Single Technology Assessment

Zinbryta (daclizumab) – for the treatment of adults with relapsing forms of multiple sclerosis

03.01.2017

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 (NoMA) 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.

NoMA has been assigned the responsibility to evaluate Single Technology Assessments (STA) of individual pharmaceuticals. A STA 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 market authorization (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 MA procedure. Information about this is provided by EMA.

STA 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).

ABSTRACT

Rationale

Single technology assessment (STA) of Zinbryta (daclizumab). NoMA has assessed the clinical efficacy, safety and cost-effectiveness of Zinbryta according to the request specifications from Ordering Forum (request number ID2015_045). Requests from Ordering Forum can be found at www.nyemetoder.no.

Background

Zinbryta is a drug used in the treatment of multiple sclerosis. The overall efficacy and safety of Zinbryta for the treatment of relapsing forms of multiple sclerosis has been evaluated by the European Medicines Agency (EMA). Approximately [redacted] new patients are eligible for treatment with Zinbryta each year, out of the total population with relapsing-remitting multiple sclerosis of approximately 6000 patients. These numbers are based on Biogen's estimates.
NoMA's assessment is mainly, but not exclusively, based on the documentation presented by Biogen.

Clinical efficacy in the Norwegian setting

Biogen has submitted a mixed treatment comparison, comparing Zinbryta to other available treatments in Norway. NoMA considers the safety and efficacy of Zinbryta to be similar to Gilenya, and that Gilenya is the most appropiate comparator in this STA.

NoMA considers the efficacy of Zinbryta to be well documented, and similar to Gilenya.

Severity and shortfall

NoMA has not calculated the proportional shortfall and absolute shortfall for the patient population under consideration in this assessment. However, NoMA has previously assessed DMTs for the treatment of RRMS and concluded that multiple sclerosis leads to a reduction of general life expectancy by approximately 5 – 10 years. NoMA considers therefore multiple sclerosis to be a severe condition.

Cost effectiveness

NoMA considers a cost minimization analysis to be the most appropriate approach in evaluating the cost effectiveness of Zinbryta vs. Gilenya for the indicated patient population. This has been done using a comparison of the annual drug costs per patient for both Zinbryta and Gilenya.
Results from the analysis show that the annual costs associated with Zinbryta are slightly higher than the costs associated with Gilenya. NoMA therefore concludes that Zinbryta should be included in the forthcoming LIS-MS tendering process on the same terms as Gilenya.

NoMA's overall assessment

NoMA´s overall assessment after taking into consideration the severity of the illness, clinical relevant efficacy in the Norwegian setting and cost-effectiveness, is that Zinbryta should be included in the forthcoming LIS-tendering process on the same terms as Gilenya.

TABLE OF CONTENTS

Log

Order number:	ID2015_045 *Daclizumab (Zinbryta) - Legemiddel til behandling av attakkvis multippel sklerose (RRMS)*
Suggested by:	Norwegian Medicines Agency
Pharmaceutical company:	Biogen
Pharmeceutical product:	Zinbryta
Active substance	daclizumab
Indication	Relapsing remitting mulitple sclerosis
ATC-number	L04A C01

Prosess

Documentation ordered by NoMA	25-09-2015
Complete documentation received by NoMA	27-05-2016
Clinicians contacted	14-12-2016
Total assessment time:	221 days
Assessors:	Ashkan Kourdalipour Marianne Rolstad Bjørn Oddvar Strøm Leung Ming Yu David Mwaura Anja Schiel
Clinical experts	Kjell Morten Myhr Elisabeth Gulowsen Celius Rune Midgard Elisabeth Farbu Stein Henry Bjelland

Clinical experts have contributed with clarifications of central assumtions in the analysis (among other things, comparators, patient population, and generalizability of trial data to Norwegian clinical practice). The Norwegian medicines agency is responsible for the contents of the report. The clinical expertes have not been included in a consus process or had any peer review in the production of this report

GLOSSARY

AE	Adverse events
ARR	Annual relapse rate
ATC	Anatomical Therapeutic Chemical
AUP	Pharmacy retail price
CNS	Central nervous system
CDP3M	Confirmed disease progression at three months
CDP6M	Confirmed disease progression at three months
CrI	Credibility interval
CUA	Cost-utility analysis
DMT	Disease modifying treatment
EDSS	Expanded disability status scale
EMA	European Medicines Agency
GP	General physician
IFNβ-1a	Interferon beta-1a
IL-2	Interleukin 2
LIS	The national purchase cooperative for the Regional Health Authorities
MS	Multiple sclerosis
MTC	Mixed treatment comparison
MRI	Magnetic resonance imaging
MSIS-29	The Multiple Sclerosis Impact Scale
NOK	Norwegian kroner
NoMA	Norwegian Medicines Agency
NK	Natural killer cells
NR	Not reported
PICO	Patients, Intervention, Comparator, Outcome
PPMS	Primary progressive multiple sclerosis
QoL	Quality of life
RCT	Randomized controlled trial
RHF	Regional Health Authorities (Norw.: Regionale helseforetak)
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SD	Standard deviation
SLR	Systematic litterature review
SPMS	secondary progressive multiple sclerosis
STA	Single technology assessment
VAT	Value Added Tax (Norw.: merverdiavgift)

1 BACKGROUND

1.1 SCOPE

This single technology assessment (STA) seeks to evaluate the cost-effectiveness of daclizumab (Zinbryta) in the treatment of relapsing remitting multiple sclerosis (RRMS). A cost-utility analysis (CUA) has been submitted by Biogen, and the Norwegian Medicines Agency (NoMA) has compared daclizumab against other disease modifying treatments (DMT) currently available in Norway.

1.2 MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a heterogeneous disorder of the central nervous system (CNS) in which chronic inflammation, demyelination and axonal degeneration are the major pathological mechanisms. The disease has a progressive nature and MS eventually leads to permanent disability and death. The aetiology of MS is poorly understood but several risk factors have been identified, most commonly smoking, low sunlight exposure/vitamin D levels, Epstein-Barr virus and genetic predisposition.

Relapsing forms of MS (RMS) can be divided into relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). Most patients are diagnosed with RRMS (approximatly 90 %) which is characterized by an acute or subacute onset of symptomatic attacks (relapses) that can last for days, weeks, or months and from which the patient may either partially or completely recover. Approximately half the patients will develop SPMS within 10 years. Most disease modifying treatments (DMT's) are indicated for RRMS therapy and the aim is to slow disease progression and reduce the annual relapse rate (ARR).

The incidence and prevalence of MS vary geographically and are high in Norway compared to other countries. A recent health technology assessment regarding the effect and cost-utility of the disease modifying medicines used for patients with RRMS conducted by the Norwegian Knowledge Centre for the Health Services , estimated a prevalence of approximately 203/100 000 (95 % CI 199 – 207) (1) . This translates into approximately 10 500 individuals with MS in Norway. Data from 2014 suggests that 50 – 60 % of the prevalent MS population were classified as RRMS and eligible for DMT (2).

1.3 SEVERITY AND SHORTFALL

NoMA has previously assessed several DMTs for the treatment of RRMS. NoMA concluded that MS is a severe disease and leads to a reduction of general life expectancy of 5 – 10 years. NoMA has not calculated absolute and proportional shortfall for RRMS in this assessment, as this has been previously assessed in other STA's (3, 4).

1.4 TREATMENT OF RELAPSING REMITTING MULTIPLE SCLEROSIS

Traditionally, medical treatment of RRMS is distinguished between acute exacerbations (relapses) and DMT to slow down disease progression. In this STA, only the latter will be assessed and the treatment of acute exacerbations will not be discussed further.

