HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

1 October 2014

CIMZIA 200 mg, solution for subcutaneous injection[1]

B/2 × 1 ml prefilled syringes with needle guard and alcohol wipe
(CIP: 34009 275 765 8.4)

CIMZIA 200 mg, solution for subcutaneous injection[2]

B/2 × 1 ml glass prefilled syringes with alcohol wipes
(CIP: 34009 397 320 0.8)

Applicant: UCB PHARMA SA

INN	Certolizumab pegol
ATC Code (2012)	L02BG05 (TNF inhibitors)
Reason for the request	**Extension of indication**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) for the glass syringes only (CIP: 34009 397 320 0.8) **Hospital use** (French Public Health Code L.5123-2) for both presentations
Indication concerned	"CIMZIA, in combination with methotrexate (MTX), is indicated for the treatment of **active psoriatic arthritis in adults** when the response to previous DMARD therapy has been inadequate. CIMZIA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate."

[1] Application for inclusion only for hospital use
[2] Application for inclusion for National Health Insurance and hospital use

Actual Benefit	**Moderate in view of the low level of evidence demonstrating its structural effect in the treatment of psoriatic arthritis.**
Improvement in Actual Benefit	**CIMZIA does not provide any improvement in actual benefit (IAB V, non-existent) over other TNF inhibitors in the treatment of active psoriatic arthritis in individuals who do not respond to treatment with disease-modifying antirheumatic drugs (DMARDs).**
Therapeutic use	**CIMZIA is an alternative to other TNF inhibitors in the treatment strategy for psoriatic arthritis.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	01/10/2009: MA in rheumatoid arthritis 25/11/2013: Extension of the indication to psoriatic arthritis
Prescribing and dispensing conditions /special status	List I Medicine for initial annual hospital prescription Initial and repeat prescription reserved for specialists in rheumatology and internal medicine Exception drug status

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AB	Tumour necrosis factor alpha (TNF-α) inhibitors
	L04AB05	Certolizumab pegol

02 BACKGROUND

CIMZIA (certolizumab pegol) is a TNF inhibitor included in the list of proprietary medicinal products refundable in pharmacies and approved for hospital use since August 2010 in rheumatoid arthritis.

The purpose of this assessment is to review the application for extension of reimbursement to psoriatic arthritis (indication of the Marketing Authorisation granted in November 2013).

The application relating to its reimbursement in axial spondyloarthritis was reviewed in another Opinion (Opinion of 23 July 2014).

03 THERAPEUTIC INDICATIONS

Indication that is the subject of the application:
"CIMZIA, in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis when the response to previous DMARD therapy[3] has been inadequate. CIMZIA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate."

Other indications not related to the application:

Rheumatoid arthritis

[3] The term "disease-modifying antirheumatic drug" (DMARD) refers, in the context of the wording of this indication, to the standard basic treatments (methotrexate, leflunomide, sulfasalazine, ciclosporin). Source: EPAR.

"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) 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."

Axial spondyloarthritis[4]
CIMZIA is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

Ankylosing spondylitis (AS),
Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Axial spondyloarthritis without radiographic evidence of AS
Adults with severe active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs."

04 DOSAGE

"Loading dose
The recommended starting dose of **CIMZIA for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4.** For rheumatoid arthritis and psoriatic arthritis, MTX should be continued during treatment with CIMZIA where appropriate.

Maintenance dose
Psoriatic arthritis
After the starting dose, **the recommended maintenance dose of CIMZIA for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered.**
MTX should be continued during treatment with CIMZIA where appropriate.
The 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."

05 THERAPEUTIC NEED

The management of psoriatic arthritis (PsA) is the same as for all chronic forms of inflammatory arthritis: a combination of symptomatic treatment (NSAID with or without analgesics) and a DMARD.
French guidelines on the management of PsA drawn up by the French Society for Rheumatology (SFR) were published in 2007[5] and subsequently updated in 2013.[6]

[4] This indication was the subject of a separate assessment in a separate application submitted by the applicant.
[5] Pham T et al. Recommendations of the French Society for Rheumatology regarding TNFα antagonist therapy in patients with ankylosing spondylitis or psoriatic arthritis: 2007. Joint Bone Spine 2007; 74: 638-46.
[6] Wendling D, et al. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis, Joint Bone Spine 2014; 81:6-14

According to these guidelines, the objective of treatment must be clinical remission or at least a low level of activity, taking into account the various aspects of the disease (axial, peripheral and extra-articular manifestations) and comorbidities.

NSAIDs, if they are not contraindicated, are the first-line symptomatic treatment. Local injections of corticosteroids at affected sites (particularly in arthritis and enthesitis) can be considered. Systemic corticosteroid treatment is not justified in the majority of cases for the treatment of axial manifestations, but may be considered in cases with inadequate control of peripheral articular manifestations where the treatment alternatives are ineffective or not possible (due e.g. to TNF inhibitors being contraindicated) and in certain specific situations (e.g. relapse associated with enteropathic arthropathies).

In peripheral arthritis that does not respond to symptomatic treatment, the standard DMARDs – methotrexate, leflunomide and sulfasalazine (off-label use) – may be considered. However, these treatments are not currently indicated in isolated axial or entheseal manifestations.

TNF inhibitors must be offered to patients in whom disease activity persists despite standard treatment. The TNF inhibitors with Marketing Authorisation in the treatment of psoriatic arthritis are adalimumab, etanercept, infliximab, golimumab and, now, certolizumab pegol. These are active against axial and peripheral forms.
If there is a primary or secondary lack of efficacy or poor tolerability to an initial TNF inhibitor, a switch to a second TNF inhibitor may be beneficial.

