HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 March 2010

CIMZIA 200 mg, solution for injection
Carton containing two pre-filled 1 ml syringes and 2 alcohol wipes (CIP: 397 320.0)

Applicant: UCB PHARMA SA

certolizumab pegol

ATC code (2009): L04AB05

Medicine requiring initial annual hospital prescription.
Initial prescription and renewal restricted to specialists in rheumatology or Internal medicine.

Date of Marketing Authorisation: 01/10/2009 (centralised, rapporteur country: Sweden)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Certolizumab pegol is a recombinant, humanised antibody Fab' fragment against tumour necrosis factor alpha expressed in *Escherichia coli* and conjugated to polyethylene glycol.

1.2. Indications

"CIMZIA, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs[1]) including methotrexate, has been inadequate.

CIMZIA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

CIMZIA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate."

1.3. Dosage

"Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients should be given the special alert card.

Posology

The recommended starting dose of CIMZIA for adult patients with rheumatoid arthritis is 400 mg (as 2 injections of 200 mg each on one day) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks. MTX should be continued during treatment with CIMZIA where appropriate.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

Missed dose

Patients who miss a dose should be advised to inject the next dose of CIMZIA as soon as they remember and then continue injecting subsequent doses every 2 weeks as originally instructed.

Paediatric population (< 18 years old)

CIMZIA is not recommended for use in children and adolescents below age 18 due to a lack of data on efficacy and safety in that patients population.

[1] The name "disease-modifying anti-rheumatic drug" (DMARD) is generally given to a medicinal product with a slow-acting symptomatic effect and an effect on the course of the disease, notably the radiographic progression of structural damage. The classical DMARDs, as opposed to the biological therapies (TNF-α inhibitors, rituximab, abatacept, tocilizumab, etc.) include MTX (reference classical DMARD in RA), leflunomide, sulfasalazine, hydroxychloroquine, gold salts, azathioprine, D-penicillamine and tiopronin.

Elderly (≥65 years old)
No dose adjustment is required. Population pharmacokinetic analyses showed no effect of age.

Renal and hepatic impairment
CIMZIA has not been studied in these patient populations. No dose recommendations can be made.

Method of administration
The total content (1 ml) of the pre-filled syringe should be administered as a subcutaneous injection only. Suitable sites for injection would include the thigh or abdomen.
After proper training in injection technique, patients may self-inject if their physician determines that it is appropriate and with medical follow-up as necessary."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L: Antineoplastic and immunomodulating agents
L04: Immunosuppressants
L04A: Immunosuppressants
L04AB: Tumour necrosis factor alpha (TNF-α) inhibitors
L04AB05: Certolizumab pegol

2.2. Medicines in the same therapeutic category

Comparator medicines
These are the other TNF-α inhibitors indicated in the treatment of RA:
- ENBREL (etanercept)
- HUMIRA (adalimumab)
- REMICADE (infliximab)
- SIMPONI (golimumab), not included on the list of reimbursable medicinal products

The medicinal products ENBREL, HUMIRA and REMICADE are also indicated as first-line therapy, i.e. in MTX-naive patients.

2.3. Medicines with a similar therapeutic aim

Other biological agents indicated in RA:
- KINERET (anakinra): interleukin-1 receptor antagonist
- ORENCIA (abatacept): T-cell costimulation inhibitor
- MABTHERA (rituximab): monoclonal antibody directed against B cells
- ROACTEMRA (tocilizumab): monoclonal antibody directed against interleukin-6

Classical DMARDs used in RA:
Medicinal products based on methotrexate (reference DMARD), sulfasalazine, leflunomide, gold salts, azathioprine, D-penicillamine and tiopronin.

In the event of inefficacy, poor tolerability or contra-indication of DMARDs: medicinal products based on ciclosporin.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The development plan for certolizumab pegol in RA is based on 4 Phase III clinical studies:

- Two studies (RAPID 1[2] and RAPID 2[3]) which were used to obtain the Marketing Authorisation. In these two studies, the efficacy of CIMZIA was assessed in combination with MTX at the dosage specified in the Marketing Authorisation, i.e. one subcutaneous injection of 400 mg in weeks 0, 2 and 4 followed by 200 mg every 2 weeks. The patients included had failed to respond adequately to or did not tolerate MTX (average MTX dose on inclusion 13.6 mg/week in the RAPID 1 study and 12.5 mg/week in the RAPID 2 study).
- Two additional studies, FAST4WARD[4] and CDP870-014 (not published), which assessed the efficacy of CIMZIA at a different dosage from the one specified in the Marketing Authorisation: 400 mg every 4 weeks. Only the FAST4WARD study will be described because it was the basis for obtaining the indication in monotherapy.