Current clinical practise divides DMTs into two categories:

1) Active Disease
2) Highly Active Disease

In the first category we have the interferon beta formulations, glatiramer acetate, dimethyl fumarate, teriflunomide, and fingolimod. In the category "Highly Active Disease" we find natalizumab and alemtuzumab.

Within each category, ranking of the various DMTs is decided by LIS (the national purchase cooperative for the Regional Health Authorities (RHF) in Norway[1]) based on the tendering process (LIS-MS-anbudet).

1.4.1 Treatment with daclizumab

- Therapeutic indication
  Zinbryta is indicated in adult patients for the treatment of relapsing forms of multiple sclerosis.

- Mechanism of action
  Daclizumab is a humanised IgG1 monoclonal antibody that binds to CD25 (IL-2Rα), and prevents IL-2 binding to CD25. Daclizumab modulates IL-2 signalling by blocking CD25-dependent, high-affinity IL-2 receptor signalling, resulting in higher levels of IL-2 available for signalling through the intermediate-affinity IL-2 receptor. Key effects of this IL-2 pathway modulation potentially related to the therapeutic effects of daclizumab in MS includes selective antagonism of activated T-cell responses, and expansion of immunoregulatory $CD56^{bright}$ natural killer (NK) cells, which have been shown to selectively decrease activated T-cells. Together, these immunomodulatory effects of daclizumab are believed to reduce CNS pathology in MS and thereby reduce the occurrence of relapses and disability progression.

[1] LIS

- Posology

  The recommended dose of Zinbryta is 150 mg injected subcutaneously once a month. In the pivotal studies, the dose was 150 mg injected subcutaneously every four weeks.

- Undesirable effects

  The most commonly reported adverse reactions from the SELECT and DECIDE studies leading to discontinuation in patients treated with Zinbryta were hepatic reactions, including elevations of serum transaminases (5%), and cutaneous reactions (4%). For a comprehensive list of other adverse effects, see the summary of product characteristics for Zinbryta (5).

1.4.2 Treatment guidelines

The aim of treating patients with RRMS is to reduce the risk of new attacks and subsequent deterioration in daily function.

DMTs are the standard treatment for patients with MS. It is possible to treat both the underlying disease, relapses and MS-related symptoms. DMTs may inhibit the inflammatory process to prevent progression and reduce disabilities due to the disease. The different treatment regimens have different mechanisms of action, routes of administration, approved indications and other differences influencing their use (6) .

The national guidelines for the treatment of MS are currently being updated. A temporary version is available for public consultation. In these guidelines choise of drug is dependant on disease-activity, patient preferences and speceific risks related to the individual DMTs.
In patients with high disease activity, a drug with higher exepcted efficacy should be used (7).

DMTs used in treating RRMS are subject to a tender process under the control of LIS which implements competitive bidding and price negotiations for drugs on behalf of all the RHF's.

The last recommendations from LIS were that the following drugs are considered first line: Betaferon, Extavia, Avonex, Rebif, Copaxone, Tecfidera, and Aubagio, whereas the second line treatment options are Tysabri, Gilenya or Lemtrada. After the last tender, Betaferon is the preferred injectible first line option, Aubagio is the preferred oral first line treatment, whereas Lemtrada is recommended in the second line.

Recommendations by LIS after the tendering process for MS apply to new patients, and patients needing to change treatment.

Daclizumab is not mentioned in the national clinical guidelines. Fingolimod is the most used drug in treating RRMS in Norway today. Because of this, and given the input from Norwegian specialist in RRMS has NoMA concluded that the relevant comparator in this STA is fingolimod (Gilenya), despite the fact that daclizumab has a wider indication.

1.4.3 Comparator

Based on the chapters over NoMA concludes that the most relevant comparator is fingolimod

1.4.4 Treatment with fingolimod

- Therapeutic indication

  Fingolimod is indicated as a single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patients groups:

  - Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy

  or

  - Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

- Mechanism of action

  Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes.

- Posology

  The recommended dose of fingolimod is one 0.5 mg capsule taken orally once daily, according to both the SPC and clinical guidelines (6-8).

- Undesirable effects

  The most serious adverse reactions reported in the pivotal clinical trials for fingolimod 0.5 mg were infections, mascular oedema and transient atrioventricular block during treatment initiation. The most frequent adverse reaction reported for fingolimod 0.5 mg leading to treatment interruption was ALT elevations (2.2 %). For a comprehensive list of other adverse effects, see the summary of product characteristics for fingolimod (8).

2 SUBMITTED DOCUMENTATION TO PROVE THE RELATIVE EFFECTIVENESS

The clinical efficacy of daclizumab was demonstrated in the phase 2 study 205MS201 (SELECT) and phase 3 study 205MS301 (DECIDE). Additionally, Biogen has conducted a systematic literature search and a detailed description of the search strategy has been provided. The searchwas conducted in October 2014. After removal of duplicates and exclusion of non-relevant publications, a total of 520 publications remained. 46 studies were identified from 512 publications and a further six ongoing studies were identified from the remaining eight publications. The identified studies were included in a mixed treatment comparison (MTC) where all relevant treatments of MS were included. In the health economic (HE) model submitted by Biogen, efficacy data is extracted from the DECIDE study and MTC.

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

2.1.1 SELECT (9)

SELECT was a double-blind, placebo-controlled, dose-finding (150 and 300 mg) study to determine the safety and efficacy of daclizumab as a monotherapy treatment in subjects with RRMS.

Table 1: Description of the SELECT-trial

SELECT	
Population	N = 621 from 76 investigational sites in 9 countries worldwide. Female/male ratio 1.7:1. Mean EDSS-score = 2.5
Intervention	Daclizumab 150 mg subcutaneous injection once every four weeks for 52 weeks, N = 208. Daclizumab 300 mg subcutaneous injection once every four weeks for 52 weeks, N = 209.
Comparator	Placebo, N = 204.
Primary outcome	Annualised relapse rate (ARR).
Secondary outcome	• Cumulative number of new gadolinium-enhancing lesions on brain MRI scans done at weeks 8, 12, 16, 20, and 24 in a subset of patients. • Number of new or newly enlarging T2 hyperintense lesions at week 52. • Proportion of relapsing patients between baseline and week 52. • Quality of life, as measured by the change from baseline to week 52 in the 29-item multiple sclerosis impact scale (MSIS-29)15 physical impact score.
Adverse events	Most common adverse events (excluding MS relapses) in patients treated with daclizumab 150 and 300 mg, number (%): • Nasopharyngitis, 60 (14%)

	• Headache, 40 (10%) • Upper respiratory tract infection, 40 (10%) • Pharyngitis, 26 (6%) • Oral herpes, 23 (6%) • Rashes, 23 (6%)

2.1.2 DECIDE (10)

DECIDE was a double-blind, randomized, parallel-group, monotherapy, active-control study to determine the efficacy and safety of daclizumab versus interferon beta-1a in patients with RRMS.