Another biologic, STELARA (ustekinumab), which is not a TNF-inhibitor but an inhibitor of IL-12 and IL-23, was granted Marketing Authorisation in this indication in September 2013 in patients showing inadequate response to non-biologic DMARD therapy and is currently being assessed by the Committee in this extension of the indication.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators are the other TNF inhibitors indicated in the treatment of PsA:

- administered subcutaneously: HUMIRA (adalimumab), ENBREL (etanercept), SIMPONI (golimumab)
- administered intravenously: REMICADE (infliximab)

They are all reimbursed and have a substantial AB (see Table 1 below).

Note:
A non-TNF-inhibitor biologic, STELARA (ustekinumab), was granted Marketing Authorisation in September 2013 in the indication: alone or in combination with MTX in active PsA in adult patients when the response to treatment with non-biologic disease-modifying antirheumatic drugs has been inadequate. This proprietary medicinal product is currently being assessed by the Committee in this indication.

Name (INN)	Company	Indication[7]	Date of TC Opinion (reason)	AB	IAB
ENBREL (etanercept)	PFIZER	"Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. ENBREL has been shown to improve physical function in patients with psoriatic arthritis, and to **reduce the rate of progression of peripheral joint damage** as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease."	29 October 2003 (inclusion in PsA)	Substantial	"ENBREL provides a substantial IAB (level II) over MTX in patients with severe, progressive, refractory peripheral PsA who do not respond adequately to this product or are unable to tolerate it. This IAB does not apply to patients with exclusively axial arthritis."
HUMIRA (adalimumab)	ABBVIE	HUMIRA is indicated for the treatment of active, progressive psoriatic arthritis in adults previously responding inadequately to disease-modifying antirheumatic drugs. HUMIRA has been shown to **reduce the rate of progression of peripheral joint damage** as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve functional capacity.	2 November 2005 (inclusion in PsA)	Substantial	"HUMIRA provides the same substantial IAB (level II) as ENBREL in patients with active and progressive PsA when the response to previous DMARD therapy has been inadequate."

[7] This indication corresponds to the current wording of the indication of these proprietary medicinal products. It should be noted that the initial Marketing Authorisations for ENBREL, HUMIRA, REMICADE and SIMPONI, which lack sufficient data, do not mention demonstration of the structural effect (shown in bold). This was added when the additional data were submitted. The initial assessment of ENBREL, HUMIRA and REMICADE by the Transparency Committee took place before inclusion of reference to this. However, the inclusion of SIMPONI was recommended on the basis of the current wording, which includes demonstration of the structural effect.

REMICADE (infliximab)	MSD France	REMICADE is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. REMICADE should be administered: in combination with methotrexate: or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated. REMICADE has been shown to improve physical function in patients with psoriatic arthritis, and to **reduce the rate of progression of peripheral arthritis as measured by X-ray** in patients with polyarticular symmetrical subtypes of the disease	26/04/2006 (inclusion in PsA)	Substantial	"In combination with MTX, REMICADE provides the same substantial IAB (level II) as other TNF inhibitors in patients with active and progressive PsA when the response to previous DMARD therapy has been inadequate." However, the Committee regrets the absence of a direct comparison versus other TNF inhibitors and versus MTX."
SIMPONI (golimumab)	MSD France	SIMPONI, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. SIMPONI has been shown to **reduce the rate of progression of peripheral joint destruction as measured by X-ray** in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.	01/02/2012 (inclusion)	Substantial	"The proprietary medicinal product SIMPONI does not provide any IAB (level V) over other TNF inhibitors in the treatment of patients with PsA."

06.2 Other health technologies

N/A

Conclusion

The comparators listed are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

At the time of writing this document, the proprietary medicinal product CIMZIA was reimbursed in the extension of indication to PsA in seven EU countries (Germany, Greece, Norway, the Netherlands, United Kingdom, Sweden and Denmark). CIMZIA has Marketing Authorisation in the USA in PsA.
There is no available NICE assessment for CIMZIA in the treatment of psoriatic arthritis.

08 ANALYSIS OF AVAILABLE DATA

Just one clinical study versus placebo has been submitted by the company in this extension of indication.

08.1 Efficacy

The efficacy of subcutaneous certolizumab pegol (CZP, CIMZIA) in the treatment of psoriatic arthritis (PsA) is based on the results of one placebo-controlled phase III study (PsA001). The controlled phase of this study was carried out between 2 March 2010 and 3 November 2011; the open phase is due to be completed in 2015. Comparison with another TNF inhibitor was possible during this period.

The last TNF inhibitor included in PsA, SIMPONI (Opinion of February 2012 and Marketing Authorisation of 1 October 2009), had a similar dossier: one study versus placebo.

Study PsA001 (RAPID-PsA)[8]
The principal objective of this study was to evaluate the safety and efficacy of CZP on the signs and symptoms of adult patients with active PsA and on inhibition of the progression of structural damage.
Two CZP maintenance regimens were evaluated: 200 mg every 2 weeks and 400 mg every 4 weeks.
The study consisted of five phases:
- a 1-5 week selection phase prior to inclusion;
- a randomised, double-blind, placebo-controlled phase from inclusion until week 24;
- a single-blind phase with no placebo group for the CZP dosage regimen from week 24 to week 48;
- an open phase between week 48 and week 216 and
- a safety evaluation phase between week 216 and week 224.

The open phase is currently underway and is due to be completed in June 2015.