The primary efficacy endpoint for both of these studies was the proportion of ACR 20 responders[5] at Week 24. The reduction in progression of structural damage was assessed in just one study (RAPID 1) using the Van der Heijde-modified total Sharp score[6] (mTSS).

The methodology for these three studies is described in Table 1 below.

[2] Keystone E et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week phase III, multicenter, randomized double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008 Nov;58(11):3319-29

[3] Smolen J et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804

[4] Fleischmann R et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11

[5] ACR (American College of Rheumatology): this score is used to assess a patient's response to treatment. It takes into account the number of tender joints, the synovitis score, patient pain assessment, patient and physician global assessment, patient disability and laboratory markers of inflammation. An ACR 20 response corresponds to a 20% improvement in the number of swollen and tender joints and an improvement of at least 20% in the following parameters:

- ESR or CRP (C-reactive protein)
- Disease activity assessed by the patient using a VAS
- Disease activity assessed by the physician using a VAS
- Pain assessed using a VAS
- Disability index

[6] the mTSS methodology enables joint erosion and reduction in joint space to be quantified for 44 and 40 joints respectively. A higher score indicates greater damage

Table 1. Summary of 3 Phase III studies which evaluated the efficacy of certolizumab pegol in RA

Study	Type of study	Patients N	Study population / inclusion criteria	Randomisation groups	Primary efficacy endpoints
RAPID 1 CDP870-027 (February 2005-September 2006)	Placebo-controlled, randomised, double-blind Duration: 52 weeks	982	Adult patients with active RA (>9 tender or swollen joints), diagnosed in accordance with the ACR criteria for at least 6 months, not controlled by MTX (> 10 mg per week).	- Pbo + MTX every 2 weeks - n= 199 - CZP 400 mg in Weeks 0, 2, 4 + MTX followed by CZP 200 mg + MTX every 2 weeks* - n= 393 - CZP 400 mg + MTX every 2 weeks - n= 390 (oral administration of MTX at an average dose of 13.6 mg/week)	ACR 20 responder rate at Week 24 Change in the mTSS between inclusion and Week 52
RAPID 2 CDP870-050 (January 2005-September 2006)	Placebo-controlled, randomised, double-blind Duration: 24 weeks	619	Adult patients with active RA (>9 tender or swollen joints), diagnosed in accordance with the ACR criteria for at least 6 months, not controlled by MTX (> 10 mg per week).	- Pbo + MTX every 2 weeks - n= 127 - CZP 400 mg + MTX in Weeks 0, 2, 4 followed by CZP 200 mg + MTX every 2 weeks* - n= 246 - CZP 400 mg + MTX every 2 weeks - n= 246 (oral administration of MTX at an average dose of 12.5 mg/week)	ACR 20 responder rate at Week 24
FAST4WARD CDP870-011 (June 2003-July 2004)	Placebo-controlled, randomised, double-blind Duration: 24 weeks	220	Adult patients with active RA (>9 tender or swollen joints), diagnosed in accordance with the ACR criteria for at least 6 months, not controlled by at least one classical disease-modifying anti-rheumatic agent	- Pbo every 4 weeks – n= 109 - CZP 400 mg every 4 weeks - n= 111	ACR 20 responder rate at Week 24

CZP: certolizumab pegol, MTX: methotrexate, Pbo: placebo, *corresponds to dosage specified in the Marketing Authorisation

Results:

3.1.1. Studies conducted in patients with RA following failure of MTX

- RAPID 1 study

Characteristics of the patients included:
The mean age was 52 and the average duration of the RA was 6.14 years. The patients had moderate-to-severe rheumatoid arthritis with an average of 31 tender joints and 22 swollen joints. The average MTX dose on inclusion was 13.6 mg/week. Around 4% of the patients had been treated previously with TNF-α inhibitors.

The results were analysed on an ITT basis (cf. Tables 2 and 3).

