Committee.

The data obtained concerning the scientific aspects of the diseases in question and their management were also taken into account (rheumatoid arthritis [34,35,36,37,38], psoriatic arthritis[39,40], ankylosing spondylitis[32]). They do not give rise to an amendment of the assessment of actual benefit given in previous opinions of the Transparency Committee.
No new recommendation has been published since the previous opinion of the Transparency Committee with respect to the treatment of Crohn's disease, psoriasis or juvenile idiopathic arthritis.

The actual benefit provided by HUMIRA remains substantial for all its indications.

6.2. Reassessment of the improvement in actual benefit (IAB)

The nature of these new data cannot change the IAB assigned to HUMIRA in the treatment for psoriasis (no IAB compared to other anti-TNF alpha agents) in previous opinion of the Transparency committee.

6.3. Recommendations of the Transparency Committee

The Transparency Committee recommends maintaining inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services for the following indications:

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

- treatment of moderate to severe active rheumatoid arthritis in adults responding inadequately to disease-modifying treatments, including methotrexate.
- treatment of severe, active, progressive rheumatoid arthritis in adults not previously treated with methotrexate.

HUMIRA may be given as monotherapy in cases of methotrexate intolerance or when continued treatment with methotrexate is inappropriate.

34 Combe B et al. EULAR recommendations for the management of early arthritis: report of a task force of the european Standing committee for international Clinical Studies including Therapeutics (ESCISIT). Ann Rheum Dis. 2007 ;66(1):34-45.
35 Fautrel B et al. Recommandations de la Société française de rhumatologie pour l'utilisation des agents anti-TNFα chez les personnes souffrant de polyarthrite rhumatoïde. Revue du Rhumatisme. 2007. 74 (12) 1301–1311
36 HAS. Polyarthrite rhumatoïde – Diagnostic et prise en charge initiale – Recommandations. Septembre 2007.
37 HAS. Polyarthrite rhumatoïde – Prise en charge en phase d'état – Recommandations. Septembre 2007
38 HAS. Polyarthrite rhumatoïde – synthèse de l'ensemble des recommandations. Septembre 2007
39 Recommandation d'utilisation des anti-TNF α au cours de la spondylarthrite ankylosante et du rhumatisme psoriasique – Actualisation 2007 – SFR/ CRI. Mai 2007
40 Zochling J. ASA/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2006 Apr;65(4):442-52.

HUMIRA has been shown to slow the progression of radiographically measured structural joint damage and to improve functional capabilities when administered in combination with methotrexate."

Polyarticular juvenile idiopathic arthritis:
"HUMIRA, combined with methotrexate, is indicated for the treatment of progressive polyarticular juvenile idiopathic arthritis in adolescents aged 13 to 17 years who have not had a satisfactory response to one or more disease-modifying treatments.
HUMIRA® may be given as monotherapy in cases of methotrexate intolerance or where continued treatment with methotrexate is inappropriate."

Psoriatic arthritis:
"HUMIRA is indicated for the treatment of active, progressive psoriatic arthritis in adults previously responding inadequately to disease-modifying treatment. It has been shown that HUMIRA slows the progression of radiographically measured structural damage of peripheral joints in patients with symmetrical polyarticular forms of the disease and improves functional capabilities."

Ankylosing spondylitis:
"HUMIRA is indicated for the treatment of severe, active ankylosing spondylitis in adults responding inadequately to conventional treatment."

Crohn's disease (restriction compared to the MA):
The Transparency Committee recommends continuing inclusion on the list of medicines reimbursed by National Insurance for the treatment of active, severe Crohn's disease in patients who have not responded despite receiving appropriate and properly administered treatment with corticosteroids and immunosuppressants, or in whom such treatment is contraindicated or poorly tolerated.

Psoriasis (restriction compared to the MA):
The Transparency Committee recommends continuing inclusion on the list of medicines reimbursed by National Insurance for severe chronic forms in adults in whom at least 2 systemic treatments out of phototherapy, methotrexate and ciclosporin have failed (non-responders or with a contraindication or intolerance).