Inclusion criteria
Included were adult patients:
- with active PsA for more than 6 months based on the CASPAR (Classification Criteria for Psoriatic Arthritis)[9] criteria. This classification is summarised in Appendix 1.
- with active rheumatoid arthritis (defined as a tender joint count ≥ 3 and swollen joint count ≥ 3 and at least one of the following two criteria: erythrocyte sedimentation rate ≥ 28 mm/h or CRP > upper limit of normal),

[8] Mease et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis 2014; 73: 48-55
[9] Taylor W, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006; 54:2665-2673

- with skin lesions due to active psoriasis or a documented history of psoriasis;
- who had failed to respond to at least one DMARD (biologic or non-biologic). The protocol allowed for the inclusion of between 30 and 70% of patients treated concomitantly with standard DMARDs and a maximum of 40% of patients who had already been treated with a TNF inhibitor.

Non-inclusion criteria

Not included were patients:

- who had already been treated with more than one TNF inhibitor for PsA or in primary failure to treatment with a TNF inhibitor,
- with a different inflammatory arthritis or with a known diagnosis of fibromyalgia,
- with active infections, history of chronic or recurrent infections, at higher risk of infections or who had recently been vaccinated.

Treatments

In the 24-week double-blind phase, patients were randomised to one of the following three groups:

- placebo;
- CZP 200 mg every 2 weeks, with patients receiving initial doses of 400 mg CZP at weeks 0, 2 and 4 and then maintenance doses of 200 mg CZP every 2 weeks;
- CZP 400 mg every 4 weeks, with patients receiving initial doses of 400 mg CZP at weeks 0, 2 and 4 and then 400 mg every 4 weeks.

Randomisation was stratified according to site, investigator and previous exposure to a TNF inhibitor.

Some concomitant treatments were allowed:

- patients being treated on inclusion with methotrexate (maximum dose 25 mg/week), leflunomide (maximum dose 20 mg/day) or sulfasalazine (maximum dose 3 g/day) were allowed to continue their treatment with no change in dose or dosage regimen during the first 48 weeks of the study (except in the event of poor tolerability);
- NSAIDs (if the dose was stable 2 weeks before inclusion), analgesics (paracetamol, opioids) and oral corticosteroids at a dosage ≤ 10 mg/day of prednisolone equivalent were allowed,
- phototherapy and topical agents could be used only after the first 48 weeks of the study.

At week 16, the protocol specified that patients in the placebo group who did not achieve a minimum 10% improvement since baseline in TJC and SJC at weeks 14 and 16 were to undergo rescue treatment. These patients were randomised again at week 16 to one of the two CZP groups and received initial doses of 400 mg CZP at weeks 16, 18 and 20 and then a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks.

At week 24, the end of the double-blind phase versus placebo, the patients who had remained in the placebo group throughout were randomised to one of the two CZP groups and received initial doses of 400 mg CZP at weeks 16, 18 and 20 and then a maintenance dose of 200 mg CZP every 2 weeks or 400 mg every 4 weeks. The patients initially randomised to one of the two CZP groups continued to be treated according to the same dosage regimen up to week 216.

Primary efficacy endpoints:

Two co-primary endpoints were defined and were as follows:

- proportion of patients achieving an ACR20 response[10] at week 12,
- change since baseline in mTSS radiological score[11] at week 24.

The secondary endpoints included:

- proportion of patients achieving an ACR20 response at week 24,
- change since baseline in HAQ-DI functional index[12] at week 24,
- proportion of patients showing a PASI75 response[13] at week 24 in the subgroup of patients with psoriasis covering > 3% of body surface area at inclusion,
- change since baseline in mTSS radiological score at week 48.

Calculation of the number of subjects required

The number of subjects required was calculated on the basis of the co-primary efficacy endpoints. Based on published data for other TNF inhibitors, a figure of 130 patients in each treatment group seemed sufficient to demonstrate:

- a difference of 25% in the proportion of patients achieving an ACR20 response at week 12 (response rate of 40% for the CZP groups and 15% for the placebo groups) with a power of 99% for each of the treatment groups versus placebo and
- a difference of 1 ± 2.4 in mean change since baseline in mTSS between the pooled CZP data and the placebo group.

Statistical analyses

A hierarchical analysis with a predefined order of performance of the tests for the endpoints was employed owing to the large number of analyses.

This predefined order was:

1. Patients achieving an ACR20 response at week 12 for CZP 200 mg/2 weeks*
2. Patients achieving an ACR20 response at week 12 for CZP 400 mg/4 weeks*
3. Patients achieving an ACR20 response at week 24 for CZP 200 mg/2 weeks
4. Patients achieving an ACR20 response at week 24 for CZP 400 mg/4 weeks
5. Change since baseline in HAQ-DI functional index at week 24 for the pooled CZP 200 mg/ 2 weeks and CZP 400 mg/4 weeks data
6. Change since baseline in mTSS score at week 24 for the pooled CZP 200 mg/2 weeks and CZP 400 mg/4 weeks data*

[10] ACR (American College of Rheumatology): This score permits evaluation of a patient's response to treatment. It takes account of the tender joint count, number of joints with synovitis, patient's evaluation of pain, patient's and physician's global evaluation, physical disability and laboratory inflammation markers. An ACR20 response equates to a 20% improvement in the swollen/tender joint score and a 20% improvement in at least three of the following parameters:

- ESR or CRP (C-reactive protein)
- disease activity evaluated by the patient using a VAS
- disease activity evaluated by the physician using a VAS
- pain evaluated using a VAS
- disability index

[11] The radiological total Sharp score modified by Van der Heijde (mTSS) evaluates structural damage caused by the disease. It allows quantification of erosion and joint-space narrowing of the hands and feet for 64 and 52 joints respectively. It was modified for the purposes of this study to include the distal interphalangeal joints. The maximal possible score is 320 for erosion and 208 for joint-space narrowing.