Table 2. Proportion of patients who achieved an ACR 20 response at 24 weeks in the RAPID 1 study (primary endpoint)

	Pbo + MTX	CZP, MA dosage	CZP 400 mg + MTX
Responders (%)	27/198 (13.6)	228/ 388 (58.8)	236/ 388 (60.8)
p vs. Pbo + MTX		< 0.001	< 0.001

CZP: certolizumab pegol, MTX: methotrexate, Pbo: placebo
MA dosage: 400 mg at Weeks 0, 2, 4 + MTX followed by 200 mg every 2 weeks

A statistically significant difference ($p<0.001$) was identified in favour of the group treated with CZP at the dosage in the Marketing Authorisation in combination with MTX compared with the placebo + MTX group in terms of the ACR 20 responder rate at 24 weeks.

Table 3. Change in the Van der Heijde-modified total Sharp score (mTSS) between inclusion and 52 weeks in the RAPID 1 study (co-primary endpoint)

	Pbo + MTX	CZP, MA dosage	CZP 400 mg + MTX
Baseline value N Average (standard deviation)	 199 39 (44.5)	 391 38.4 (49.4)	 389 38.3 (47.1)
Change in the mTSS between inclusion and Week 52 N Average (standard deviation)	 181 2.8 (7.8)	 364 0.4 (5.7)	 363 0.2 (4.8)
p vs. Pbo + MTX		< 0.001	< 0.001

CZP: certolizumab pegol, MTX: methotrexate, Pbo: placebo
MA dosage: 400 mg at Weeks 0, 2, 4 + MTX followed by 200 mg every 2 weeks

The progression of radiographic signs was significantly lower among the patients treated with CZP than among those in the placebo group at Week 52.

The percentage of treatment discontinuations was high, particularly in the placebo + MTX group. The primary reasons for treatment discontinuation were poor efficacy, the occurrence of adverse effects and patient decision (cf. Table 4).

Table 4. Results for primary discontinuations of treatment (RAPID 1 study)

	Pbo + MTX N = 199 (%)	CZP, MA dosage N = 393 (%)	CZP 400 mg + MTX N = 390 (%)	Total N = 982 (%)
Discontinuations of treatment n (%)	156 (78.4)	138 (35.1)	116 (29.7)	410 (41.8)
Primary reasons for discontinuation of treatment				
Poor efficacy n (%)	141 (70.9)	98 (24.9)	74 (19.0)	313 (31.9)
Adverse effect n (%)	3 (1.5)	17 (4.3)	22 (5.6)	42 (4.3)
Patient decision n (%)	10 (5.0)	15 (3.8)	11 (2.8)	36 (3.7)

CZP: certolizumab pegol, MTX: methotrexate, Pbo: placebo
MA dosage: 400 mg at Weeks 0, 2, 4 + MTX followed by 200 mg every 2 weeks

A 2-year open-label extension phase demonstrated maintenance of the efficacy of CZP.

- RAPID 2 study

Characteristics of the patients included:
The mean age was 51.9 and the average duration of the RA was 6.16 years. The patients had moderate-to-severe rheumatoid arthritis with an average of 30 tender joints and 21 swollen joints. The average MTX dose on inclusion was 12.5 mg/week. Around 5% of the patients had been treated previously with TNF-α inhibitors.

The results were analysed on an ITT basis. A statistically significant difference ($p < 0.001$) was identified in favour of the group treated with CZP at the dosage in the Marketing Authorisation in combination with MTX compared with the placebo + MTX group in terms of the ACR 20 responder rate at 24 weeks (cf. Table 5).

Table 5. Proportion of patients who achieved an ACR 20 response at 24 weeks in the RAPID 2 study (primary endpoint)

	Pbo + MTX	CZP, MA dosage	CZP 400 mg + MTX
n (%)	11/127 (8.7)	141/246 (57.3)	141/245 (57.6)
p vs. Pbo + MTX		<0.001	<0.001

CZP: certolizumab pegol, MTX: methotrexate, Pbo: placebo
MA dosage: 400 mg at Weeks 0, 2, 4 + MTX followed by 200 mg every 2 weeks

The percentage of treatment discontinuations was high, notably in the placebo + MTX group. The primary reasons for treatment discontinuation were poor efficacy and the occurrence of adverse effects (cf. Table 6).

