Single Technology Assessment

ID2018_068: Cost minimization analysis of certolizumab pegol (Cimzia).

04.04.2019

Norwegian Medicines Agency

PREFACE

Implementation of the National System for the introduction of new technologies in the specialist healthcare system will help ensure that assessment of appropriate new technologies happens in a systematic manner with respect to efficacy and safety, as well as impacts on health and society. The main aim of the new system is described in the National Health and Care Plan 2011-2015 and the White Paper 10 (2012-2013), Good quality - safe services. The regional health authorities, the Norwegian Knowledge Centre for Health Services, the Norwegian Medicines Agency and the Directorate of Health collaborate on tasks related to the establishment and implementation of the new system. Eventually, the National System for the introduction of new technologies in the specialist healthcare system will assist in the rational use of health care resources.

The Norwegian Medicines Agency has been assigned the responsibility to evaluate Single Technology Assessments of individual pharmaceuticals. A Single Technology Assessment is a systematic summary of evidence based on research on efficacy, safety and impact assessment. For pharmaceuticals, this will usually revolve around budgetary consequences or resource allocation. The burden of proof relating to the documentation of efficacy, safety and cost-effectiveness is borne by the MA-holder for the pharmaceutical under review. NoMA can, when necessary, provide guidance to pharmaceutical companies.

NoMA assesses the submitted evidence for all important clinical outcomes, resource use as well as the assumptions made in the analysis presented by the MA-holder and the presented results. NoMA does not perform its own health economic analyses. If required, NoMA may request additional information and perform additional calculations of the costs and cost effectiveness using the submitted model.

NoMA evaluates the relative efficacy and incremental costs in relation to a relevant comparator. NoMA does not assess the benefit risk balance already assessed under the marketing-authorization procedure. Information about this is provided by EMA (1).

Single Technology Assessment of pharmaceuticals is intended to support sound decision making on potential introductions of new technologies, and prioritization made at the Health Authority level. NoMA has no decision-making authority in this system.

All assessments are published and available to the public (www.legemiddelverket.no).

OPPSUMMERING

Formål
Hurtig metodevurdering av legemiddelet certolizumab pegol (Cimzia) i henhold til godkjent preparatomtale og bestilling ID2018_068: Kost-minimeringsanalyse for certolizumab pegol (Cimzia) til behandling av plakkpsoriasis.

Vurderingen tar utgangspunkt i dokumentasjon innsendt av UCB pharma.

Bakgrunn
Cimzia er et legemiddel til behandling av voksne pasienter med moderat til alvorlig plakkpsoriasis som er kandidater for systemisk terapi. Den generelle kliniske effekten ved behandling av moderat til alvorlig plakkpsoriasis er dokumentert gjennom utstedelse av markedsføringstillatelse. Om lag 1500-2500 pasienter er aktuelle for behandling med biologiske legemidler for plakkpsoriasis hvert år i Norge.

Effektdokumentasjon i henhold til norsk klinisk praksis
Cimzia har i den kliniske studien CIMPACT vist å være minst like god som etanercept med hensyn på å redusere sykdomsaktivitet ved moderat til alvorlig plakkpsoriasis.

Alvorlighet og helsetap
Alvorlighetsgraden kan påvirke om kostnadene vurderes å stå i rimelig forhold til nytten av behandlingen. Dette kriteriet får kun betydning dersom legemiddelfirma dokumenterer kostnadseffektivitet ved hjelp av en kostnad-effekt analyse. Denne metodevurderingen er avgrenset til å vurdere om Cimzia har sammenlignbar effekt og sikkerhet med komparator. Legemiddelverket har derfor ikke utført tentative beregninger av alvorlighetsgrad

Kostnadseffektivitet
Legemiddelverket har ikke vurdert om behandling med Cimzia er kostnadseffektiv, kun om det har sammenlignbar effekt og sikkerhet som andre biologiske legemidler til behandling av plakkpsoriasis.

Legemiddelverkets vurdering
Legemiddelverket mener det er godt dokumentert at Cimzia har minst like god effekt og sikkerhet som etanercept med hensyn på behandling av moderat til alvorlig plakkpsoriasis.

Budsjettkonsekvenser
Budsjettkonsekvenser er ikke beregnet i denne metodevurderingen.

LIS-anbud
UCB pharma har levert tilbud på Cimzia til LIS TNF/BIO-anbudet. Behandlingskostnader ved bruk av Cimzia sammenlignet med øvrige biologiske legemidler i anbefalingene fra anbudet vil fremkomme i et separat notat fra LIS.