[12] The HAQ-DI (Health Assessment Questionnaire – Disability Index) functional index permits evaluation of the patient's physical functional impairment. It is a self-questionnaire on a scale from 0 to 3. The minimum clinically relevant difference for PsA is 0.3.

[13] The PASI (Psoriasis Area Severity Index) is a composite score of psoriasis activity. It is a measure of erythema, induration, desquamation and affected body surface area on a scale from 0 (no psoriasis) to 72 (maximum severity). A PASI 75 response of demonstrates a decrease of at least 75% in the initial PASI score.

7. Percentage of patients who were PASI 75 responders at week 24 in the subgroup of patients with psoriasis covering ≥ 3% of BSA at inclusion for the pooled CZP 200 mg/2 weeks and CZP 400 mg/4 weeks data
8. Change since baseline in mTSS score at week 48 for the pooled CZP 200 mg/2 weeks and CZP 400 mg/4 weeks data

* analyses for the primary endpoints

If the first test was statistically significant, the second hypothesis could be tested with the same uncertainty α = 0.05 versus placebo, and so forth until statistical significance was not reached for an endpoint on the list.

The analyses of the efficacy endpoints were performed in the ITT population, on all patients who underwent randomisation.

Results:

- Demographic and clinical patient characteristics

A total of 409 patients underwent randomisation, 136 to the placebo group, 138 to the CZP 200 mg/2 weeks group and 135 to the CZP 400 mg/4 weeks group. At week 16, a total of 59 patients in the placebo group underwent randomisation a second time, 30 to the CZP 200 mg/ 2 weeks group and 29 to the CZP 400 mg/4 weeks group, until the end of the study.

The majority of patients included were women (55.3%) and the mean age was 47.6 ± 11.4 years. The mean disease duration since diagnosis was 8.5 ± 8.18 years, 61.6% of patients had psoriasis covering ≥ 3% of body surface area and 73.3% of patients had nail psoriasis. Over 60% of patients were being treated with MTX at the time of inclusion. Previous use of a TNF inhibitor was reported in 19.6% of patients, of whom 97.8% had already been treated with a standard non-biologic DMARD.

Table 1. Demographic and medical characteristics of patients in study PsA001

	Placebo n=136	CZP 200 mg/2 weeks n=138	CZP 400 mg/4 weeks n=135
Age [years], mean (SD)	47.3 (11.1)	48.2 (12.3)	47.1 (10.8)
Women, n [%]	79 (58.1)	74 (53.6)	73 (54.1)
Disease duration since diagnosis, [years], mean (SD)	7.9 (7.7)	9.6 (8.5)	8.1 (8.3)
TJC, mean (SD)	19.9 (14.7)	21.5 (15.3)	19.6 (14.8)
SJC, mean (SD)	10.4 (7.6)	11.0 (8.8)	10.5 (7.5)
HAQ-DI, mean (SD)	1.3 (0.7)	1.3 (0.7)	1.29 (0.6)
CRP [mg/l], median (min; max)	9.00 (0.2; 131.0)	7.00 (0.2; 238.0)	8.70 (0.1; 87.0)
ESR [mm/h], median (min; max)	34.0 (6; 125)	35.0 (5; 125)	33.0 (4; 120)
Patient's evaluation of pain VAS, mm (SD)	60.0 (22.0)	59.7 (20.7)	61.1 (18.5)
Patient's global evaluation of disease activity VAS, mm (SD)	57.0 (22.4)	60.2 (21.0)	60.2 (18.4)
Physician's global evaluation of disease activity VAS, mm (SD)	58.7 (18.7)	56.8 (18.2)	58.2 (18.9)
Enthesitis, n [%]	91 (66.9)	88 (63.8)	84 (62.2)
Dactylitis, n [%]	45 (33.1)	47 (34.1)	47 (34.8)

BASDAI score ≥ 4 (suspected axial involvement), n [%]	114 (83.8)	119 (86.2)	114 (84.4)
mTSS, mean* (SD)	24.4 (49.7)	18.0 (30.6)	23.2 (46.5)
Psoriasis ≥ 3% body surface area, n [%]	86 (63.2)	90 (65.2)	76 (56.3)
PASI, median (min, max) [#]	7.1 (0.3; 55.2)	7.0 (0.6; 72.0)	8.1 (0.6; 51.8)
Nail psoriasis, n [%]	103 (75.7)	92 (66.7)	105 (77.8)
Previous exposure to a TNFα inhibitor, n [%]	26 (19.1)	31 (22.5)	23 (17.0)
Previous use of ≥ 1 non-biologic DMARD, n [%]	134 (98.5)	134 (97.1)	132 (97.8)
Previous use of NSAIDs	83.8%	81.9%	91.1%
Concomitant treatment Treatment with MTX at time of inclusion [%]	61.8%	63.8%	65.2%

TJC: Tender joint count; SJC: Swollen joint count; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; mTSS: Modified total Sharp score; SD: Standard deviation; MTX: Methotrexate
[#] PASI score for patients with BSA ≥ 3%. * Use of PsA with imputation *Source: EPAR*

- Treatment discontinuation:

Of the 409 patients who underwent randomisation, 40 patients (9.8%) discontinued treatment before week 24: 15 (11%) in the placebo group, 10 (7.2%) in the CZP 200 mg/2 weeks group and 15 (11.1%) in the CZP 400 mg/4 weeks group.
The principal reasons for stopping treatment were withdrawal of consent in 14/409 (3.4%) and occurrence of an adverse event in 13/409 (3.2%).