Table 2: Description of the SELECT-trial

DECIDE	
Population	N = 1841 from 246 investigational sites in 28 countries worldwide. Female/male ratio 2.1:1. Mean EDSS-score = 2.5
Intervention	N = 919. Daclizumab 150 mg subcutaneous injection once every four weeks for 96 to 144 weeks.
Comparator	N = 922. Interferon beta-1a 30 µg intramuscular injection once weekly for 96 to 144 weeks.
Primary outcome	Adjusted annual relapse rate (ARR).
Secondary outcome	• New or newly enlarged hyperintense lesions on T2-weighted images over period of 96 weeks. • Disability progression confirmed at 12 weeks at week 144. • Proportion of patients free from relapse at week 144. • Clinically meaningful worsening on the MSIS-29 physical subscale score at week 96.
Adverse events	Most common adverse events (excluding MS relapses) in patients treated with daclizumab, number (%): • Nasopharyngitis, 226 (25%) • Headache, 159 (17%) • Upper respiratory tract infection, 149 (16%) • Pyrexia, 104 (11%) • Injection-site pain, 96 (10%) • Urinary tract infection, 96 (10%) • Influenza-like illness, 88 (10%)

2.1.3 Submitted mixed treatment comparison

A MTC was conducted from the trials identified above to evaluate the efficacy of daclizumab versus other DMTs. The MTC is described in more detail in Appendix 1 Mixed treatment comparisson.

2.2 NoMA's assessment of the submitted evidence

NoMA considers the submitted clinical trials as having sufficient quality to document the efficacy of daclizumab compared to interferon beta-1a and placebo.

As regards the submitted MTC, NoMA has the following comments:
The study selection is the main driving force for the MTC results. Despite the similar scope, the MTC selection presented here is substantially different to that of the Cochrane review (11). In particularly the inclusion of short term follow up studies is considered problematic. This is because short term changes are not considered to have added value for the patient but have a tendency to overestimate the effectiveness of drugs in this setting.

Several deviations from the protocol have been detected. The technical report provides neither an explanation nor does it discuss the potential impact of the deviations.

The MTC methodology has been described in detail and a number of sensitivity analyses are provided to allow the assessment of the impact of the statistical approach as well as the effect of potentially confounding factors present in the clinical studies.

Every MTC is only as good as the underlying data and is driven by the selection of the included studies. The sheer numerical differences presented in this MTC can be questioned, in particular if compared to the results reported in the Cochrane review that has been conducted in the same period and a very similar scope. The most important conclusion is that the qualitative ranking of treatments is comparable between both MTCs. Alemtuzumab and natalizumab are considered more effective while all other treatments can be considered to be of comparable effectiveness.

Based on this NoMA finds the submitted documention sufficient to establish similar effect between daclizumab and fingolimod, but that the MTC is not of sufficent quality to quantify the relative effectiveness for daclizumab compared to fingolimod. Treatment of mulitple sclerosis is associated with high costs, and even a small delay in disease worsening may lead to significant savings.

As NoMA considers the efficacy input based on MTC to be uncertain, a cost-utility model would not give credible information regarding the cost-effectiveness of daclizumab. If the effects are assumed to be similar, the disease costs would also be similar and the only differences in costs would be costs related to the use of the drugs.

NoMA has decided to perform a cost-minimization analysis. The submitted cost-utility analysis will therefore not be validated and hence should not be used as a validated reference in any future analyses .

3 PICO[2]

3.1 PATIENT POPULATION

Norwegian clinical practice
MS is, on average, diagnosed at an age of approximately 30 years. The prevalence and incidence of MS is higher in women than in men.

The patient population in the submitted clinical studies related to Norwegian setting
The population for this economic evaluation was based on the population in the DECIDE-trial. The population was 68 % female with an average age of 36 years. The patients had on average had RRMS for a period of about 4 years. The baseline characteristics of these patients are summarised in the table below.

[2] Patients, Intervention, Comparator, Outcome.

Table 3: Patient characteristics from the DECIDE-trial (10)

Table 1. Characteristics of the Intention-to-Treat Population at Baseline.*

Characteristic	Interferon Beta-1a (N=922)	Daclizumab HYP (N=919)
Age — yr	36.2±9.3	36.4±9.4
Female sex — no. (%)	627 (68)	625 (68)
White race — no. (%)†	828 (90)	823 (90)
Previous therapy — no. (%)		
Disease-modifying therapy‡	376 (41)	380 (41)
Interferon beta	311 (34)	308 (34)
Time since diagnosis — yr	4.1±4.7	4.2±5.0
Time since first symptoms — yr	6.9±6.3	7.0±6.3
No. of relapses in previous 12 mo	1.6±0.8	1.5±0.7
EDSS score§		
Mean	2.5±1.3	2.5±1.2
Median	2.2	2.0
MSIS-29 physical subscale score¶	21.9±19.2	21.5±19.7
No. of hyperintense lesions on T_2-weighted MRI‖	51.8±37.4	49.2±35.5
Gadolinium-enhancing lesions		
Mean no. of lesions**	2.3±5.9	2.0±5.9
≥1 lesions — no./total no. (%)	414/909 (46)	398/900 (44)

* Plus–minus values are means ±SD. The characteristics at baseline were well balanced between the treatment groups (nominal P>0.05). The intention-to-treat population included all the patients who underwent randomization and received at least one dose of study drug. Daclizumab high-yield process (HYP) was administered subcutaneously at a dose of 150 mg every 4 weeks, and interferon beta-1a was administered intramuscularly at a dose of 30 μg once weekly.

† Race was determined by the investigator.

‡ Disease-modifying therapy included any prior disease-modifying or immunomodulatory therapy for multiple sclerosis, such as interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab, mitoxantrone, azathioprine, fumaric acid, laquinimod, cyclophosphamide, mycophenolic acid, fingolimod, teriflunomide, methotrexate, alemtuzumab, cladribine, immune globulin, or temsirolimus.

§ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10.0, with higher scores indicating worse disability.[8]

¶ Data on the 29-item Multiple Sclerosis Impact Scale (MSIS-29) were missing for eight patients in each treatment group. Scores range from 1 to 100, with higher scores indicating a greater physical or psychological effect of multiple sclerosis from the patient's perspective.[10]

‖ Data were missing for 14 patients in the interferon beta-1a group and for 19 in the daclizumab HYP group.

** Data were missing for 13 patients in the interferon beta-1a group and for 19 in the daclizumab HYP group.

NoMA's assessment
The patient population from the DECIDE trial has a similar composition to what would be expected in Norwegian clinical practice. The population is also similar, in particular as regards age, time with disease, and previous treatment, to what has been seen in other STA-reports for MS (3, 4).

NoMA accepts the patient population based on the intention-to-treat population from the DECIDE-trial.

3.2 INTERVENTION

Norwegian clinical practice
Daclizumab is not yet in use in Norway. The dosing regimen in the SPC of 150 mg given subcoutanously once monthly (5), is assumed to be the same dosing that would be used in clinical practice. The clinical guidelines states that all DMTs should be continued as long as the patients are clinically stable (7).

Intervention in the submitted clinical studies related to Norwegian setting.
In the pivotal clinical trial (DECIDE) a dose of 150 mg was given subcoutanously every four weeks for 96 to 144 weeks. Patient with stable disease at the end of the DECIDE-trial had the option of entering the EXTEND trial, and receiving further treatment (10).

NoMA's assessment
The dosing of daclizumab in the clinical documentation is consistent with the approved SPC and presumed clinical practice.

NoMA accepts 150 mg daclizumab given once monthly as a relevant intervention.

3.3 COMPARATOR

Norwegian clinical practice
Several treatment regimens are available for MS. These include interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab, and natalizumab. In the latest LIS recommendations, interferon alfa-1b and teriflunomide are grouped as options for first line treatment, whereas fingolimod, alemtuzumab, and natalizumab are second line options. Fingolimod and teriflunomide are the most used drugs in clinical practice. It seems that fingolimod is the most sutiable comparator, based on sales, input fra clinicians an relative efectivenes results form the MTC.

Comparator in the submitted clinical studies related to Norwegian setting.