6.3.1 Packaging: appropriate for the prescription conditions.

6.3.2 Reimbursement rate: 65%

6.3.3 Exception drug status

Initial SPC	Current SPC following amendments of July and August 2009
4.2 Posology and method of administration Treatment with HUMIRA must be initiated and supervised by a specialist experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or psoriasis. Patients being treated with HUMIRA are to be given a special alert card. After proper training in the injection technique, patients may self-inject with HUMIRA if their doctor considers it feasible, subject to appropriate medical monitoring. During treatment with HUMIRA, other concomitant treatments (such as corticosteroids and/or immunomodulators) should be optimised. <u>Interruption of treatment</u> The data available suggest that the reintroduction of HUMIRA after discontinuation for 70 days or more results in a clinical response of the same magnitude and with a similar safety profile to that observed before the interruption of treatment. <u>Adults</u> **Rheumatoid arthritis** The recommended dosage of HUMIRA in adults with rheumatoid arthritis is a single 40 mg subcutaneous injection of adalimumab every two weeks. Methotrexate should continue to be administered during HUMIRA treatment. Administration of glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs and analgesics may be continued during treatment with HUMIRA. See sections 4.4 and 5.1 for information on combination with disease-modifying antirheumatic drugs other than methotrexate. In monotherapy, some patients in whom a decrease in response to HUMIRA has been observed may benefit from having the dose increased to 40 mg adalimumab every week.	**4.2 Posology and method of administration** Treatment with HUMIRA must be initiated and supervised by a specialist experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or psoriasis. Patients being treated with HUMIRA are to be given a special alert card. After proper training in the injection technique, patients may self-inject with HUMIRA if their doctor considers it feasible, subject to appropriate medical monitoring. During treatment with HUMIRA, other concomitant treatments (such as corticosteroids and/or immunomodulators) should be optimised. <u>Adults</u> **Rheumatoid arthritis** The recommended dosage of HUMIRA in adults with rheumatoid arthritis is a single 40 mg subcutaneous injection of adalimumab every other week. Methotrexate should continue to be administered during HUMIRA treatment. Administration of glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs and analgesics may be continued during treatment with HUMIRA. See sections 4.4 and 5.1 for information on combination with disease-modifying antirheumatic drugs other than methotrexate. In monotherapy, some patients in whom a decrease in response to HUMIRA has been observed may benefit from having the dose increased to 40 mg adalimumab every week. **Interruption of treatment** **It may be necessary to interrupt treatment, for example before surgery or in the event of severe infection**. The data available suggest that the reintroduction of HUMIRA after discontinuation for 70 days or more results in a clinical response of the same magnitude and with a similar safety profile to that observed before the interruption of treatment.
4.4 Special warnings and precautions for use <u>*Serious infections*</u>*:* Serious infections, including septicaemias due to bacterial and mycobacterial infections, invasive fungi, viral or other opportunistic infections, such as listeriosis and pneumocystosis have been reported in patients treated with HUMIRA.	**4.4 Special warnings and precautions for use** <u>*Serious infections*</u>*:* Serious infections, including septicaemias due to bacterial and mycobacterial infections, invasive fungi, **parasites**, viral or other opportunistic infections, such as listeriosis and pneumocystosis have been reported in patients treated with HUMIRA.

4.8 Undesirable effects
Clinical trials

HUMIRA was studied in 6,593 patients in controlled and open-label clinical trials with a maximum duration of 60 months. These trials included patients with recent or long-standing rheumatoid arthritis, polyarticular juvenile idiopathic arthritis or patients with psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis. The data in Table 1 are based on pivotal controlled studies in 4,355 patients who received HUMIRA and 2,487 patients who received placebo or an active comparator during the controlled phase.

The percentage of patients interrupting treatment due to adverse effects during the double-blind controlled phase in the pivotal studies was 4.5% of patients treated with HUMIRA and 4.5% of patients in the control group.