- Results for the co-primary endpoint ACR20 response

The main ITT analysis demonstrated a higher proportion of patients achieving an ACR20 response at week 12 (co-primary endpoint) for CZP 200 mg/2 weeks (58%) and CZP 400 mg**/**4 weeks (51.9%) than for placebo (24.3%), p<0.001.

- Results of the main analysis and additional analyses for the co-primary endpoint-radiographic response[14]

The main analysis specified in the protocol did not demonstrate any difference between CZP and placebo for the radiological co-primary endpoint. The mean change since baseline in radiological total Sharp score modified by Van der Heijde (mTSS) at week 24 for the pooled CZP 200 mg/ 2 weeks and CZP 400 mg/4 weeks data was 18.3 ± 6.07 versus 28.9 ± 7.73 for placebo, NS.

In this analysis, the method of imputation prespecified for patients with fewer than two available mTSS scores was to use the lowest value observed at inclusion (if the baseline value was missing, a value of 0 was used) and the highest observed value (if the value at week 24 was missing, a value of 356.5 was used).
In total, data were judged to be missing in 26 patients:

- In 21 patients (8 in the placebo group, 4 in the CZP 200 mg/2 weeks group and 9 in the CZP 400 mg/4 weeks group) there was no available X-ray or only one.
- 5 patients with two X-rays taken less than 8 weeks apart were judged to be missing radiographic data (1 patient in the placebo group, 1 patient in the CZP 200 mg/2 weeks group, 3 patients in the CZP 400 mg/4 weeks group).

Linear imputation was carried out to assign implausible progressions to some patients with missing values. Thus, for a patient who had shown an improvement of -1 at week 1, linear extrapolation would suggest that this patient had shown an improvement of -24 points in 24 weeks, which is not realistic. The lowest observed mTSS value at inclusion was 0 and the highest value at week

[14] Van der Heidje et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the rapid-PsA 24-week phase III double-blind randomized placebo-controlled study of certolizumab pegol. Ann Rheum Dis, 2014; 73, 233-237

24 was 356.5. This resulted in 4 patients with no mTSS being assigned a progression of 356.5. In addition, 16 patients who had only analysable mTSS scores on inclusion were assigned mTSS progressions varying from 287.5 to 356.5, whereas the majority of patients (for whom X-rays were available) showed no change in mTSS during the 24 weeks of the study.

Linear imputation thus led to implausible conclusions and overestimation of radiographic progression, as demonstrated by the results (changes of 11.5 for CZP 200 mg/2 weeks and 25.1 for CZP 400 mg/4 weeks versus 28.9 ± 7.73 for placebo). Such values were not observed in any of the other studies carried out with the comparators.

Taking account of these points, the CHMP has accepted the post-hoc analyses employing other methods of imputation that were carried out by the company and presented below.

In these post-hoc analyses, the median value for mTSS progression for the study population as a whole (0 in this case) was used as the mTSS score in the imputation of the missing data for patients with fewer than two available mTSS scores.
In patients for whom at least two X-rays taken at least 8 weeks apart were available, linear extrapolation or interpolation was carried out for the other missing data. This method was found to give more realistic results and was used in the golimumab study.[15]

In this post-hoc analysis (with imputation of the median change since baseline in the whole study population and specification of a minimum interval of 8 weeks between successive X-rays), the progression in structural damage in the CZP groups (pooled analysis) was lower than that observed in the placebo group (0.06 versus 0.28, i.e. a difference of -0.22 [-0.38; -0.06], p=0.007). In the group treated with CZP 200 mg every 2 weeks, the difference versus placebo was -0.27 [-0.5; -0.1], p=0.004. It should, however, be noted that even this analysis did not demonstrate a statistically significant difference between the CZP 400 mg/4 weeks group and placebo (0.11 versus 0.28, i.e. a difference of -0.17, NS).

In a predefined analysis carried out using the post-hoc method of imputation, the proportion of patients who were radiographic responders at week 24 was 83.3% for CZP 200 mg and 76.3% for CZP 400 mg, versus 34.6% for placebo (p<0.001 for the two comparisons).

- Results for certain secondary endpoints:

ACR20 response at week 24
The percentage of patients with an ACR20 response at week 24 was higher in the two CZP groups than for placebo: 63.8% for CZP 200 mg/2 weeks and 56.3% for CZP 400 mg**/**4 weeks, versus 23.5% for placebo, p<0.001.

PASI 75 response
This analysis was to be performed only if the result of the preceding analysis of the criterion mTSS at week 24 was significant. However, this was not done except in the post-hoc analysis. The analysis of the criterion PASI 75 at week 24 in the predefined analysis was therefore considered to be not significant.
A post-hoc analysis of PASI 75 at week 24 was carried out following the post-hoc analysis of the criterion mTSS at week 24: for the patients with psoriasis covering at least 3% of body surface area at inclusion, the percentage who were PASI 75 responders at week 24 was significantly higher (61.4%) in the CZP 200 mg and 400 mg groups (pooled analysis) than in the placebo group (15.1%), a statistically significant difference of 46.3% (95% CI: [35.7; 56.9]), p<0.001.

At 48 weeks, the percentage of patients who were PASI 75 responders was 67% in the CZP 200 mg/2 weeks group and 62% in the CZP 400 mg/4 weeks group.

[15] Kavanaugh A et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. Arthritis Rheum 2012; 64: 2504-2517.