In DECIDE, daclizumab was compared to IFNβ-1a. Biogen has also submitted a MTC that enables comparisons between most approved drugs for MS.

NoMA's assessment
Biogen argues that daclizumab has shown similar effect to fingolimod and is likely to replace fingolimod, mostly as a treatment after first-line treatment with glatiramer acetate or teriflunomide, but before treatment with alemtuzumab or natalizumab.

NoMA is uncertain of whether daclizumab and fingolimod will be used to treat highly active patients or active disease patients. However, NoMA agrees that the effect of fingolimod and daclizumab is more comparable than the effect of daclizumab vs. interferons or natalizumab.

NoMA accepts the use of fingolimod as the comparator..

3.4 OUTCOMES

3.4.1 Efficacy

Submitted clinical documentation
The primary endpoint in the DECIDE trial was annualised relapse rate (ARR) over a period of 144 weeks. Secondary efficacy endpoints included new lesions as shown on MRI and disease progression, defined as a worsening of at least 1.0 points on EDSS-score over a period of 144 weeks, or 1.5 points if the patients had an EDSS-score of 0 at the start of the study.

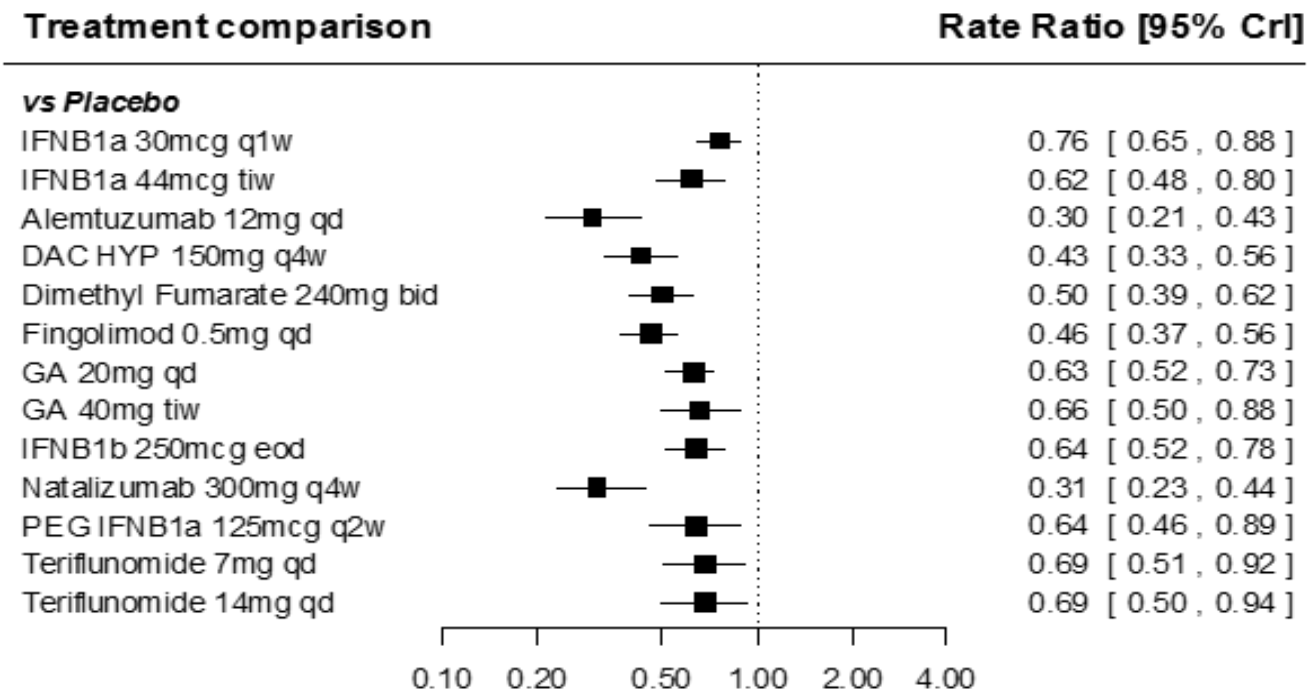
In the submitted MTC, the main endpoints compared are ARR and confirmed disease progression at three months (CDP3M) and six months (CDP6M). In addition the discontinuation rates due to adverse events and discontinuation for any cause are analysed.

The results presented for ARR (Figure 1 and Table 4) support the conclusion that daclizumab is less effective than alemtuzumab and natalizumab. All other treatments show largely overlapping confidence intervals and in general there is little evidence to support significant differences compared to any of the active comparators. The results for CDP3M and CDP6M are less robust and difficult to interpret due to less information in the network, but they also show similar effects for the treatments that are available, and in particular for fingolimod and daclizumab.

Table 4: MTC estimated hazard ratios and 95% credible intervals versus daclizumab for selected drugs

	Fingolimod	Teriflunomide (14 mg)	Alemtuzumab	Placebo
ARR	1.06 (0.76, 1.44)	1.59 (1.07, 2.37)	0.70 (0.46, 1.04)	2.33 (1.79, 3.03)
CDP3M	1.22 (0.53, 2.81)	1.11 (0.45, 2.82)	0.38 (0.11, 1.30)	1.59 (0.75, 3.33)
CDP6M	1.10 (0.45, 2.75)	NR	NR	1.64 (0.73, 3.70)

Figure 1: Indirect comparison of ARR the relevant treatment alternatives in MS



NoMA's assessment

ARR is a recognized endpoint in MS, and is thus acceptable to use in comparing the relative efficacy of the different drugs. Disease progression is probably a more relevant endpoint in clinical practice, as it directly measures the effects on the patients disease over time.

In the most relevant clinical trial it was shown that daclizumab is superior to interferon beta-1a with respect to the primary endpoint (ARR) (10). As interferon beta-1a is not considered a relevant comparator in this STA, NoMA does not assess this comparison further.

The submitted MTC shows little difference between daclizumab and fingolimod for the most relevant endpoints. There is significant uncertainty related to indirect comparison, in particular regarding disease progression. Although the effect size differs from the submitted MTC, a published indirect comparison also showed very similar effect between daclizumab and fingolimod (11). Based on an assessment of the relevant data, NoMA finds the effect of daclizumab to be similar to fingolimod in treating RRMS.

NoMA considers fingolimod and daclizumab to have comparable efficacy in the treatment of RRMS.

3.4.2 Safety

Submitted clinical documentation

As previously mentioned, the hepatic reactions are most likely to lead to treatment discontinuation for patients receiving both daclizumab and fingolimod (5, 8, 10). The rate of hepatic reactions was higher for daclizumab than for fingolimod, which is reflected by the hazard ratio for discontinuation due to adverse events, 0.56 (95 % CrI: 0.05, 5.26). More frequent monitoring of hepatic function is thus recommended when using daclizumab than when using fingolimod (5, 8).

NoMA's assessment

NoMA acknowledges that the hepatic adverse events are somewhat more common for daclizumab than fingolimod, and that this has an effect on discontinuation rates.

NoMA finds it appropriate to compare the safety profiles using the reported discontinuation rates. It would have been useful to compare the rates of the most important adverse events as well (in this case the hepatic events), but it is acknowledged that the comparisons are not powered to detect differences in this domain.

NoMA finds that the effect and safety of daclizumab and fingolimod are similar enough to justify a cost-minimization approach in this STA.

NoMA concludes that the effect and safety of daclizumab and fingolimod are similar enough to justify a cost-minimization approach.

3.4.3 Utility/disutility

NoMA has not validated the QoL-data used in the model as this is not relevant for the cost-minimization analysis hence should not be used as a validated reference in any future analyses.