Adverse effects in paediatric patients with polyarticular juvenile idiopathic arthritis

In general, the frequency and type of adverse events observed in paediatric patients were comparable to those observed in adult patients.

Clinical and biological adverse effects having at least a possible causal relationship with adalimumab in the pivotal studies are presented in Table 1 below by system organ class and by frequency (very common ≥ 1/10 ; common ≥ 1/100 to < 1/10 ; uncommon ≥ 1/1000 to <1/100 and rare ≥ 1/10 000 to < 1/1000). Within each frequency grouping, the adverse events are presented in decreasing order of seriousness.

6.3.3.1.1.1.1.1.1
6.3.3.1.1.1.1.1.2 Table 1
Adverse effects observed during clinical trials

Class (system-organ)	**Frequency**	*Adverse effects*
Laboratory tests	Uncommon	Elevated serum creatine phosphokinase, prolongation of the activated partial thromboplastin time, presence of autoantibodies.
Cardiac disorders	Uncommon Rare	Arrhythmias, tachycardia Cardiac arrest, coronary insufficiency, angina,

4.8 Undesirable effects
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Clinical and biological adverse effects having at least a possible causal relationship with adalimumab in the **clinical** studies are presented in Table 1 below by system organ class and by frequency (very common ≥ 1/10 ; common ≥ 1/100 to < 1/10 ; uncommon ≥ 1/1000 to <1/100 and rare ≥ 1/10 000 to < 1/1000 and **very rare < 1/10,000**). Within each frequency grouping, the adverse events are presented in decreasing order of seriousness. **The highest frequency observed in the various indications has been included. The presence of an asterisk (*) in the column "system organ class" indicates that more detailed information is available in sections 4.3, 4.4 and 4.8.**
Based on the adverse effects most frequently observed with adalimumab in controlled clinical trials, reactions at the injection site are to be expected in approximately 15% of patients.

Table 1
Adverse effects observed during clinical trials

System organ class	**Frequency**	***Adverse effects***
Infections and infestations	**Very common:**	**Respiratory tract infections (including lower and upper respiratory tract infections, pneumonia, sinusitis, pharyngitis, rhinopharyngitis and herpetic pneumonia).**

		pericardial effusion, congestive heart failure, palpitations.
Blood and lymphatic system disorders	Uncommon Rare	Neutropenia (including agranulocytosis), leucopenia, thrombocytopenia, anaemia, lymphadenopathy, leucocytosis, lymphocytopenia Pancytopenia, idiopathic thrombocytopenic purpura
Nervous system disorders	Common Uncommon Rare	Dizziness (including vertigo), headache, sensory neurological disorders (including paraesthesia) Syncope, migraine, tremor, sleep disorders Multiple sclerosis, facial paralysis
Eye disorders	Uncommon Rare	Vision disorders, sensory eye disorders, infection, irritation or inflammation of the eyes Panophthalmia, iritis, glaucoma
Ear and labyrinth disorders	Uncommon Rare	Ear problems (including pain and swelling). Hearing loss, tinnitus
Respiratory, thoracic and mediastinal disorders	Common Uncommon Rare	Cough, nasopharyngeal pain Asthma, dyspnoea, dysphonia, nasal congestion Pulmonary oedema, pharyngeal oedema, pleural effusion, pleurisy
Gastrointestinal disorders	Common Uncommon Rare	Diarrhoea, abdominal pain, stomatitis and mouth ulcers, nausea Rectal bleeding, vomiting, dyspepsia, distension, constipation Pancreatitis, intestinal stenosis, colitis, enteritis, oesophagitis, gastritis
Renal and urinary tract disorders	Uncommon Rare	Haematuria, renal failure, vesical and urethral symptoms. Proteinuria, renal pain.
Skin and	Common	Rash, pruritus.