HAQ-DI index
At week 24, the reduction in HAQ-DI functional index was greater (-0.5 points) in the CZP 200 mg and 400 mg groups (pooled analysis) than in the placebo group (-0.2 points), a statistically significant difference of -0.3 points, p<0.001.

mTSS at week 48
No statistically significant difference at week 48 was observed for this criterion between the CZP 200 mg/400 mg groups (pooled analysis) and placebo or between either of the two CZP groups individually and placebo (with the method of imputation used for the post-hoc analysis at week 24).
The mean change in mTSS since baseline was:

- -0.17 ± 0.14 between CZP 200 mg/2 weeks and placebo;
- -0.21 ± 0.14 between CZP 400 mg/4 weeks and placebo;
- -0.19 ± 0.12 between CZP 200 mg/400 mg (pooled analysis) and placebo.

In each of these comparisons, the difference was not statistically significant.

The data for the placebo group at week 48 were obtained by extrapolation from the two available examinations between week 12 and week 24, as the placebo group was terminated at week 24.
In a subgroup judged to be at high-risk of radiographic progression (patients with mTSS > 6 on inclusion), inhibition of radiographic progression versus placebo was statistically significant for CZP 200 mg and 400 mg (pooled analysis): -0.52 ± 0.26. p=0.048, but not for CZP 200 mg (-0.47 ± 0.30) or CZP 400 mg (-0.57 ± 0.30) individually. This result is exploratory, as this subgroup was not defined in the initial study protocol and the analysis on the whole population was inconclusive.

Sub-group analysis
A subgroup analysis was carried out in patients previously treated and not previously treated with a TNF inhibitor. Stratification on this criterion had been carried out at the time of randomisation. This analysis suggested that the percentage of patients achieving an ACR20 response in the CZP 200 mg and 400 mg groups (pooled analysis) was similar with (53.7%) or without (55.3%) prior treatment with a TNF inhibitor.

Two thirds of patients had been treated concomitantly with DMARDs. Although such treatment was not used as a basis for stratification, a subgroup analysis was carried out, which suggested that the proportion of patients achieving an ACR20 response was higher in patients treated concomitantly with DMARDs (absolute benefit versus placebo of 33.5% for the pooled CZP 200 mg/400 mg groups) than in those who had not been treated (absolute benefit versus placebo of 28.1% for the pooled CZP groups).
In the patients treated concomitantly with DMARDs, the percentage who were ACR20 responders was 57.8% for the pooled CZP groups (57.4% for CZP 200 mg, 58.2% for CZP 400 mg), versus 29.8% for placebo, p<0.001 for all comparisons.
In the patients who were not treated concomitantly with DMARDs, this was 48.9% for the pooled CZP groups (59.1% for CZP 200 mg, 38.6% for CZP 400 mg), versus 15.4% for placebo, a statistically significant difference with p<0.001 for the comparison pooled CZP groups and CZP 200 mg/2 weeks versus placebo and p=0.011 for the comparison CZP 400 mg versus placebo.

Comparison with an active treatment
There are no data comparing CZP with an active treatment in the management of PsA.

08.2 Safety/Adverse effects

- Clinical study data

During the 24-week comparative phase of the study versus placebo, 62.3% of patients treated with CZP (68.1% for CZP 200 mg/2 weeks and 71.1% for CZP 400 mg/4 weeks) and 67.6% of patients who had received placebo reported at least one adverse event (AE). The incidence of treatment-related AEs was 25.9% for the pooled CZP groups (28.3% for CZP 200 mg/2 weeks and 30.4% for CZP 400 mg/4 weeks) and 27.2% for placebo. The incidence of serious AEs was 6.6%

for the pooled CZP groups and 4.4% for placebo. The incidence of AEs resulting in discontinuation of treatment was 3% for the pooled CZP groups and 1.5% for placebo. Two deaths were reported in the CZP groups (1 in each group), but were not judged to be connected with the treatment.

The most commonly reported AEs during treatment with CZP were upper respiratory tract infections (7.8% vs. 5.1% for placebo), transaminase elevations (ALT: 3.6% vs. 1.5% and AST: 3.0% vs. 0.7%), headache (3.6% vs. 1.5%) and sinusitis (2.7% vs. 0.7%). The most common serious AEs were infections (1.2% in the CZP groups vs. 0.7% for placebo). Reactions at the injection site were reported in 1.8% of patients in the pooled CZP groups and 0.7% of patients in the placebo group.

One case of tumour (cervical carcinoma in situ) was reported in a 31-year-old woman in the CZP 400 mg every 4 weeks group. The event was judged to be unconnected with the treatment, but treatment was discontinued.
Four patients reported serious cardiovascular AEs: two in the CZP 200 mg/2 weeks group: (one case of acute myocardial infarction and one case of cardiac arrest) and two in the CZP 400 mg/4 weeks group (one case of angina and one case of stroke).

The total percentage of patients in whom anti-Cimzia antibodies were detected on at least one occasion up to week 24 was 11.7% in the phase III placebo-controlled study in patients with psoriatic arthritis. The development of antibodies was associated with a decrease in the plasma concentration of the drug. The number of patients developing anti-Cimzia antibodies in the course of this study was not sufficient enough to justify an assessment of the impact of antibody development on efficacy.

One case of lymphoma was observed during the phase III clinical study in psoriatic arthritis.

In summary, no new safety signals for CZP were detected in study PsA001.