4 HEALTH ECONOMIC ANALYSIS

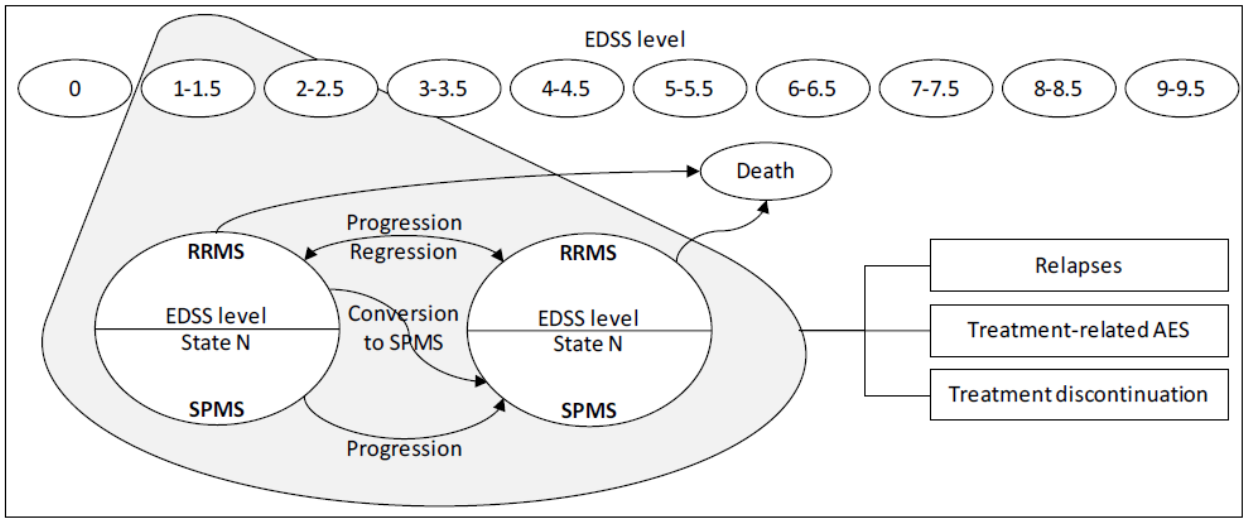
In the base case analysis daclizumab is compared with fingolimod.

4.1 DESCRIPTION OF THE MODEL, METHOD, AND ASSUMPTIONS

Model description

Biogen has developed a Markov cohort model to track the cohort's disease progression and costs throughout their lifetime. Figure 1 illustrates the model structure.

Figure 2: Structure of the Markov cohort model



Abbreviations: AE, adverse event; EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis; State N, current EDSS state

Ovals represent health states. Rectangles represent events that patients can experience at any time. Treatment-related AEs and treatment discontinuation can only occur for patients receiving treatment.

Treatment acts to delay disability progression (i.e., transition to a higher EDSS level) and reduce the frequency of relapses. Patients receiving treatment can experience treatment-related adverse events (AEs) at any time, and can discontinue treatment as a result of various pre-defined reasons. After treatment discontinuation, patients are assumed to follow the natural disease progression course.

The cost-utility-analysis was conducted from the societal perspective in Biogen's basecase. The time horizon for the analysis was 20 years. An annual discount rate of 4.0% was applied to the costs and health benefits occurring beyond the first year.

NoMA has not evaluated nor validated the the model structure and the underlying assumptions, as this is not relevant for the cost-minimization analysis.

4.1.1 Costs

As mentioned previously, NoMA has decided to perform a cost-minimization-analysis. The cost data used in the model have therefore not been validated. The costs specifically related to the drug treatment (monitoring costs and administration costs) may be relevant in a cost minimization analysis, and are shown below.

The administration costs are sourced from a report on MS drugs (1). Monitoring following the first administration of fingolimod (start-up costs) is calculated as part of the administration costs in the submitted documentation (3 750 NOK).

The annual cost of monitoring while receiving treatment was considered separately for the first year on treatment and the subsequent years. The cost of monitoring in the first and subsequent years was calculated from the expected resource use per patient per year on treatment, and Biogen's assumptions are shown below.

Table 5: Monitoring costs for daclizumab and fingolimod the first year

Treatment	Annual Monitoring Cost (NOK)	Resource Use
Daclizumab	10 846 NOK	4 Physician controls 1 MRI 8 blood tests (4 deducted as they are assumed part of the physician control)
Fingolimod	12 562 NOK	4 Physician controls 1 MRI 1 blood test 1 eye exam

Table 6 Monitoring costs for daclizumab and fingolimad in subsequent years

Treatment	Annual Monitoring Cost (NOK)	Resource Use
Daclizumab	7 395 NOK	2 Physician controls 1 MRI 10 blood tests (2 deducted as they are part of the physician control)
Fingolimod	6 275 NOK	2 Physician controls 1 MRI

Daclizumab patients are assumed to visit their physician more frequently. The table below shows Biogen's assumptions on travel costs associated with the physician visits

Table 7: Travel costs related to treatment with daclizumab and fingolimod

Treatment	Annual travel cost first year (NOK)	Resource use first year	Annual travel cost subsequent years (NOK)	Resource use subsequent years

Daclizumab	2 492	4 visits to physician 8 visits to GP for blood tests (4 deducted as they are part of the physician control)	1 915	2 visits to physician 10 visits to GP for blood tests (2 deducted as they are part of the physician control)
Fingolimod	1 600	4 visits to physician	800	2 visits to physician

The frequencies of visits and costs are mostly based on the SPC for daclizumab and fingolimod (5, 8).

4.2 RESULTS

As discussed previously, NoMA has chosen to do a cost-minimizing analysis. Drug costs are determined each year in the LIS-tender, and are thus variable. The costs shown below (table 8) are based on the maximum retail price, and may change based on the results of the LIS-tender.

Table 8: Annual drug costs for daclizumab and fingolimod at maximum retail price (excl. VAT)

	Drug cost	Annual costs
Daclizumab (150 mg)	16805,92 NOK	201671 NOK
Fingolimod (0.5 mg, 28 capsules)	15653,36 NOK	203562 NOK

The annual monitoring, administration, and travel costs related to daclizumab and fingolimod treatments are similar for both drugs (approximately 10 000 NOK).

4.3 NOMA´S CONCLUSION ON COST-EFFECTIVENESS

NoMA has assessed the cost-effectivenness of daclizumab compared to fingolimod in the treatment of RRMS-patients in Norway based on drug costs only. Other costs have been assessed as similar for both drugs, and as having minimal impact on the overall analysis.

NoMA is of the view that daclizumab is a cost-effective treatment for RRMS if the annual drug costs are lower than, or equal to, the annual drug costs of fingolimod. The prices are determined by the annual LIS-MS tender, and NoMA concludes that daclizumab should be included in the forthcoming LIS-MS tender process on the same terms as fingolimod.

5 BUDGET IMPACT ANALYSIS

Biogen estimates that there are roughly 6300 patients with RMS who are eligible for treatment with Zinbryta. Additionally Biogen assumes that there might be approximately [redacted] new theoretically eligible patients per year, with approximately [redacted] of these being potentially eligible for Zinbryta treatment each year.