	Common	**Systemic infections (including sepsis, candidiasis and influenza)** **Intestinal infections (including viral gastroenteritis)** **Infections of the skin and soft tissues (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster)** **Ear infections** **Oral infections (including herpes simplex, oral herpes and tooth infections)** **Reproductive tract infections (including vulvovaginal mycosis)** **Urinary tract infections (including pyelonephritis)** **Fungal infections.**
	Uncommon	**Opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and Mycobacterium avum complex)** **Neurological infections (including viral meningitis)** **Eye infections** **Bacterial infections** **Joint infections.**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**Common**	**Benign neoplasm** **Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)**
	Uncommon	**Lymphoma**** **Tumours of solid organs (including breast, lung and thyroid cancer)** **Melanoma****
Blood and lymphatic system disorders	**Very common:**	**Leucopenia (including neutropenia and agranulocytosis)** **Anaemia**
	Common	**Thrombocytopenia** **Leucocytosis**
	Uncommon	**Idiopathic thrombocytopenic purpura**
	Rare	**Pancytopenia**

subcutaneous tissue disorders	Uncommon Rare	Urticaria, psoriasis, increased ecchymoses and contusion, purpura, dermatitis and eczema, alopecia Erythema multiforme, panniculitis
Musculoskeletal and connective tissue and bone disorders	Common Rare	Musculoskeletal pain Rhabdomyolysis
Endocrine disorders	Rare	Thyroid disorders (including goitre)
Metabolism and nutrition disorders	Uncommon Rare	Hypokalaemia, hyperlipidaemia, appetite disorders (including anorexia), hyperuricaemia Hypercalcaemia, hypocalcaemia
Infections and infestations	Common Uncommon Rare	Lower respiratory tract infections (including pneumonia, bronchitis), viral infections (including influenza, herpes infections), candidiasis, bacterial infections (including urinary tract infections), upper respiratory tract infections Sepsis, opportunistic infections (including tuberculosis, histoplasmosis), abscesses, articular infection, cutaneous infection (including cellulitis and impetigo), superficial fungal infections (including of the skin, nails and feet). Necrotising fasciitis, viral meningitis, diverticulitis, wound infections
Injury and poisoning	Uncommon	Accidental injury, poor wound healing
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon Rare	Cutaneous papilloma Lymphoma, solid organ tumours (including tumours of the breast, ovary, testes), malignant melanoma, squamous cell carcinoma
Vascular disorders	Uncommon Rare	Hypertension, congestion, haematomas Vascular occlusion, aortic stenosis, thrombophlebitis, aortic aneurysm
General disorders and administration	Very common:	Reactions at the injection site (pain, swelling, redness or pruritus)

Immune system disorders	**Common**	**Hypersensitivity** **Allergies (including seasonal allergy)**
Metabolism and nutrition disorders	**Very common**	**Elevated lipid levels**
	Common	**Hypokalaemia** **Elevated uric acid levels** **Abnormal blood sodium levels** **Hypocalcaemia** **Hyperglycaemia** **Hypophosphataemia** **Elevated blood potassium levels**
	Uncommon	**Dehydration**
Psychiatric disorders	**Common**	**Mood disorders (including depression)** **Anxiety, insomnia.**
Nervous system disorders	**Very common**	**Headache**
	Common	**Paraesthesia (including hypoaesthesia)** **Migraine** **Sciatica**
	Uncommon	**Tremors**
	Rare	**Multiple sclerosis**
Eye disorders	**Common**	**Vision disorders** **Conjunctivitis**
	Uncommon	**Blepharitis** **Swelling of the eyes** **Diplopia.**
Ear and labyrinth disorders	**Common**	**Vertigo**
	Uncommon	**Deafness** **Tinnitus**

site conditions	Common Uncommon	Pyrexia, fatigue (including asthenia and malaise) Thoracic pain, oedema, flu-like syndrome
Immune system disorders	Uncommon Rare	Systemic lupus erythematosus, angioedema, drug-associated hypersensitivity Serum sickness, seasonal allergy
Hepatobiliary disorders	Common Rare	Elevated liver enzymes Hepatic necrosis, hepatitis, hepatic steatosis, biliary lithiasis, hyperbilirubinaemia
Reproductive system and breast disorders	Uncommon	Menstrual disorders and uterine bleeding
Psychiatric disorders	Uncommon	Mood disorders, anxiety (including nervousness and agitation).