Table 6. Results for primary discontinuations of treatment (RAPID 2)

	Pbo + MTX N = 127	CZP, MA dosage N = 246	CZP 400 mg + MTX N = 246	Total N = 619
Discontinuations of treatment n (%)	110 (86.6)	72 (29.3)	65 (26.4)	247 (39.9)
Main reasons for discontinuation of treatment				
Poor efficacy n (%)	107 (84.3)	54 (22.0)	53 (21.5)	214 (34.6)
Adverse effect n (%)	2 (1.6)	11 (4.5)	6 (2.4)	19 (3.1)

CZP: certolizumab pegol, MTX: methotrexate, Pbo: placebo
MA dosage: 400 mg at Weeks 0, 2, 4 + MTX followed by 200 mg every 2 weeks

An open-label extension phase is in progress.

3.1.2. Additional data

FAST4WARD study conducted in patients with RA following failure of classical DMARD treatments (unapproved dosage)

Characteristics of the patients included:
The mean age was 53.8, and the average duration of the RA was 8.7 years in the CZP 400 mg group and 10.4 years in the placebo group. The patients had moderate-to-severe rheumatoid arthritis with an average of 29 tender joints and 20.5 swollen joints.

The results were analysed on an ITT basis (cf. Table 7).

Table 7. Proportion of patients who achieved an ACR 20 response at 24 weeks in the FAST4WARD study (primary endpoint).

	Pbo	CZP 400 mg /4 weeks
Responders (%)	10/108 (9.3%)	50/110 (45.5%)
p vs. Pbo		<0.001

CZP: certolizumab pegol, Pbo: placebo

A statistically significant difference ($p < 0.001$) was identified in favour of the group treated with CZP 400 mg compared with the group treated with placebo in terms of the ACR 20 responder rate at 24 weeks.

The percentage of treatment discontinuations was high, notably in the placebo group. The primary reasons for treatment discontinuation were poor efficacy and the occurrence of adverse effects (cf. Table 8).

Table 8. Results for primary discontinuations of treatment (FAST4WARD)

	Pbo N = 109	CZP 400 mg N = 111	Total N = 220
Discontinuations of treatment n (%)	81 (74.3)	35 (31.5)	116 (52.7)
Main reasons for discontinuation of treatment			
Poor efficacy n (%)	75 (68.8)	24 (21.6)	99 (45)
Adverse effect n (%)	2 (1.8)	5 (4.5)	7 (3.2)

CZP : certolizumab pegol, MTX : methotrexate, Pbo : placebo

The CHMP[7] considered the results of this study to be clinically relevant and granted CIMZIA the indication in monotherapy. However, in view of the higher proportions of ACR 20 responders among the patients treated with CZP in combination with MTX and the high proportion of auto-antibodies developed in patients treated with CZP as monotherapy, combination with MTX is recommended as first-line therapy.

An open-label extension phase is in progress.

[7] EMA/664021/2009. Assessment report for Cimzia. EPAR

Comparative data versus other TNF-α inhibitors

No study has compared CZP with the other TNF-α inhibitors available in the treatment of RA, notably adalimumab, etanercept or infliximab. The pharmaceutical company proposed a meta-analysis[8] comparing CZP indirectly with these medicinal products. The objective was to demonstrate the non-inferiority of CZP compared with the other TNF-α inhibitors in terms of efficacy. However, this meta-analysis is associated with methodological limitations which make it difficult to interpret the results. In particular:

- the procedure for selecting articles (criteria, expert) is not sufficiently precise
- an analysis based on per protocol data would have been more useful

3.2. Adverse effects

The analysis of the tolerance of CIMZIA (certolizumab pegol –CZP) took into account the data from controlled clinical studies and extension phases as well as pharmacovigilance data (temporary authorisations for use by a named patient (ATU nominatives) in France and PSURs from Switzerland and the USA).

3.2.1. Adverse effects in clinical trials

CIMZIA has been studied in 2,367 patients with rheumatoid arthritis in controlled and open-label clinical studies (extension phases) over a maximum duration of 57 months. Discontinuations of treatment because of adverse events were reported in 5% of patients treated with CZP and in 2.5% of patients who received a placebo. The most frequently observed adverse effects were infections, with a frequency of 15.5% with CZP and 7.6% with placebo, and "general disorders and administration site conditions", with a frequency of 10% with CZP and 9.7% with placebo.

Deaths

Overall, 32 deaths were reported with CZP and 1 with placebo: 10 in the controlled studies (9 with CZP and 1 with placebo) and 23 in the open-label phases. Most of these deaths were of cardiac (19 cases) or infectious (6 cases) origin.