Biogen assumes that ocrelizumab (Ocrevus), which is a forthcoming treatment but currently unapproved for the same patient population, will have an impact on the market for MS DMTs. For this reason, Biogen has included Ocrevus in its BIM analyses. In order to capture the possible acquisition cost associated with Ocrevus, Biogen has chosen to present a BIM analysis that includes the following scenarios:

- A world where ocrelizumab is reimbursed at a Gilenya-like price
- A world where ocrelizumab is reimbursed at a Lemtrada-like price
- A world where ocrelizumab is reimbursed at a Tysabri-like price
- A world without ocrelizumab

Biogen considers Scenario 1 (a world where ocrelizumab is reimbursed at a Gilenya-like price) to be the most likely scenario. Additionally, an extra scenario that also includes monitoring and administration costs has been included. Monitoring and administration costs are derived from the Knowledge Center for Health Services report on MS medicines (4). For ocrelizumab Biogen assumes two infusions a year, with infusion costs equal to Tysabri. The monitoring costs are also assumed to be equal to Tysabri.

The acquisition cost for Zinbryta is based on a price offer that is NOK [redacted] per pack (LIS AUP [redacted] NOK without VAT). 12 packs are used per year (1 monthly).

The budget impact analysis is calculated for the first 5 years based on two scenarios; the assumption that Zinbryta is recommended for use by the regional health authorities vs. the assumption that the current status quo is maintained. The budget impact is the difference between the two scenarios.

5.1 APPROXIMATION OF THE NUMBER OF PATIENTS POTENTIALLY SUITABLE FOR THE TREATMENT

Table 9: Patient population eligible for treatment with daclizumab

Input	2016	2017	2018	2019	2020	Source
Population size	5 225 558	5 283 472	5 340 336	5 395 780	5 450 106	SSB
MS Prevalence rate	0,20 %	0,20 %	0,20 %	0,20 %	0,20 %	(12)

MS Incidence rate	0,005 %	0,005 %	0,005 %	0,005 %	0,005 %	(13)
Estimated number of prevalent cases	10 608	10 725	10 841	10 953	11 064	SSB, (14)
Estimated number of incident cases						
Total number of MS patients	10 879	11 000	11 118	11 233	11 347	(2)
Mortality	2,030 %	2,030 %	2,030 %	2,030 %	2,030 %	
Net number of prevalent patients with the condition	10 393	10 508	10 621	10 731	10 839	
Eligible population						
Estimated size of eligible incident population						
Estimated size of eligible prevelant population						

The eligible incident population provides the number of patients that can get treatment with zinbryta.

5.2 COST ESTIMATION

The following table shows Biogen's estimate of the annual costs associated with the different treatment options for MS patients.

Table 10: Annual drug costs as estimated by Biogen

Product	Annual costs (NOK)
Avonex	
Plegridy	
Copaxone	
Betaferon	
Extavia	
Rebif	
Tecfidera	
Aubagio	
Zinbryta	
Tysabri	

Gilenya	[redacted]
Lemtrada	[redacted]

Source: Legemiddelinnkjøpssamarbeidet (LIS) tender for 2016 for all prices except Zinbryta. Price for Rebif is calculated as an average for the Rebif-prices

5.3 BUDGET IMPACT

Biogen's estimation of the budget impact of recommending Zinbryta for use in the specialist health service are as follows:

- A world where ocrelizumab is reimbursed at a Gilenya-like price
- A world where ocrelizumab is reimbursed at a Lemtrada-like price
- A world where ocrelizumab is reimbursed at a Tysabri-like price
- A world without ocrelizumab

Table 11: The expected budget impact for Zinbryta as estimated by Biogen

Budget impact	2016	2017	2018	2019	2020
Ocrelizumab is reimbursed at a Gilenya-like price	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab is reimbursed at a Lemtrada-like price	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab is reimbursed at a Tysabri-like price	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A world without ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on the data and assumptions above, Biogen estimates that treating current patients with Zinbryta (daclizumab) will lead to total annual budget savings of approximately [redacted] NOK including VAT in the fifth fiscal year.

Biogen also estimates that the total budget savings in the scenario where administration and monitoring costs are included will range from approximately [redacted] million NOK to [redacted] million NOK in the fifth year.

NoMA's assessment

NoMA reiterates that budget calculations are uncertain and simplistic. However, NoMA disagrees with Biogen's use of an unapproved drug in the calculation of the budget impact. This is because the inclusion introduces more uncertainty based on the fact that we still do not know;

- If ocrelizumab will get approval
- When the MT will be granted i.e uncertainty about the timelines and their impact on the budgeting
- If ocrelizumab will be accepted for use by the Decision forum

- The type of patient population ocrelizumab will be indicated for.

NoMA therefore considers the scenario without ocrelizumab to be more realistic/appropriate for this analysis. Further, NoMA has chosen not to consider the inclusion of administration and monitoring costs in the budget impact analysis according to the guidelines.
Results from Biogen's scenario that NoMA considers most realistic (without the inclusion of ocrelizumab, administration and monitoring costs), show possible savings of about [redacted] NOK in the fifth year. Results from NoMA's cost minimization analysis show that the annual costs associated with zinbryta per patient are higher (by approximately 1 400 NOK) than the costs associated with gilenya. This means that zinbryta will have a higher budget impact than the one estimated in Biogen's analysis. However, NoMA expects the budget impact to be minimal given that the LIS-tender will set the premise for consumption.

6 DISCUSSION

NoMA has assessed daclizumab's placement in the treatment algorithm for RRMS patients in Norwegian clinical practice. Fingolimod is the most used drug in treating RRMS in Norway, and has similar efficacy to daclizumab. NoMA therefore considers fingolimod to be the most relevant comparator in this case.

NoMA considers that the relative effect and safety of daclizumab and fingolimod can be considered to be similar enough to justify an inclusion in the annual tender system on equal terms.

NoMA has chosen to disregard costs related to drug administration and monitoring, as these are assumed to be fairly comparable.

As it is assumed that the introduction of daclizumab will not expand the patient population receiving treatment for RRMS, the budgetary consequences are assumed to be limited.

7 CONCLUSION

NoMA considers, with the available documentation, that:

- *The criterion for disease severity is fulfilled*
  NOMA considers relapsing-remitting multiple sclerosis to be a severe condition that meets the criterion of severe illness, or risk factors that in all probability lead to or exacerbate severe disease.
- *The criterion for relative efficacy is fulfilled.*
  The submitted documentation is of acceptable quality, but is insufficient to quantify the relative effect of fingolimod and daclizumab. The submitted documentation is sufficent to demonstrate similar efficacy between fingolimod and daclizumab.
- *The criterion for cost-effectiveness is fulfilled, if the price is equal to, or lower than, fingolimod*
  NoMA has chosen a cost-minimization analysis where effect of daclizumab and fingolimod are assumed to be similar. Other costs related to drug administration are also considered to be relatively similar.

NoMA finds that daclizumab can be included in the LIS-MS tender on the same conditions as fingolimod.

Norwegian Medicines Agency, xx-xx-2016

Kristin Svanqvist (e.f.)