TABLE OF CONTENTS

LOG

Bestilling:	ID2018_068: Kost-minimeringsanalyse for certolizumab pegol (Cimzia) til behandling av plakkpsoriasis.
Forslagstiller:	Legemiddelverket
Legemiddelfirma:	UCB pharma
Preparat:	Cimzia
Virkestoff:	Certolizumab pegol
Indikasjon:	
ATC-nr:	L04AB05

Prosess

Dokumentasjon bestilt av Legemiddelverket	18-06-2018
Fullstendig dokumentasjon mottatt hos Legemiddelverket	01-10-2018
Klinikere kontaktet for første gang	Med bakgrunn kostnadsminimerings bestilling er klinikere ikke blitt kontaktet
LIS kontaktet for første gang av Legemiddelverket.	29-03-2019
Legemiddelverket bedt om ytterligere dokumentasjon	Ikke aktuelt
Ytterligere dokumentasjon mottatt av Legemiddelverket	Ikke aktuelt
Rapport ferdigstilt:	04-04-2019
Saksbehandlingstid:	184 dager hvorav 0 dager i påvente av ytterligere opplysninger fra legemiddelfirma.
Saksutredere:	Pilar Martin Vivaldi

GLOSSARY

BSA	Body surface area
DLQI	Dermatology life quality index
EMA	European Medicines Agency
EPAR	European public assessment report
FASca	Fatigue Assessment Scale
H2H	Head to head
MA	Market authorisation
NoMA	Norwegian Medicines Agency
PASI	Psoriasis area and severity index
PGA	Physician's Global Assessment
PsO	Plaque psoriasis
SPC	Summary of product characteristics
STA	single technology assessment

1 BACKGROUND

1.1 SCOPE

The purpose of this single technology assessment (STA) is to assess whether certolizumab pegol demonstrates similar clinical efficacy and safety compared to current available treatment options in Norway for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy, according to request specifications from Ordering Forum (request number ID2018_068: Cost minimization analysis of certolizumab pegol (Cimzia)).

1.2 PLAQUE PSORIASIS

Psoriasis is a chronic, inflammatory skin disease. Psoriasis may differ in many forms and the degree of severity varies. Symptoms of psoriasis occur sporadically and is characterized as flaky red plaques that differ in size and shape.

There are several types of psoriasis. The most common type is chronic plaque psoriasis (PsO) and constitutes approximately 90% of the incidences. The plaques are irregular and normally located on the scalp, trunk, buttocks, knees, and elbows. Approximately 80 % of the affected patients have mild to moderate, and 20 % have moderate to severe plaque PsO (Menter et al., 2008, HelseNorge, 2017, WHO, 2016, Fuskeland, 2007). This STA concerns moderate to severe plaque PsO.

A report from 2007 states that there are approximately 100.000 persons suffering from psoriasis in Norway (Fuskeland, 2007). There exists no cure for psoriasis and symptom control is the only treatment option.

Sources from the Norsk legemiddelhåndbok report that psoriasis has an incidence of 2-3% in the overall population (120 000 people in Norway suffer from psoriasis (2)).

1.3 SEVERITY AND SHORTFALL

The severity criterion is meaningful in the context of a cost utility analysis. UCB Pharma has submitted documentation regarding relative efficacy (efficacy and safety) in order to document that certolizumab pegol has similar relative efficacy compared to relevant treatment.

NOMA has therefore not calculated severity and shortfall for this patient group.

1.4 TREATMENT OF PLAQUE PSORIASIS

1.4.1 Treatment with certolizumab pegol (1)

- Therapeutic indications
  Plaque psoriasis: Certolizumab pegol is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. It is this therapeutic indication that is the object of this STA. In addition certolizumab pegol has the following indications:
  Rheumatoid arthritis
  Axial spondyloarthritis
  Ankylosing spondylitis
  Axial spondyloarthritis without radiographic evidence of Ankylosing spondylitis
  Psoriatic arthritis
  Please refer to certolizumab pegol SPC for further information. (1)
- Mechanism of action

  Certolizumab pegol has a high affinity for human TNFα and binds with a dissociation constant (KD) of 90 pM. TNFαis a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralises TNFα but does not neutralise lymphotoxin α (TNFβ). Certolizumab pegol was shown to neutralise membrane associated and soluble human TNFα in a dose-dependent manner.
  Certolizumab pegol does not contain a fragment crystallisable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause antibody-dependent cell-mediated cytotoxicity *in vitro*.

- Posology and method of administration
  Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which certolizumab pegol is indicated. Patients should be given the special reminder card.
  Loading dose
  The recommended starting dose of Certolizumab pegol for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4.
  Maintenance dose
  After the starting dose, the maintenance dose of certolizumab pegol for adult patients with plaque psoriasis is 200 mg every 2 weeks. A dose of 400 mg every 2 weeks can be considered in patients with insufficient response. Available data in adults with plaque psoriasis suggest that a clinical response is usually achieved within 16 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.
- Adverse events

The most common adverse reactions reported through Week 16 belonged to the system organ classes, infections and infestations, general disorders and administration site conditions, and skin and subcutaneous tissue disorders.

Please refer to SPC for further information about adverse reactions and contraindications. (1)

1.4.2 Treatment guidelines

Currently there are not official Norwegian national guidelines for the treatment of PsO with biological agents. Biological agents for the treatment of autoimmune diseases fall within the national tender system and the drug with the lowest price is to be used, except when there are medical reasons for choosing other, more expensive options.
The following products are currently part of the national tender for the treatment of PsO (current tender period 01.05.2018-30.04-2019):

Table 1: products currently part of the national tender for the treatment of PsO,2019-2020

Mechanism of action	Active substance	Posiology
TNF-inhibitor	Adalimumab	Subcutaneous injection
TNF-inhibitor	Infliximab	Infusion
TNF-inhibitor	Etanercept	Subcutaneous injection
IL-17A, F og A/F-inhibitor	Brodalumab	Subcutaneous injection
IL-17A-inhibitor	Secukinumab	Subcutaneous injection
IL-12 og IL-23-inhibitor	Ustekinumab	Subcutaneous injection

The most relevant comparator may vary from year to year according to the national tender results. Any of the products above may be considered as a relevant comparator.