PSUR data

The analysis of new safety data obtained through pharmacovigilance since Marketing Authorisation of CIMZIA has not brought to light any new information likely to change the assessment of its safety. However, some changes have been made to the SPC:
Section 4.4 “Special warnings and precautions for use”:

- The section “Hepatitis B virus reactivation” has been updated, as was the case for all TNF inhibitors, to recommend testing for HBV infection before initiating treatment with CIMZIA in all patients, not just in those at high risk of HBV infection, and to stress the importance of close monitoring and treatment by a physician with expertise in the treatment of carriers of HBV requiring treatment with CIMZIA.
- The section “Vaccination” has been updated to take account of the results of the clinical study carried out in accordance with the RMP, which had shown that vaccinations against pneumococcal infection and influenza were effective and well tolerated in rheumatoid arthritis patients treated with CZP. The recommendation not to administer attenuated vaccines during treatment with CIMZIA has accordingly been deleted.
- The section “Malignancies and lymphoproliferative disorders” has been updated with addition of the following risks: leukaemia and – in the paediatric population – other malignancies and in particular lymphomas, skin cancers, particularly melanomas and Merkel cell carcinomas, necessitating periodic skin examinations, particularly in patients with risk factors for skin cancer, and hepatosplenic T-cell lymphoma (a rare and very aggressive form of lymphoma typically occurring in adolescent and young adult males with Crohn’s disease or ulcerative colitis undergoing concomitant treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine).

Section 4.6 “Fertility, pregnancy and lactation”

- The section “Pregnancy” has been updated to include both the results of preclinical studies and clinical data indicating that CZP crosses the placental barrier in small amounts. Children

exposed to CZP in utero may therefore be at increased risk of infection and administration of live vaccines in this population is not recommended for a minimum of five months after the mother's last administered dose during pregnancy.

- The section "Fertility" has been updated to take account of the results of the clinical study carried out in accordance with the RMP, which had shown that treatment with CIMZIA had no observed effect on semen quality in healthy subjects compared with placebo.

Section 4.8 "Undesirable effects":

- The word "psoriasis" was replaced by "new onset or worsening of psoriasis (including palmoplantar pustular psoriasis)",
- The words "auditory neuropathy, trigeminal neuralgia" were replaced by "cranial nerve inflammation",
- The words "gastrointestinal fistula" were replaced by "fistula (any site)",
- The words "lymphoma and leukaemia" were replaced by "blood and lymphatic system malignancies (including lymphoma and leukaemia)",
- The following effects were added: anaphylactic shock, seizure, Guillain-Barré syndrome, nausea, Merkel cell carcinoma.
- The data from the controlled clinical studies and their open-label extension (number of patients, duration of follow-up, frequency of certain adverse effects) have been updated.

The ANSM [French National Agency for Medicines and Health Products Safety] has put in place a national pharmacovigilance system administered by the Nancy regional pharmacovigilance centre. The Technical Committee conclusions of May 2012 were as follows: "Certolizumab pegol has a safety profile similar to that of other TNF inhibitors, with, in particular:
- a confirmed risk of infection
- hypersensitivity reactions, mainly cutaneous
- psoriasis-type effects on the skin."

08.3 Summary and discussion

Certolizumab pegol (CZP, CIMZIA) as subcutaneous injection has been evaluated in the treatment of psoriatic arthritis in a randomised, placebo-controlled, double-blind study over 24 weeks.
The choice of placebo as comparator in this study was inappropriate given that other TNF inhibitors were already available at the time of performance of this study.

The double-blind phase was followed by a single-blind phase up to 48 weeks, beyond which the study was open (follow-up for 216 weeks), with provision for the evaluation of safety up to 224 weeks.
The patients included had an active form of PsA despite treatment with MTX on inclusion in 65% of cases, with 20% already having been treated with a TNF inhibitor. Two CZP dosage regimens were evaluated versus placebo. The patients were treated initially either with placebo or with loading doses of CZP 400 mg at weeks 0, 2 and 4, followed by maintenance treatment with placebo every 2 weeks or CZP at doses of 200 mg every 2 weeks or 400 mg every 4 weeks. Patients were allowed to be treated concomitantly with standard DMARDs (this occurred in 65.7% of cases).
Two co-primary endpoints were defined: the ACR20 response at week 12 and change in the modified total Sharp score (mTSS) at week 24 since baseline.
A hierarchical analysis with a predefined order of performance of the tests for the endpoints was carried out owing to the large number of analyses.
The proportion of patients achieving an ACR20 response at week 12 (co-primary endpoint) was statistically higher:

- for CZP 200 mg/2 weeks (58%) than for placebo (24.3%), i.e. an absolute difference of 33.7%; 95% CI [22.8; 44.6], p<0.001.
- for CZP 400 mg/4 weeks (51.9%) than for placebo (24.3%), i.e. an absolute difference of 27.6%; 95% CI [16.5; 38.7], p<0.001.

For the second, radiological co-primary endpoint, linear imputation resulted in implausible conclusions and overestimation of radiographic progression (change in mTss of 11.5 for CZP 200 mg/2 weeks, 25.1 for CZP 400 mg/4 weeks and 28.9 ± 7.73 for placebo).

Post-hoc analyses in patients with at least two available mTSS scores, with imputation of the median value for the change in the whole study population suggested that the progression in structural damage at week 24 was statistically lower for CZP 200 mg and 400 mg (pooled analysis) than for placebo (0.06 versus 0.28, i.e. a difference of -0.22 [-0.38; -0.06], p=0.007). It should, however, be noted that even this analysis did not demonstrate a statistically significant difference between the CZP 400 mg/4 weeks group and placebo (0.11 versus 0.28, i.e. a difference of -0.17, NS).

In a post-hoc analysis, the proportion of patients who were radiographic responders at week 24 was 83.3% for CZP 200 mg and 76.3% for CZP 400 mg, versus 34.6% for placebo (p<0.001 for the two comparisons).