Infections

The incidence of infections was higher with CZP (0.91 per patient-year) than with placebo (0.72 per patient-year). The infections were mainly in the upper and lower respiratory tract infections, herpes infections and urinary tract infections. The incidence of serious infections was higher with CZP (0.06 per patient-year) than with placebo (0.02 per patient-year). The serious infections included tuberculosis (CZP: 0.5% compared with placebo: 0%) and opportunistic invasive infections (herpes zoster, pneumocystis pneumonia, etc.).

Injection site reactions

In clinical studies, 6.4% of patients treated with CZP and 6.5% of patients treated with placebo experienced reactions at the injection site (redness, itching, haematoma, pain, swelling or bruising). Pain at the injection site was observed in 1.5% of patients treated with CZP, but in no case necessitated discontinuation of treatment.

Cancer

According to the SPC, 30 cases of cancer have been observed in patients treated with CZP, not counting non-melanoma skin cancers, including 3 cases of lymphoma. The incidence of lymphoma was 0.07 per 100 patient-years and that of melanoma 0.02 per 100 patient-years.
Despite the limitations of indirect comparisons, the estimated risk of cancer for CZP does not appear to be higher than the risk estimated on the basis of the available data for the other TNF-α inhibitors.

[8] Not published, performed by the REES (réseau d'évaluation en économie de la santé).

Immunogenicity

According to the SPC, "the overall percentage of patients with antibodies to CIMZIA detectable on at least 1 occasion was 7.7% in the Phase III RA placebo-controlled trials. Approximately one-third of antibody-positive patients (2.6% of the total population) had antibodies with neutralising activity *in vitro*. Patients treated with concomitant immunosuppressants (MTX) had a lower rate of antibody development than patients not taking immunosuppressants at baseline. Antibody formation was associated with lowered drug plasma concentration and in some patients, reduced efficacy."

Cardiovascular adverse events

In clinical studies, 61 patients treated with CZP (3.4%) and 13 patients in the placebo group (2%) experienced a cardiovascular adverse event. The percentage of patients with arterial hypertension was higher in the CZP group (5.1%) than in the placebo group (1.2%). However, no difference was identified between the CZP and placebo groups in terms of variations in arterial blood pressure compared with the baseline values. A serious cardiovascular adverse event (ischaemic coronary artery disorders, arrhythmia) was reported in 16 patients treated with CZP (0.9%) and 3 patients in the placebo group (0.5%). Congestive heart failure was reported in 10 patients treated with CZP. Like other TNF-α inhibitors, CZP is contraindicated in cases of moderate-to-severe heart failure.

3.2.2. Data derived from temporary authorisations for use by a named patient (ATU nominatives) in France

Between 5 May 2006 (date on which the first temporary authorisation for use by a named patient (ATU nominative) was granted) and 4 May 2009, 123 patients received at least one injection of CZP under the terms of temporary authorisations for use by a named patient (ATU nominatives) in the indication of Crohn's disease (following failure or poor tolerability of treatment with infliximab and adalimumab).

Overall, 9 pharmacovigilance cases, including 5 serious cases, have been reported. In 6 out of 9 cases, the adverse effects resulted in definitive discontinuation of treatment. No deaths have been reported. The adverse effects reported were cardiovascular (1 case of heart failure with renal impairment), infectious (1 case of pneumonia, 1 case of herpes zoster) and cutaneous (1 case of urticaria, 1 exacerbation of a psoriasis-like rash). Symptoms evocative of serum sickness were also reported in 2 cases. Furthermore, 2 cases of pregnancy exposed to CZP have been reported (normal outcome). CZP is not recommended during pregnancy.

3.2.3. Data derived from PSURs (Switzerland and USA)

According to the accumulated data from the two half-yearly PSURs available covering the period from 7 September 2007 to 6 September 2008, the post-marketing exposure was 1,976 patients. Overall, 55 cases were reported by healthcare professionals, including 5 serious cases, in the USA:

- 1 case of episcleritis, closed angle glaucoma and herpes zoster
- 1 case of gastrointestinal haemorrhage
- 1 case of absence seizures, joint pains and flu-like syndrome
- 1 case of generalized seizures and
- 1 case of nausea, vomiting, diarrhoea, abdominal distension and suspected intestinal ileus

3.2.4. Conclusion regarding safety data

Overall, the safety of CIMZIA does not appear to differ from that of the other TNF-α inhibitors currently available, although the long-term data are still limited with CZP. Like other medicinal products in this category, CIMZIA is subject to a risk management plan which provides for the monitoring of identified and potential risks, notably of infection and carcinogenicity.