Clinical efficacy of certolizumab pegol has been demonstrated in several studies. In one of them etanercept was used as an active comparator arm (CIMPACT study). This study will be used as main documentation to show similar relative efficacy between certolizumab pegol and etanercept.

Please refer to SPC for each product for further information about therapeutic indications, method of administration, posology and adverse events. (https://www.ema.europa.eu/en)

1.4.3 Comparator

Based on chapters above the chosen comparator for this STA is etanercept (clinical evidence from a head to head study), even though in clinical practice any of the above might be considered also relevant..

2 RELATIVE EFFECTIVENESS

UCB pharma has sent a brief documentation about the clinical studies for certolizumab pegol. A network meta-analysis has also been performed and sent. Because a head to head clinical study against etanercept is available, NoMA has considered this one as more relevant for this STA. NMA has not been thoroughly assessed but the results do not deviate from direct clinical evidence. Submitted documentation was scarce informing about the H2H study against etanercept. NoMA has therefore searched at the European Medicines Agency site (www.ema.europa.eu) and will summarize in this chapters the findings for this study (from EPAR).

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

The clinical efficacy and safety of certolizumab pegol for the treatment of PsO was demonstrated thorough 5 clinical studies

• Completed Phase 2 studies C87040 and C87044

• Phase 3 double-blind, placebo-controlled studies PS0005 and PS0002 (hereafter referred to as the CIMPASI studies, where PS0005 is CIMPASI-1 and PS0002 is CIMPASI-2). The Initial Treatment Period (Week 0 to Week 16) and the Maintenance Treatment Period (Week 16 to Week 48) have been completed. The Open-Label Extension (OLE) Treatment Period (Week 48 to Week 144) is ongoing.

• Phase 3 double-blind, placebo- and active-controlled study PS0003 (hereafter referred to as CIMPACT). The Initial Treatment Period (Week 0 to Week 16) and the Maintenance Treatment Period (Week 16 to Week 48) have been completed. The OLE Treatment Period (Week 48 to Week 144) is ongoing. Study CIMPACT is the most relevant study for this STA.

Studies CIMPASI-1 and CIMPASI-2 had identical design. Study CIMPACT had a somewhat different design and differences compared with the CIMPASI studies.

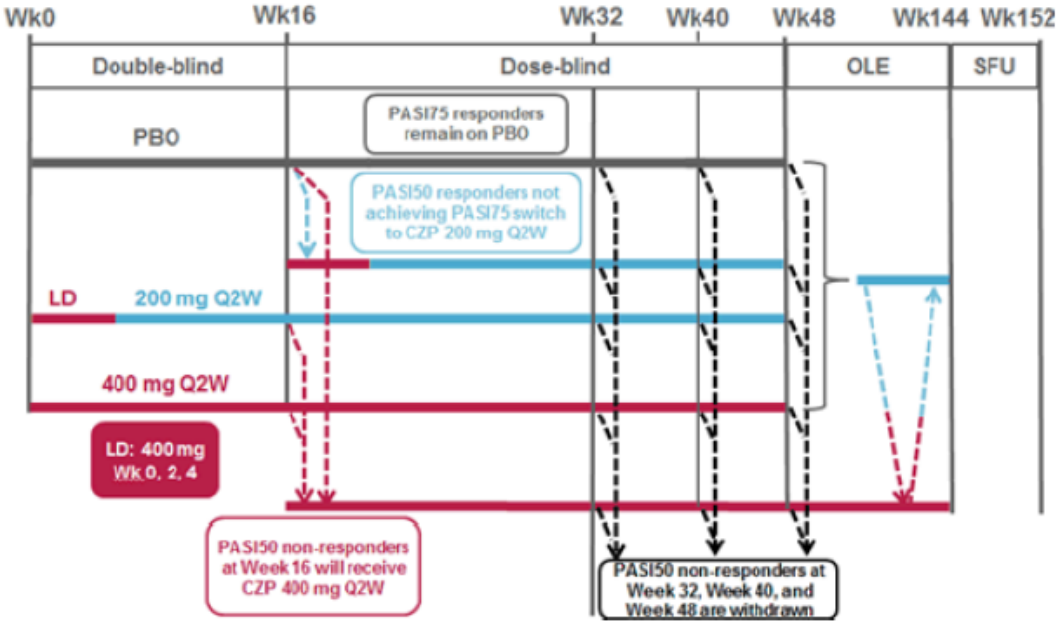
In addition, UCB pharma has submitted information about studies CRIB and CRADLE. These two studies provide clinical information about the use of TNF-inhibitors in pregnant patients and about transfer to breast milk. These two studies previously been assessed by EMA. NoMA will therefore refer to use recommendations in pregnant and breast feeding women as stated in certolizumab pegol SPC (1):