Although the data at week 48 did not show any statistically significant difference in mTSS between the pooled CZP groups and placebo, the data for the placebo group at week 48 had been obtained by extrapolation from the two available examinations between week 12 and week 24, as the placebo group was terminated at week 24.
The level of evidence of the data demonstrating the structural effect of CZP can therefore be regarded as low. In particular, the superiority of the 400 mg every 4 weeks dosage regimen over placebo in the inhibition of joint damage was not demonstrated regardless of the analysis employed or the analysis period (24 or 48 weeks).

No new safety signals have been identified in PsA; the most common adverse events associated with certolizumab pegol were infections. However, long-term safety data are limited. The open-label phase of the study is likely to document this better and is still in progress.

09 THERAPEUTIC USE

There is no available direct comparison between CIMZIA (certolizumab pegol) and other available biologics in the treatment of psoriatic arthritis. When considering treatment with a TNF inhibitor, e.g. in active forms of psoriatic arthritis refractory to standard DMARDs including methotrexate, CIMZIA as subcutaneous injection every 2 weeks could be an alternative to other available TNF inhibitors.
It should be noted that the efficacy versus placebo of the proposed alternative dosage regimen in maintenance treatment of 400 mg only every 4 weeks has not been demonstrated in the inhibition of joint damage.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual benefit

◗ Psoriatic arthritis is a chronic disease, some forms of which can be serious and incapacitating.
◗ CIMZIA is intended as a symptomatic treatment.
◗ Its efficacy and safety have been evaluated only against placebo. The level of evidence demonstrating a structural effect is low, as this was obtained from a post-hoc analysis. Its efficacy/adverse effects ratio is modest.
◗ There are treatment alternatives.
◗ CIMZIA is a second-line treatment for patients who do not respond or respond only inadequately to DMARDs, in particular methotrexate, or in whom such treatment is contraindicated.

◗ Public health benefit
In view of the low burden represented by patients responding inadequately to previous DMARD therapy, which is due to the small numbers affected, despite the seriousness of the disease and the identified public health need, and the limited efficacy data versus placebo and safety data that are currently available, the proprietary medicinal product CIMZIA is not expected to have any additional impact on public health in the treatment of psoriatic arthritis compared with the existing alternatives.

Taking account of the low level of evidence demonstrating its structural effect, the Committee considers that the actual benefit of CIMZIA is <u>moderate</u> in the indication of the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

The proprietary medicinal product CIMZIA does not provide any improvement in actual benefit (IAB V, non-existent) over other TNF inhibitors in the treatment of active psoriatic arthritis in individuals who do not respond to treatment with disease-modifying antirheumatic drugs (DMARDs).

010.3 Target population

According to its Marketing Authorisation, the target population of CIMZIA in this extension of indication consists of adult patients with active psoriatic arthritis in whom the response to previous non-biologic DMARD therapy has been inadequate.

French epidemiological data are limited and old.
According to the epidemiological survey (Epirhum)[16] conducted in 2001 by the Epidemiology section of the French Society for Rheumatology the incidence of psoriatic arthritis in the population aged 18 years and over is 0.19%, 95% CI = [0.08-0.35]. Applying this figure to INSEE data of 1 January 2013 (50,979,747), the population with psoriatic arthritis in France can be estimated at approximately 97,000 adults (estimate between 41,000 and 178,400 persons).

The absence of precise epidemiological data on the incidence of the severe and progressive peripheral forms and on rates of response to DMARD therapy leads to the following hypotheses (expert opinions):
- 50 to 60% of patients with psoriatic arthritis have a severe and progressive peripheral form and need to use methotrexate;
- 15 to 20% of patients respond inadequately to methotrexate.

On this basis, 7000 to 12,000 patients with severe and progressive peripheral psoriatic arthritis respond inadequately to DMARDs.

Conclusion
The target population of CIMZIA in psoriatic arthritis is therefore between 7000 and 12,000 patients.

011 COMMITTEE RECOMMENDATIONS

◗ **The Committee recommends inclusion of CIMZIA 200 mg, solution for subcutaneous injection on the list of medicines refundable by National Health Insurance (box of 2 glass prefilled syringes) and on the list of medicines approved for hospital use (box of 2 glass prefilled syringes and box of 2 × 1 ml prefilled syringes with needle guard) in the indication and at the dosages in the Marketing Authorisation.**

◗ **Proposed reimbursement rate: 30%**

◗ **Packaging**
Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.

◗ **Specific requests relating to reimbursement**
The Committee wishes to reiterate that CIMZIA has exception drug status.

◗ **Request for data**
The Committee would like to be provided with the final data from study PsA001, for which the final report is expected in the second half of 2016.

[16] Saraux A. et al. Prevalence of spondyloarthropathies in France: 2001. Ann Rheum Dis 2005; 64: 1431-35.

Appendix 1: Summary of the CASPAR classification criteria

1. Inflammatory arthritic involvement (peripheral, axial or entheseal)

2. Clear presence of psoriasis at the examination or history of psoriasis:	
Psoriatic skin or scalp lesion diagnosed by a doctor at the physical examination	**2**
Psoriasis reported by patient or doctor	**1**
Familial history of psoriasis in a first- or second-degree relative	**1**
3. Nail involvement	
Psoriatic nail dystrophy at the clinical examination: onycholysis, pitting or hyperkeratosis	**1**
4. Negative rheumatoid factor	
Absence of serum RF (ELISA or nephelometry)	**1**
5. Presence or history of dactylitis	
Current diagnosis of dactylitis by a doctor	**1**
History of dactylitis reported by a doctor	**1**
6. Radiological evidence of new bone formation	
Presence of radiographic signs of juxta-articular new bone formation (X-rays of the hands and feet)	**1**

For confirmation of diagnosis: Criterion 1 must be satisfied, plus at least 3 points (sensitivity 91.4%, specificity 98.7%).