Cardiac disorders	**Common**	**Tachycardia**
	Uncommon	**Arrhythmias** **Congestive heart failure**
	Rare	**Cardiac arrest.**
Vascular disorders	**Common**	**Hypertension.** **Hot flushes** **Haematomas**
	Rare	**Vascular occlusion** **Thrombophlebitis** **Aortic aneurysm**
Respiratory, thoracic and mediastinal disorders:	**Common**	**Cough** **Asthma** **Dyspnoea**
	Uncommon	**Chronic obstructive pulmonary disease (COPD)** **Interstitial lung disease** **Pneumopathy**
Gastrointestinal disorders	**Very common**	**Abdominal pain** **Nausea and vomiting**
	Common	**Gastrointestinal haemorrhage** **Dyspepsia** **Gastro-oesophageal reflux** **Sjögren's syndrome**
	Uncommon	**Pancreatitis** **Dysphagia** **Facial oedema**
Hepatobiliary disorders*	**Very common**	**Elevated liver enzymes**
	Uncommon	**Cholecystitis and biliary lithiasis** **Hyperbilirubinaemia** **Hepatic steatosis**
Skin and subcutaneous tissue disorders	**Very common**	**Rash (including exfoliative rash)**
	Common	**Pruritus**

		Urticaria **Ecchymoses (including purpura)** **Dermatitis (including eczema)** **Onychoclasis** **Hyperhidrosis**
	Uncommon	**Nocturnal sweats** **Scarring**
Musculoskeletal and systemic disorders	**Very common**	**Musculoskeletal pain**
	Common	**Muscle spasms (including elevated serum creatine phosphokinase)**
	Uncommon	**Rhabdomyolysis**
	Rare	**Systemic lupus erythematosis**
Renal and urinary tract disorders	**Common**	**Haematuria** **Renal impairment**
	Uncommon	**Nycturia**
Reproductive system and breast disorders	**Uncommon**	**Erectile dysfunction**
General disorders and administration site conditions	**Very common**	**Reaction at the injection site (including erythema at the injection site).**
	Common	**Chest pain** **Oedema**
	Uncommon	**Inflammation.**
Investigations	**Common**	**Coagulation and bleeding disorders (including prolongation of activated partial thromboplastin time)** **Positive results for autoantibodies (including anti-double-stranded DNA antibody)** **Elevated blood lactate dehydrogenase**
Injury, poisoning and	**Common**	**Poor wound healing**