Fertility, pregnancy and lactation
Women of childbearing potential
The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last Certolizumab pegol dose due to its elimination rate, but the need for treatment of the woman should also be taken into account.
Pregnancy
Data from more than 500 prospectively collected pregnancies exposed to Certolizumab pegol with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of Certolizumab pegol. However, the available clinical experience is too

limited to, with a reasonable certainty, conclude that there is no increased risk associated with Certolizumab pegol administration during pregnancy.
Animal studies using a rodent anti-rat TNFα did not reveal evidence of impaired fertility or harm to the foetus. However, these are insufficient with respect to human reproductive toxicity. Due to its inhibition of TNFα, Certolizumab pegol administered during pregnancy could affect normal immune response in the new-born.
Certolizumab pegol should only be used during pregnancy if clinically needed.
Non-clinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of certolizumab pegol (no Fc region).
In a clinical study 16 women were treated with certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks) during pregnancy. Certolizumab pegol plasma concentrations measured in 14 infants at birth were Below the Limit of Quantification (BLQ) in 13 samples; one was 0.042 µg/ml with an infant/mother plasma ratio at birth of 0.09%. At Week 4 and Week 8, all infant concentrations were BLQ. The clinical significance of low levels certolizumab pegol for infants is unknown. It is recommended to wait a minimum of 5 months following the mother's last Certolizumab pegol administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants.
Breastfeeding
In a clinical study in 17 lactating women treated with Certolizumab pegol, minimal transfer of certolizumab pegol from plasma to breast milk was observed. The percentage of the maternal certolizumab pegol dose reaching an infant during a 24 hour period was estimated to 0.04% to 0.30 %. In addition, since certolizumab pegol is a protein that is degraded in the gastrointestinal tract after oral administration, the absolute bioavailability is expected to be very low in a breastfed infant. Consequently, Certolizumab pegol can be used during breastfeeding.

Studies CIMPASI-1 and CIMPASI-2:
Main inclusion criteria
• Adult men and women ≥18 years.
• Chronic plaque psoriasis for at least 6 months.
• Baseline PASI ≥12 and BSA ≥10% and Physician's Global Assessment (PGA) score ≥3.
• Candidates for systemic PsO therapy and/or phototherapy and/or chemophototherapy.
• Female subjects must have been either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception. Male subjects must have agreed to ensure they or their female partner(s) used adequate contraception during the study and for at least 10 weeks after the subject received his final dose of study medication.

Study design:



CZP=certolizumab pegol; LD=loading dose; OLE=open-label extension; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; SFU=Safety Follow-Up; Wk=week

Objectives

The primary objective in both CIMPASI-1 and CIMPASI-2 was to demonstrate the efficacy of certolizumab pegol administered sc at the doses of certolizumab pegol 400 mg every 2 weeks (Q2W) and certolizumab pegol 200 mg Q2W after a loading dose of certolizumab pegol 400 mg at Weeks 0, 2, and 4 in the treatment of moderate to severe chronic plaque PsO.

Secondary objectives were to assess the optimal initial treatment dose for the treatment of moderate to severe chronic plaque PsO; assess durability of the clinical response with continued treatment; assess the safety and tolerability of certolizumab pegol and improvement of skin-related quality of life (DLQI).

Co-primary efficacy variables:

- PASI75 at Week 16

- PGA Clear or Almost clear (with at least 2-category improvement) at Week 16

Secondary efficacy variables:

- PASI90 at Week 16
- PGA Clear or Almost clear (with at least 2-category improvement) at Week 48
- PASI75 at Week 48
- Change from Baseline in DLQI at Week 16

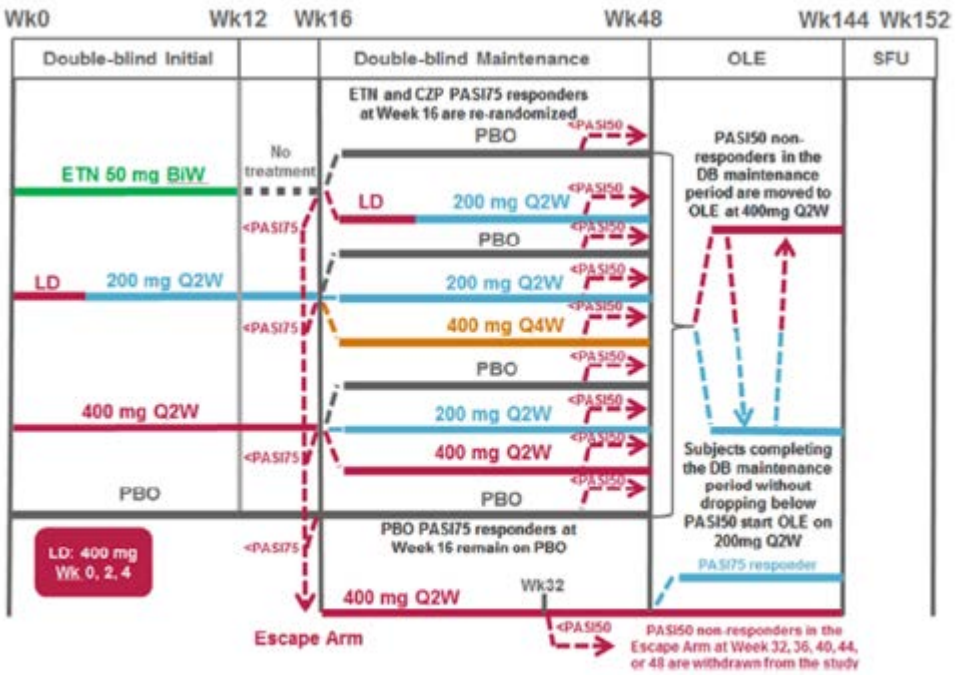
Study CIMPACT:

The inclusion and exclusion criteria were the same as in studies CIMPASI-1 and CIMPASI-2, with the following exceptions:

• Subjects with a known hypersensitivity to latex or any excipients of etanercept were excluded.