Marianne Rolstad
Bjørn Oddvar Strøm
Ashkan Kourdalipour
Leung Ming Yu
David Mwaura

REFERENCES

1. Couto E, Hamidi V, Ringerike T, Odgaard-Jensen J, Harboe I, Klemp M. Medicines used for Multiple Sclerosis – A HealthTechnology Assessment. Report from Norwegian Institute of Public Health. In: Health NIoP, editor. Oslo: Norwegian Institute of Public Health; 2016. p. 232.
2. biobank NM-ro. Geografisk variasjon i sykdomsmodulerende behandling ved multippel sklerose for 2014. Available from: https://www.kvalitetsregistre.no/registers/505/resultater/504.
3. Statens Legemiddelverk. Hurtig metodevurdering - Teriflunomid (Aubagio) til behandling av relapserende-remitterende multippel sklerose 2014. Available from: https://legemiddelverket.no/Documents/Refusjon%20og%20pris/Helse%C3%B8konomiske%20rapporter/A/Aubagio_MS_2014.pdf.
4. Statens Legemiddelverk. Hurtig metodevurdering - Dimetylfumarat (Tecfidera) til behandling av relapserende-remitterende multippel sklerose 2014. Available from: https://legemiddelverket.no/Documents/Refusjon%20og%20pris/Helse%C3%B8konomiske%20rapporter/T/Tecfidera_MS_2014.pdf.
5. SPC. Zinbryta - Summary of product characteristics. 2016.
6. Kunnskapssenteret. Medicines used for Multiple Sclerosis - A Health Technology Assessment. Folkehelseinstitutet, 2016.
7. Helsedirektoratet. Høringsutkast - Nasjonale faglige retningslinjer for diagnostikk, attakk- og sykdomsmodifiserende behandling av multippel sklerose 2016. Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/276/Nasjonale-faglige-retningslinjer-diagnostikk-attakk-og-sykdomsmodifiserende-behandling-av-multippel-sklerose-IS-1905.pdf.
8. SPC. Gilenya - Summary of product characteristics. 2016.
9. Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet (London, England). 2013;381(9884):2167-75.
10. Kappos L, Wiendl H, Selmaj K, Arnold DL, Havrdova E, Boyko A, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. The New England journal of medicine. 2015;373(15):1418-28.
11. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. The Cochrane database of systematic reviews. 2015(9):Cd011381.
12. Berg-Hansen P, Moen S, Harbo H, Celius E. High prevalence and no latitude gradient of multiple sclerosis in Norway. Multiple Sclerosis Journal. 2014;20(13):1780-2.
13. Grytten N, Aarseth JH, Lunde H, Myhr K-M. A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway. Journal of Neurology, Neurosurgery & Psychiatry. 2015:jnnp-2014-309906.

14. Torkildsen NG, Lie S, Aarseth J, Nyland H, Myhr K. Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in Western Norway. Multiple sclerosis. 2008;14(9):1191-8.

APPENDIX 1 MIXED TREATMENT COMPARISSON

In absence of head-to-head randomized controlled trials against relevant comparators, comparisons with other treatments have to be derived from indirect comparisons of relative efficacy via common treatment arms in other studies. Many studies, in particular older ones, included placebo arms and by this allow indirect comparisons with a multitude of treatments.

Biogen has submitted the following documentation to support their mixed treatment comparison (MTC) that partly informed the HE-model:

- A systematic literature review (dated March 2015; performed by Kleijnen Systeamtic Reviews, (KSR))
- A Meta-analysis plan (dated 15 May 2015; performed by BresMed)
- The Meta-analysis (dated 21 September 2015; performed by Biogen)

Systematic Literature Review (SLR)

Methodology:

The literature searches and systematic review adhered to published methods including those recommended by NICE, the Cochrane Collaboration and CRD (York, UK), in order to reduce the risk of bias and error. Electronic databases and grey literature sources including trial registries and conference abstracts were searched up to October 2014. Trials were independently selected for inclusion by two reviewers. Inclusion was not limited by language or publication date.

Eligible trials were randomised controlled trials (RCTs) in adults (≥18 yrs) with a confirmed diagnosis of relapsing-remitting multiple sclerosis (RRMS), rapidly evolving severe (RES) RRMS or secondary progressive multiple sclerosis (SPMS).

The main efficacy outcomes were annualised relapse rate (ARR), confirmed disability progression (CDP), proportion of patients with/without relapse and change from baseline in EDSS. Outcomes related to safety, treatment discontinuation, quality of life and MRI were also considered.

Results:

The combined results of all searches yielded 18,182 records before de-duplication. After removing 5,954 duplicates, a total of 12,218 references were available for screening of titles and abstracts. A

further 10 records were identified from reference checking and internal clinical study reports provided by Biogen to give a final total of 12,228 records.

Titles and abstracts of 12,228 references were screened and 730 potentially relevant papers ordered as full texts. Screening of full text papers identified 512 relevant publications reporting 46 studies. A further six ongoing studies were reported in eight publications.

Reports for all screened references (with detailed information on quality and why thwy were included or excluded) were available but are not further described here.

Of the 46 included in the SLR 37 were considered relevant for the scope. Eight completed trials had no available data at the relevant time points for the review (12 or 24 months) (CombiRx, CORAL, Crentsil 2012, IMA 04001, Kira 2011, O'Connor 2006, TENERE and TOWER). SELECTION was a phase 2b extension study that enrolled patients who previously completed the SELECT study. As these patients were already counted in any analysis from the SELECT study the data from the SELECTION study could not also be included. These studies were not considered further in the remainder of the review.

As can be expected considerable heterogeneity between studies was detected since the oldest trial was published in 1987 (Bornstein 1987) and the most recent nine were published or data made available in 2014 (ADVANCE, BRAVO, FREEDOMS II, GLOW, Mokhber 2014, SELECTION, TOWER, TENERE) or 2015 (DECIDE).

Heterogeneity was mainly due to difference in the inclusion criteria of the different trials with respect to:

- Age
- MS diagnostic criteria used
- EDSS baseline score
- Criteria with respect to previous treatments received

he SLR provided a comprehensive overview of the characteristics of the included studies which is considered of high quality but not reproduce here.

NoMA's assessment:

The SLR is considered of high quality. We agree with the authors that they have used rigorous methods to ensure the best possible quality to answer the research question. We consider the report transparent and exhaustive, all relevant information to assess the actual results as well as the quality of the SLR itself have been provided.

In the SLR it is mentioned that the same authors would provide a critical review of the MTC analysis plan as well as the final report. Yet no such reports have been submitted, neither on the MCT analysis plan from BresMed nor the final analysis report by Biogen.

NoMA is aware of a Cochrane Review performed with a comparable scope to the SLR provided here (11). In contrast, the Cochrane review excluded studies with follow-up less or equal to six month, because they consider short term outcomes not clinically relevant to patients with MS. NoMA supports this view on lack of clinical relevance of short term measures. The Cochrane Review also included additional treatments (mitoxantrone, ocrelizumab, laquinimod, azathioprine and immunoglobulins) that were not considered in the SLR submitted here. Consequently, there is only a moderate overlap between included studies in both reviews, despite a comparable research questions and a comparable patient population.

It is also noted that for those studies selected by both research teams a certain discrepancy can be detected in terms of quality assessment of the individual studies.

This emphasises that despite the technical quality of the SLR uncertainty remains about the true relative effect between treatments. This will be further discussed in the assessment of the MTC.

Mixed treatment comparison (MTC)

Methodology:

The endpoints/outcomes of Interest for these analyses are:

- Annualized relapse rate (ARR)
- Proportion of patients relapse free
- Confirmed disability progression at 3 months (CDP3M)
- Confirmed disability progression at 6 months (CDP6M)
- Change from baseline EDSS
- Discontinuations due to adverse events
- All cause discontinuation

Other endpoints, such as MRI and quality of life based outcomes, and/or qualitative assessment of adverse events, may be considered for analysis outside of, and following, the endpoint analyses described in this document.

There were 52 studies (including 6 ongoing studies) that met the inclusion criteria for the systematic review and they are the basis for the Meta-analysis reported. Of the 52 studies included in the systematic review, 28 were included in the meta-analysis treatment network. Inclusion in the network was determined by inclusion of at least one treatment of interest in the trial, a link into the treatment network via a common comparator and data availability for at least one outcome of interest. The reasons for exclusion of the meta-analysis treatment network are: no treatment of interest (7 trials, including 2 ongoing trials), ongoing trial (4 trials), no reported outcomes of interest (7 trials), does not link into the network (4 trials), extension trial (1 trial), and conference abstract only/not enough information (1 trial).