	complications associated with procedures | | | **** including open-label extension studies**
Malignant tumours and lymphoproliferative disorders No case of cancer was observed in 171 patients representing an exposure of 192.5 patient-years during a study of HUMIRA in polyarticular juvenile idiopathic arthritis. During the controlled periods of pivotal clinical trials with HUMIRA lasting at least 12 weeks in patients with moderate to severe active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis, the observed rate (95% confidence interval) of cancers other than lymphomas or non-melanoma skin cancers was 5.9 (3.5-9.9) per 1000 patient-years in 3853 patients treated with HUMIRA and 4.3 (1.8-10.4) per 1000 patient-years in 2183 patients in the control group (mean duration of treatment of 5.5 months in patients treated with HUMIRA and 3.9 months in patients in the control group). The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (5.7-13.5) per 1000 patient-years in patients treated with HUMIRA and 2.6 (0.8-8.0) per 1000 patient-years in patients in the control group. Of these skin cancers, squamous cell carcinomas occurred at rates of 2.5 (1.1-5.6) per 1000 patient-years in patients treated with HUMIRA and 0 per 1000 patient-years in patients in the control group (95% confidence interval). The rate (95% confidence interval) of lymphomas was 0.8 (0.2-3.3) per 1000 patient-years in patients treated with HUMIRA and 0.9 (0.1-6.1) per 1,000 patient-years in patients in the control group. When the controlled periods of these trials are combined together with open-label extension studies currently underway, giving a mean duration of approximately 1.7 years, 6539 included patients and more than 16,000 patient-years of treatment, the observed rate of cancers other than lymphomas and non-melanoma skin cancers is approximately 10.1 per 1000 patient-years. The observed rate of non-melanoma skin cancers is approximately 9.0 per 1000 patient-years and the observed rate of lymphomas is approximately 1.1 per 1000 patient-years.	Malignant tumours and lymphoproliferative disorders No case of cancer was observed in 171 patients representing an exposure of 192.5 patient-years during a study of HUMIRA in polyarticular juvenile idiopathic arthritis. During the controlled periods of pivotal clinical trials with HUMIRA lasting at least 12 weeks in patients with moderate to severe active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis, the observed rate (95 % confidence interval) of cancers other than lymphomas or non-melanoma skin cancers was 5.9 (3.5-9.9) per 1000 patient-years in 3853 patients treated with HUMIRA and 4.3 (1.8-10.4) per 1000 patient-years in 2183 patients in the control group (mean duration of treatment of 5.5 months in patients treated with HUMIRA and 3.9 months in patients in the control group). The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (5.7-13.5) per 1000 patient-years in patients treated with HUMIRA and 2.6 (0.8-8.0) per 1000 patient-years in patients in the control group. Of these skin cancers, squamous cell carcinomas occurred at rates of 2.5 (1.1-5.6) per 1000 patient-years in patients treated with HUMIRA and **0.9 (0.1-6.1)** per 1000 patient-years in patients in the control group (95 % confidence interval). The rate (95 % confidence interval) of lymphomas was 0.8 (0.2-3.3) per 1000 patient-years in patients treated with HUMIRA and 0.9 (0.1-6.1) per 1,000 patient-years in patients in the control group. When the controlled periods of these trials are combined together with open-label extension studies currently underway, giving a mean duration of approximately **2.7** years, **4767** included patients and more than **15,332** patient-years of treatment, the observed rate of cancers other than lymphomas and non-melanoma skin cancers is approximately **8.3** per 1000 patient-years. The observed rate of non-melanoma skin cancers is approximately **9.3** per 1000 patient-years and the observed rate of lymphomas is approximately **1.2** per 1000 patient-years.

6.3.3.1.1.2 <u>Other adverse effects observed during post-marketing surveillance or phase IV clinical trials</u>

Table 2

Adverse effects during post-marketing surveillance and phase IV clinical trials

System organ class	Adverse event
Gastrointestinal disorders	Intestinal perforation
Hepatobiliary disorders	Reactivation of hepatitis B
Nervous system disorders	Demyelinating disease (for example optic neuritis, Guillain-Barré syndrome)
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease including pulmonary fibrosis
Skin and subcutaneous tissue disorders	Cutaneous vasculitis
Immune system disorders	Anaphylactic reactions
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Hepatosplenic T-cell lymphoma

6.3.3.1.1.3 <u>Other adverse effects observed during post-marketing surveillance or phase IV clinical trials</u>

Table 2

Adverse effects during post-marketing surveillance and phase IV clinical trials

System organ class	**Adverse event**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Hepatosplenic T-cell lymphoma
Immune system **disorders**	**Anaphylaxis**
Nervous system **disorders**	Demyelinating disease (for example optic neuritis, Guillain-Barré syndrome), **stroke**
Gastrointestinal disorders	Intestinal perforation
Hepatobiliary **disorders**	Reactivation of hepatitis B
Skin and subcutaneous tissue **disorders**	**Cutaneous vasculitis, Stevens-Johnson syndrome, angioedema, onset or aggravation of psoriasis (including palmoplantar pustular psoriasis)**
Musculoskeletal and systemic disorders	**Lupus-like syndrome**
Cardiac disorders	**Myocardial infarction**