• With respect to Prior medications exclusions, subjects must not have received any previous treatment with etanercept for the treatment of PsO.

Study design:



BiW=twice weekly; CZP=certolizumab pegol; DB=double-blind; ETN=etanercept; LD=loading dose; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; OLE=Open-Label Extension; Q2W=every 2 weeks; Q4W=every 4 weeks; SFU=Safety Follow-Up; Wk=week

Objectives

The primary objective of the study was to compare the efficacy of certolizumab pegol administered sc at the doses of certolizumab pegol 400 mg every 2 weeks (Q2W) and certolizumab pegol 200 mg Q2W after a loading dose of certolizumab pegol 400 mg Q2W at Weeks 0, 2, and 4 to placebo in the treatment of moderate to severe chronic plaque PsO.

Secondary objectives were to compare the efficacy of certolizumab pegol at two dose levels to etanercept at a weekly dose of 100 mg in the treatment of moderate to severe chronic plaque PsO; to assess the optimal initial treatment dose and maintenance dose for the treatment of PsO and to assess the safety and tolerability of certolizumab pegol. Other objectives were similar to those in the CIMPASI studies, with the addition of assessment of fatigue, as measured by the Fatigue Assessment Scale (FASca).

Primary efficacy variable:

• PASI75 at Week 12

Secondary efficacy variables:
- PASI75 at Week 16
- PASI90 at Week 12 and Week 16
- PGA Clear or Almost Clear (with at least 2 category improvement) at Week 12
- PGA Clear or Almost Clear (with at least 2 category improvement) at Week 16
- PASI75 at Week 48 for those achieving PASI75 at Week 16

Ongoing studies
All three pivotal studies have open-label extension (OLE) treatment periods (Week 48 to Week 144) that are still ongoing.

NoMA's assessment of submitted clinical documentation
Clinical efficacy of certolizumab pegol is properly documented through several randomized double-blinded controlled trials. NoMA considers submitted documentation, together with the EPAR sufficient to assess the relative efficacy and safety of certolizumab pegol compared to etanercept. For this, it is CIMPACT study the most relevant.

3 PICO[1]

3.1 PATIENT POPULATION

Norwegian clinical practice

Based on previous STA for the treatment of PsO in this population (STA iksekizumab, Taltz):
Criteria for start with biological drugs are defined as follow:
PASI >10, BSA >10 %,
DLQI >10
Patients must have had active psoriasis for at least 6 months
Patients have been treated previously with UV therapy (UV-B, UV-B-TL 01 or PUVA), at least three months with adequate dose of acitretin and with methotrexate for at least three months: please refer to acitretin SPC regarding warnings treatment of fertile women .

Submitted clinical studies (CIMPACT) (1)

A total of 731 subjects were screened for the study, 174 of whom were screen failures; the most common reason being ineligibility (136 subjects, 18.6%). A total of 559 randomized subjects started the Initial Treatment Period.
Overall, 535 subjects (95.7%) completed the Initial Treatment Period. The percentages of subjects who completed the Initial Treatment Period were similar across the certolizumab pegol and placebo groups, and slightly lower in the etanercept group (93.5%); mainly due to a higher percentage of subjects discontinuing due to an AE in the etanercept group (2.4%) compared with the other groups (≤0.6% each).

Patient base line for CIMPACT study is shown below:

[1] Patients, Intervention, Comparator, Outcome.

Table 2Patient baseline CIMPACT

	Placebo, N = 57	Etanercept, N = 170	CZP 200 mg Q2W, N = 165	CZP 400 mg Q2W, N = 167
Age, mean ± SD	46.5 ± 12.5	44.6 ± 14.1	46.7 ± 13.5	45.4 ± 12.4
Male, n (%)	34 (59.6)	127 (74.7)	113 (68.5)	107 (64.1)
Geographic region, n (%)				
North America	10 (17.5)	29 (17.1)	26 (15.8)	27 (16.2)
Central and Eastern Europe	36 (63.2)	111 (65.3)	07 (64.8)	109 (65.3)
Western Europe	11 (19.3)	30 (17.6)	32 (19.4)	31 (18.6)
Weight, kg, mean ± SD	93.7 ± 29.7	88.6 ± 20.7	89.7 ± 20.6	86.3 ± 20.0
Duration of disease, years[1] mean ± SD	18.9 ± 12.9	17.4 ± 12.0	19.5 ± 13.2	17.8 ± 11.5
PASI Score mean ± SD	19.1 ± 7.1	21.0 ± 8.2	21.4 ± 8.8	20.8 ± 7.7
DLQI, mean ± SD	13.2 ± 7.6	14.1 ± 7.4	12.8 ± 7.0	15.3 ± 7.3
BSA, % mean ± SD	24.3 ± 13.8	27.5 ± 15.5	28.1 ± 16.7	27.6 ± 15.3
PGA score, n (%)				
3: moderate	40 (70.2)	115 (67.6)	114 (69.1)	113 (67.7)
4: severe	17 (29.8)	55 (32.4)	51 (30.9)	54 (32.3)
Prior biologic therapies, n(%)[2]	11 (19.3)	51 (30.0)	44 (26.7)	48 (28.7)
anti–TNF-α	5 (8.8)	8 (4.7)	4 (2.4)	4 (2.4)
anti–IL-17A	8 (14.0)	39 (22.9)	38 (23.0)	35 (21.0)
anti–IL-12/23	1 (1.8)	9 (5.3)	5 (3.0)	16 (9.6)