3.3. Conclusion

The efficacy of CIMZIA in combination with MTX in the treatment of rheumatoid arthritis was demonstrated in two controlled clinical studies (RAPID 1 and RAPID 2) in a total of 1,601 patients who had responded inadequately to or did not tolerate MTX (dose > 10 mg/week). The ACR 20 response rate at 24 weeks (primary endpoint) was higher in the group treated with CIMZIA at a dosage of 400 mg at Weeks 0, 2, 4 followed by 200 mg every 2 weeks in combination with MTX than in the group treated with placebo + MTX:

- 58.8% with CIMZIA + MTX and 13.6% with placebo + MTX, $p < 0.001$ in the RAPID 1 study
- 57.3% with CIMZIA + MTX and 8.7% with placebo + MTX, $p<0.001$ in the RAPID 2 study

The progression of structural damage, assessed by the Van der Heijde-modified total Sharp score (mTSS) at 52 weeks (co-primary endpoint in the RAPID 1 study) was significantly lower in the group treated with CIMZIA (0.4 points) than in the group treated with placebo (2.8 points), $p < 0.001$.

An open-label extension phase of the RAPID 1 study over a period of 2 years demonstrated maintenance of the efficacy of CIMZIA in 449 patients.

In one clinical study (FAST4WARD), CIMZIA as monotherapy was superior to placebo in patients who had responded inadequately to or did not tolerate MTX. The ACR 20 response rate at 24 weeks was 45.5% with CIMZIA and 9.3% with placebo, $p < 0.001$. However, the CIMZIA dosage used (400 mg every 4 weeks) does not correspond to the dosage recommended in the Marketing Authorisation.

No study is available comparing CIMZIA with the other TNF-α inhibitors available. An indirect meta-analysis suggesting the non-inferiority of CZP compared with other TNF-α inhibitors was supplied by the pharmaceutical company. However, it contains methodological limitations which make it difficult to interpret its results.

The adverse events most frequently observed in clinical studies were infections and "general disorders and administration site conditions". The tolerance of CIMZIA does not appear to differ from that of the other TNF-α inhibitors currently available, although the long-term data are still limited. This medicinal product is subject to a risk management plan which incorporates notably monitoring of the infection and carcinogenic risk.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Rheumatoid arthritis is a serious and debilitating chronic disease.
CIMZIA is a curative treatment.
This medicinal product is a second-line therapy. Its role in the management of RA in patients who did not respond to or did not tolerate DMARDs, including methotrexate, is significant.
Its efficacy/adverse effects ratio is high.

Public health benefit

The burden represented by rheumatoid arthritis, a serious and debilitating chronic disease, is substantial. The burden represented by the subpopulation likely to benefit from the treatment is moderate.

Improving the management of patients with rheumatoid arthritis and their quality of life remains a public health need which comes within the scope of the established priorities (Public Health Law 2004, Plan for improving the quality of life of patients with chronic diseases), despite the existence of available therapeutic agents.
The medicinal product CIMZIA should contribute in the same way as the other TNF-α inhibitors to covering this identified need.
In the light of the available clinical data, it is not expected that there will be an additional impact on patients morbidity and quality of life.
Consequently, in view of the other therapeutic agents available, it is not expected that the medicinal product CIMZIA will provide public health in this indication.

Alternative medicinal products exist.

The actual benefit of CIMZIA is substantial.

4.2. Improvement in actual benefit (IAB)

In adult patients with moderate-to-severe active RA who have not responded adequately to or have not tolerated previous treatment with one or more classical DMARDs, including MTX used at the maximum tolerated dose, CIMZIA provides no improvement in actual benefit (level V) compared with other TNF-α inhibitors (ENBREL, HUMIRA and REMICADE) in the management of this condition.

4.3. Therapeutic use

The current management of rheumatoid arthritis consists of prescribing fast-acting anti-inflammatory agents (NSAIDs, corticosteroids) and a DMARD in order to bring about clinical and biochemical remission.
Methotrexate is the reference classical DMARD for rheumatoid arthritis. The maximum tolerated dose is 25 mg/week but must be adapted to the clinical context and to the treatment tolerance
Where the response is inadequate or methotrexate is contra-indicated, the following options are available depending on the clinical and biochemical presentation of the disease and the physiopathological setting:
- a different classical DMARD as monotherapy or
- a combination of classical DMARDs or
- a TNF-α inhibitor

TNF-α inhibitors such as etanercept and adalimumab are used alone or in combination with methotrexate in cases of inadequate response or where DMARDs, including methotrexate, have been poorly tolerated. Infliximab must be used in combination with a DMARD, particularly methotrexate. According to the 2007 HAS recommendations, TNF-α inhibitors may be used as a first-line therapy in certain active and severe forms of rheumatoid arthritis.