[1]at screening
[2]Patients may have had exposure to >1 prior biologic therapy but ≤2 per exclusion criteria

Abbreviations:
PASI = Psoriasis Area and Severity Index; BSA = Body Surface Area; PGA = Physician Global Assessment; DLQI = Dermatology Quality of Life Index;

Source: (Lebwohl et al., 2018)

In study CIMPACT, previous use of etanercept was excluded, while previous use of other biologics targeting TNF α was allowed after a washout of 12 weeks.

NoMA´s assessment

Inclusion criteria for CIMPACT study are similar enough to the criteria for criteria used in Norwegian clinical practice with biological drugs. NoMA considers that the patient population in CIMPACT is sufficiently close to the patient population that might be candidate for the treatment with certolizumab pegol.

3.2 INTERVENTION

Norwegian clinical practice

NoMA considers that certolizumab pegol will be administrated according to the SPC:

Starting dose : 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4.

Maintenance dose: 200 mg every 2 weeks. A dose of 400 mg every 2 weeks can be considered in patients with insufficient response

Submitted clinical studies (CIMPACT)

Patients were randomized to certolizumab pegol 200 mg Q2W (with initial certolizumab pegol 400 mg doses at Weeks 0, 2, and 4, followed by certolizumab pegol 200 mg Q2W starting at Week 6); certolizumab pegol 400mg Q2W.
In study CIMPACT, all subjects who did not achieve PASI75 at Week 16 were removed from blinded study medication and escaped to certolizumab pegol 400 mg Q2W. For PASI75 responders at Week 16, subjects initially randomized to placebo continued to receive blinded placebo; subjects initially randomized to etanercept were re-randomized (2:1) to either certolizumab pegol (400 mg at Weeks 16, 18, and 20 followed by 200 mg Q2W) or placebo; subjects initially randomized to certolizumab pegol 200 mg Q2W were re-randomized (2:2:1) to receive either certolizumab pegol 200 mg Q2W or certolizumab pegol 400 mg every 4 weeks or placebo; subjects initially randomized to certolizumab pegol 400 mg Q2W were re-randomized (2:2:1) to certolizumab pegol 200 mg Q2W or certolizumab pegol 400 mg Q2W or placebo.

NoMA´s assessment

NoMA considers that certolizumab pegol will be used according to the SPC. NoMA assumes that patients treated with certolizumab pegol will be treated as long as they respond to treatment or not present adverse reactions that could compromise patient safety.

3.3 COMPARATOR

Norwegian clinical practice

Please refer to chapter1.4

Submitted clinical studies (CIMPACT) (1)

According to EPAR, the rationale for using etanercept as the active comparator was that it is the first TNF inhibitor approved for the treatment of PsO and is part of the standard armamentarium. The approved initial dose is 50 mg twice weekly. Etanercept was agreed as an acceptable active comparator. However, its efficacy in plaque psoriasis seems to be in the lower range when compared with other biologics approved in this indication.
All etanercept-treated subjects who did not achieve a PASI75 response were switched to certolizumab pegol 400 mg Q2W at Week 16. The Applicant considered that these subjects can be considered primary non-responders to anti-TNF, and that the Week 32 and 48 efficacy results in this population could provide relevant data on the benefit of certolizumab pegol in primary non-responders. Even if this reasoning can

be followed, this relates only to one other anti-TNF product and etanercept is generally one of the anti-TNF monoclonal antibodies with lowest response in plaque psoriasis

Comparison of certolizumab pegol over etanercept was measured at Week 12 because the approved duration of initial etanercept treatment at 50 mg twice weekly is 12 weeks and in the etanercept plaque psoriasis studies, the primary endpoint was assessed at week 12.

NoMA´s assessment

NoMA considers that posology for etanercept in CIMPACT study is relevant.

3.4 OUTCOMES

3.4.1 Efficacy

Submitted clinical studies (CIMPACT) (1)

The most relevant efficacy measures are presented in tables below-

Table 3 ***PASI75 responder rate at Week 12 by randomized treatment group (RS) (CIMPACT)***

	PBO N=57	ETN N=170	CZP 200mg Q2W N=165	CZP 400mg Q2W N=167
Primary analysis: MCMC method for multiple imputation [a]				
Responder rate (%)	5.0	53.3	61.3	66.7
Estimate (95% CI) for difference in proportion of responders vs PBO			56.2 (46.4, 66.0)	61.6 (52.1, 71.2)
Odds ratio vs PBO			30.023	37.988
95% CI for odds ratio			8.971, 100.48	11.312, 127.576
P-value			<0.0001	<0.0001
Sensitivity analysis: NRI [b]				
Responder rate (%)	4.8	51.2	59.8	65.7
Odds ratio vs PBO			29.333	37.821
95% CI for odds ratio			8.786, 97.930	11.296, 126.633
P-value			<0.0001	<0.0001
Sensitivity analysis: model-based multiple imputation [c]				
Responder rate (%)	4.9	54.3	61.7	67.6
Odds ratio vs PBO			31.387	40.656
95% CI for odds ratio			9.376, 105.072	12.108, 136.514
P-value			<0.0001	<0.0001
Observed results				
Responders, n/Nobs (%)	3/54(5.6)	91/159 (57.2)	102/157 (65.0)	113/162 (69.8)

CI=confidence interval; CZP=certolizumab pegol; ETN=etanercept; MCMC=Markov Chain Monte Carlo; Nobs=number of subjects with a nonmissing result; NRI=nonresponder imputation; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set

Note: Estimates of percentages of responders, odds ratios, CIs, and p-values were based on using a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no).

[a] Missing data were imputed using multiple imputation based on the MCMC method.

[b] Subjects with missing PASI75 response at Week 12 were considered to be nonresponders.

[c] Missing data were imputed using multiple imputation based on the same logistic regression model as used for the analysis.

Table 4 ***PASI75 responder rate at Week 48 by re-randomized blinded treatment group in CIMPACT – Maintenance Treatment Period (WK16RS)***

	CZP 200mg Q2W/ PBO N=22	CZP 200mg Q2W/ CZP 200mg Q2W N=44	CZP 200mg Q2W/ CZP 400mg Q4W N=44	CZP 400mg Q2W/ PBO N=25	CZP 400mg Q2W/ CZP 200mg Q2W N=50	CZP 400mg Q2W/ CZP 400mg Q2W N=49
Nonresponder imputation						
Responder rate, n (%)	10 (45.5)	35 (79.5)	39 (88.6)	9 (36.0)	40 (80.0)	48 (98.0)
Observed results						
Responders, n/Nobs (%)	10/12 (83.3)	35/36 (97.2)	39/41 (95.1)	9/15 (60.0)	40/42 (95.2)	48/48 (100)

CZP=certolizumab pegol; Nobs=number of subjects with a nonmissing result; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; WK16RS=Week 16 Randomized Set

Note: For the analysis based on nonresponder imputation, subjects with missing data at Week 48 or who relapsed prior to Week 48 were treated as nonresponders

Table 5 ***PGA responder rates at Weeks 16 and 48 by re-randomized blinded maintenance treatment group for subjects initially randomized to certolizumab pegol in CIMPACT - Maintenance Treatment Period (Weeks 16 to 48) (MS [NRI])***

Visit Statistic	CZP 200mg Q2W/ PBO N=22	CZP 200mg Q2W/ CZP 200mg Q2W N=44	CZP 200mg Q2W/ CZP 400mg Q4W N=44	CZP 400mg Q2W/ PBO N=25	CZP 400mg Q2W/ CZP 200mg Q2W N=50	CZP 400mg Q2W/ CZP 400mg Q2W N=49
Week 16						
Responder rate (%)	72.7	68.2	81.8	72.0	84.0	81.6
95% CI	54.12, 91.34	54.42, 81.94	70.42, 93.21	54.40, 89.60	73.84, 94.16	70.79, 92.47
Week 48						
Responder rate (%)	13.6	61.4	70.5	12.0	64.0	87.8
95% CI	0.00, 27.98	46.98, 75.75	56.97, 83.94	0.00, 24.74	50.70, 77.30	78.58, 96.93

CI=confidence interval; CZP=certolizumab pegol; MS=Maintenance Set; NRI=nonresponder imputation; PBO=placebo; PGA=Physician's Global Assessment; Q2W=every 2 weeks; Q4W=every 4 weeks

Note: PGA responders=Clear or Almost Clear (with ≥2-category improvement from Baseline) at each visit

Study CIMPACT met its primary end-point, i.e. to demonstrate superiority vs. placebo with respect to PASI 75 response at week 12 (61.3% for certolizumab pegol 200 mg; 66.7% for certolizumab pegol 400 mg and

5% for placebo). Both certolizumab pegol doses were superior to placebo with a difference of approximately 5% in favour of the 400 mg arm.
The testing for superiority of certolizumab pegol vs. etanercept was included as a rather late , the last step in the sequential testing procedure in study CIMPACT. Superiority vs. etanercept could be concluded for PASI75 at Week 12 for the higher 400 mg certolizumab pegol dose (66.7% vs. 53.3%, p=0.0152) and non-inferiority for the 200 mg dose (61.3% vs. 53.3%; 8% difference, 95% CI: -2.9; 18.9). For PGA response at Week 12 in CIMPACT (secondary end-point), there was no difference in response for this variable for the 200 mg certolizumab pegol dose vs. etanercept (40% vs. 39%) while the 400 mg certolizumab pegol dose showed a larger response (50%) than etanercept.

3.4.2 Safety:

Certolizumab pegol has been on the market for almost a decade. Its anti-TNF safety profile is considered well characterised. Special warning and precautions are in line with the therapeutic class. The safety profile of certolizumab in psoriasis does not appear different from what that previously observed with certolizumab in other indications and is in line with other anti-TNFs.