According to the experts, however, around 30% of patients have an inadequate or insufficient response to TNF-α inhibitors after 2 years.

In the event of failure of treatment with TNF-α inhibitors, the possible alternatives are:
- recourse to a different TNF-α inhibitor
- recourse to one of the three "third-line" biological agents available: rituximab (monoclonal antibody directed against B cells), abatacept (T-cell costimulation inhibitor), tocilizumab (monoclonal antibody directed against interleukin-6). Tocilizumab is also indicated as a second-line therapy, i.e. following failure of classical DMARDs, including MTX.

Therapeutic use of CIMZIA
CIMZIA constitutes an alternative to the other TNF-α inhibitors available in the management of RA. In combination with MTX, it may be used in cases of inadequate response to classical DMARDs, including MTX. It may also be used as monotherapy if MTX is poorly tolerated or when continuation of treatment with MTX is inappropriate. No study has compared it with other TNF-α inhibitors. No data are available evaluating its efficacy in patients who have failed to respond to one of the three TNF-α inhibitors: adalimumab, etanercept, infliximab.

4.4. Target population

The prevalence of rheumatoid arthritis in France can be estimated on the basis of the 2001 Guillemin and Saraux study[9] at 0.31% in the population aged over 18.
If this figure is applied to the INSEE 2009 data (48,750,000), the population with RA in France can be estimated at 151,000 patients.
Moreover, based on the CNAMTS[10] data relating to the number of people with RA classified as a long-term illness ("affection de longue durée"), after adjustment, the population of patients with serious progressive RA in 2009 can be estimated at around 200,000 patients.

Indeed, according to the CNAMTS data, the number of people with serious progressive RA classified as a long-term illness was 150,032 in 2007, and an increase of 6.2% was observed between 2005 and 2006 and 6.8% between 2006 and 2007. Assuming that the number of people with RA classified as a long-term illness continues to grow at a rate of 6% per year, the number of people with serious RA classified as a long-term illness in 2009 will be around 168,576.

Taking into consideration the fact that the CNAMTS data cover 88% of the French population, the number of people with serious progressive rheumatoid arthritis in France in 2009 can be estimated at 191,000.

According to expert opinion, 45% to 60% of these patients are currently treated with methotrexate. Treatment escape is observed in 18% of patients treated with methotrexate (expert opinion), i.e. a population of between 16,000 and 20,000 patients.

[9] Guillemin F, Saraux A. et al. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis 2005; 64 : 1427-1430.
[10] Points de repère n°20 - November 2008 – people wit h a long-term illness on 31 December 2007

Starting from the principle that MTX is the reference classical DMARD, it can be estimated that the population with RA which has failed to respond to at least one classical DMARD and which is liable to be treated with CIMZIA is at most between 16,000 and 20,000 patients.

4.5. Transparency Commission recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

4.5.3. Exception medicinal product:

The Committee recommends granting CIMZIA "exception medicinal product" status.

4.5.4. Request for post-marketing surveillance study:

At the request of the General Directorate of Health, the Transparency Committee wishes a long-term follow-up study to be conducted for CIMZIA® in patients under treatment for rheumatoid arthritis, the objectives of which should be:

- to describe the prescription details (dosage, combination with methotrexate and other co-prescriptions, etc.), the patients treated (socio-demographic data, disease history and severity, disability and invalidity, previous medical history, comorbidities, etc.)
- to evaluate the impact of treatment on the health of the population concerned in terms of morbidity and mortality (notably disease and disability progression, patient quality of life, monitoring of the onset of resistance to treatment, the occurrence of long-term adverse events, etc.)
- to describe the therapeutic use (failures of previous treatments, including MTX or other TNF-α inhibitors with the reasons for discontinuation, recourse to other biological therapies, etc.) and the use of health care and services

The duration of the study should be justified by an independent scientific committee.
Should it not be possible for the studies which are planned or in progress, notably within the scope of the European Risk Management Plan, to answer all the questions posed by the Transparency Committee, a specific study will have to be conducted.