4 SUMMARY

The Norwegian Medicines Agency considers that the clinical efficacy and safety of certolizumab pegol compared to etanercept have been sufficiently documented through CIMPACT study. NoMA considers that it is sufficiently documented that certolizumab pegol is at least as effective as etanercept, with regard to reducing disease activity in patients with moderate to severe plaque psoriasis. The relative efficacy compared to etanercept in CIMPACT was documented at 12 weeks after initiation of treatment, but NoMA believes it is unlikely that the effect of etanercept would appear to exceed the effect of certolizumab pegol with longer follow-up time than 12 weeks. Certolizumab pegol is generally well tolerated, with a side effect profile that did not differ significantly from etanercept or other biological treatments within the same therapeutic class.
The Norwegian Medicines Agency has not considered (according to request nr. ID2018_068) whether treatment with certolizumab pegol is cost-effective. The submitted documentation has not documented that any benefits of treatment with certolizumab pegol, may justify that certolizumab pegol may have a higher price than other approved biological treatment options.

Statens legemiddelverk, 04.04.2019

Elisabeth Bryn
enhetsleder

Pilar Martin Vivaldi
saksutreder

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1. European Medicines Agency. SPC -Cimzia 2019 [Available from: https://www.ema.europa.eu/en/documents/product-information/cimzia-epar-product-information_en.pdf.
2. Psoriasis- og eksemforbundet. Om psoriasis [Available from: http://www.levmedpsoriasis.no/Nyttig-info/Artikler.

APPENDIX 1 COMMENTS FROM MAH (ATTACHED SEPARATELY)

[redacted]

Alvorlig psoriasis medfører en høyere risiko for prematur fødsel og lav fødselsvekt. I tillegg er det en forhøyet risiko for svangerskapsdiabetes, hypertensive svangerskapskomplikasjoner, svangerskapsforgiftning, planlagt og akutt keisersnitt. (1) Cimzia er den eneste TNF-hemmeren uten FC-del og har derfor ingen eller veldig lav overføring til morkaken, og er det eneste behandlingsalternativet hvor dette er dokumentert i en prospektiv farmakokinesisk fase 4-studie. (2)

Da det ikke eksisterer retningslinjer for biologisk behandling av plakkpsoriasis vises det til følgende relevante omtaler av problemstillingen:

1. Nasjonal kompetansetjeneste for svangerskap og revmatiske sykdommer (NKSR) er et globalt ledende miljø på sitt felt og skriver følgende om bruk av TNF-hemmere under svangerskap i sin behandlingsveileder:

   Bruk av TNF-hemmere i svangerskap må alltid være en avveiing av risiko og nytte i hvert enkelt tilfelle. Indikasjonen for behandling bør dokumenteres i pasientens journal. Certolizumab har lavest passasje over placenta (mindre enn 10 % i siste trimester) og etanercept (Enbrel®) nest lavest (mindre enn 30% i siste trimester). Fra januar 2018 er certolizumab godkjent av legemiddelmyndigheter i EU området for bruk i svangerskap. Adalimumab, infliksimab (Remicade®) og golimumab har høy medikamentpassasje i 3. trimester. Hos nyfødte er det påvist høyere medikamentkonsentrasjoner enn hos moren. (3)

2. I ”Nationella riktlinjer för vård vid psoriasis” publisert i mars 2019, skriver Socialstyrelsen følgende på side 34:

   Hälso- och sjukvården bör erbjuda certolizumabpegol till personer med svår psoriasis. Avgörande för rekommendationen är att tillståndet har en stor till mycket stor svårighetsgrad och att åtgärden har stor effekt på psoriasissymtom. Läkemedlet passerar med största sannolikhet inte moderkakan och går inte över i bröstmjölk, till skillnad från övriga TNF-hämmare. Behandlingskostnaden enligt listpris är dock högre än för flera andra TNF-hämmare, där årsbehandlingskostnaden har sjunkit till följd av upphandlingar och avtal om rabatter. Åtgärden kan vara ett alternativ för personer som vill bli gravida, är gravida eller ammar.(4)

UCB er av den oppfatning at inklusjon av Cimzia i anbudsrangeringen for plakkpsoriasis vil kunne muliggjøres innenfor dagens budsjettrammer, og gi foreldre den tryggheten de har behov for å kontrollere kvinnens sykdom før, under og etter et svangerskap.

Referanser

(1) Bröms G et al. Effect of Maternal Psoriasis on Pregnancy and Birth Outcomes: A Population-based Cohort Study from Denmark and Sweden. Acta Derm Venereol 2018; 98:
(2) Mariette X. et al. Lack of placental transfer of certolizumab pegol during pregnancy. Results from CRIB, a prospective, postmarketing, pharmacokinetic study;Ann Rheum Dis;2018;77;2:228-233
(3) Veileder i svangerskap og revmatiske sykdommer. Nasjonal kompetansetjeneste for svangerskap og revmatiske sykdommer (NKSR). https://www.nksr.no/medikament/dmards-og-biologiske-legemidler/tnf-hemmere/
(4) Nationella riktlinjer för vård vid psoriasis. Socialstyrelsen. https://www.socialstyrelsen.se/riktlinjer/nationellariktlinjer/psoriasis