NoMA's assessment:

It is noted that 37 studies were identified in the SLR as applicable but only 28 studies were found applicable by BresMed.

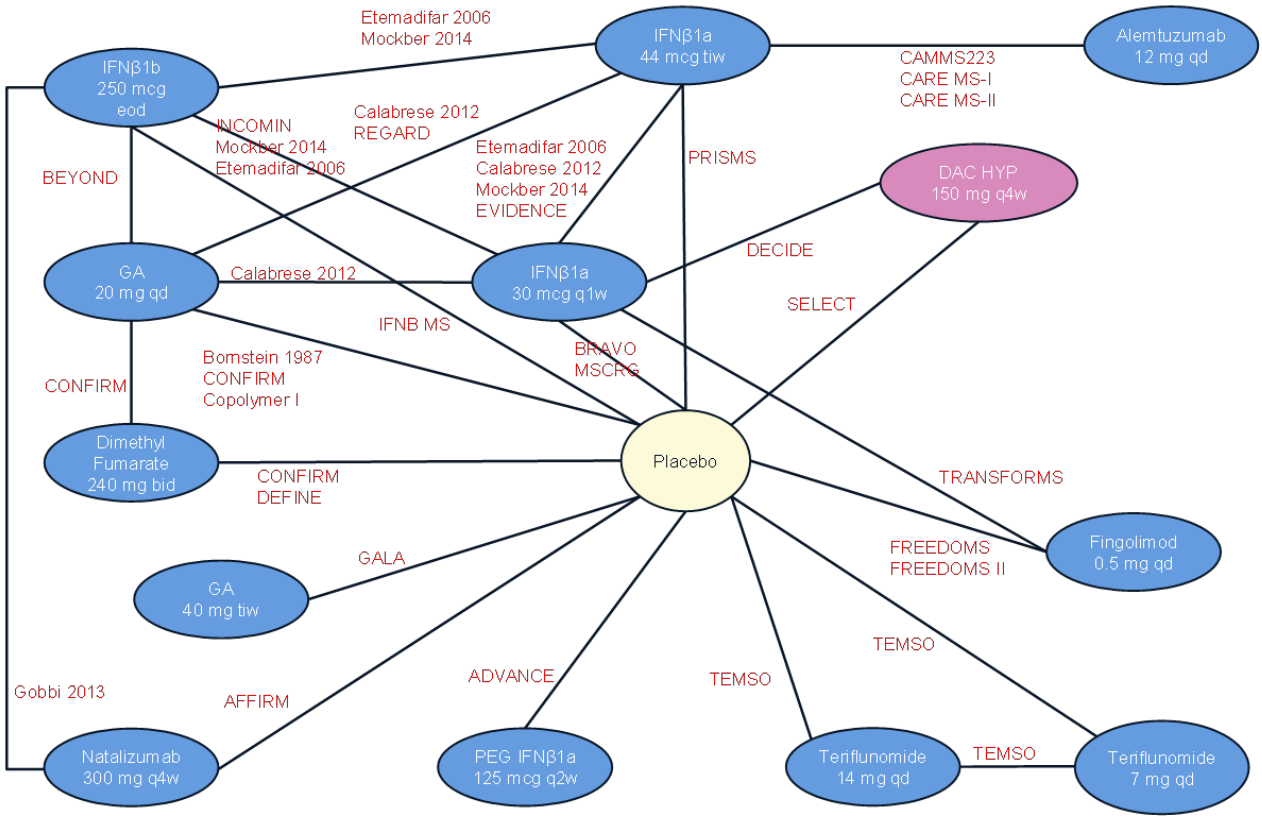
In the Network construction study arms of no interest were excluded from the primary Meta-analyses. Simply excluding arms can be problematic when no appropriate measure are taken to correct for changes in multi-arm studies impact in the context of a Meta-analysis.

It is unclear if the modified criteria that lead to exclusion of additional studies were necessary or actually improved the quality of the Meta-analysis. Again, in comparison to the Cochran report, it is emphasised that small changes in the selection criteria for any Meta-analysis can lead to poorly comparable sets of included studies.

Results Meta-analysis:

A primary network was constructed based on the 28 selected trials.

Figur 1: ***Network diagram for Primary Meta-Analysis***
Includes trials/treatments that are included in the primary network. Endpoint and timepoint specific analyses will be a subset of this network.



A comprehensive analysis on trial characteristics is provided in the Meta-analysis plan.

NoMA's assessment:

As can be expected a reasonable heterogeneity is present since studies have been published over a long period of time, had differences in the inclusion criteria (baseline EDSS, Age, relapse criteria and MS diagnostic criteria), study length, sample size and disease duration.

Sources of heterogeneity are assessed and discussed, a number of sensitivity analyses are proposed, several of which, but not all of them have been presented in the technical document.

Technically the construction of the network is considered acceptable, but the robustness of the network is largely dependent on the selection of included/excluded studies, something already pointed out in earlier comments.

Different studies report different end-points, for the ARR 19 studies were included into the network according to the Meta-analysis plan document. For confirmed disease progression at 3 and 6 months, fewer studies contributed to the network, something that leads to less robust data. In addition, the analyses are based on hazard ratios partly imputed rather than proportions reported directly. The use of hazard ratios might be questioned in a situation where multi arm trials were included in the literature review but no correction is performed for excluding arms of no interest in the Meta-analysis. It is not possible to assess the potential impact of this approach in the current submission but it must be considered a potential source of uncertainty.

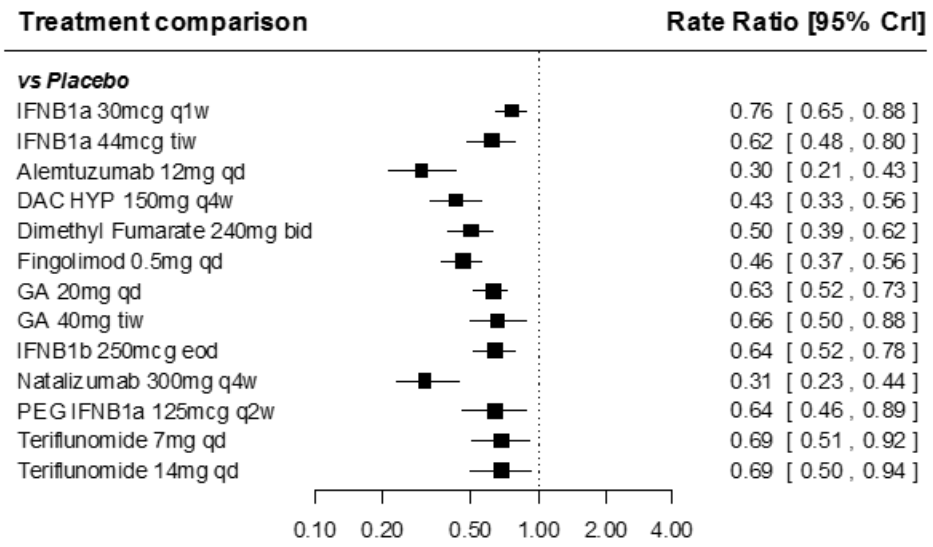
The 1 year network for discontinuation due to adverse events includes very few studies and is not considered robust enough to draw conclusions from. The 2 year network is more extensive and considered more robust.

Several analyses are conducted to confirm the robustness of the results and explore potential confounders.

Main results of the mixed treatment analysis:

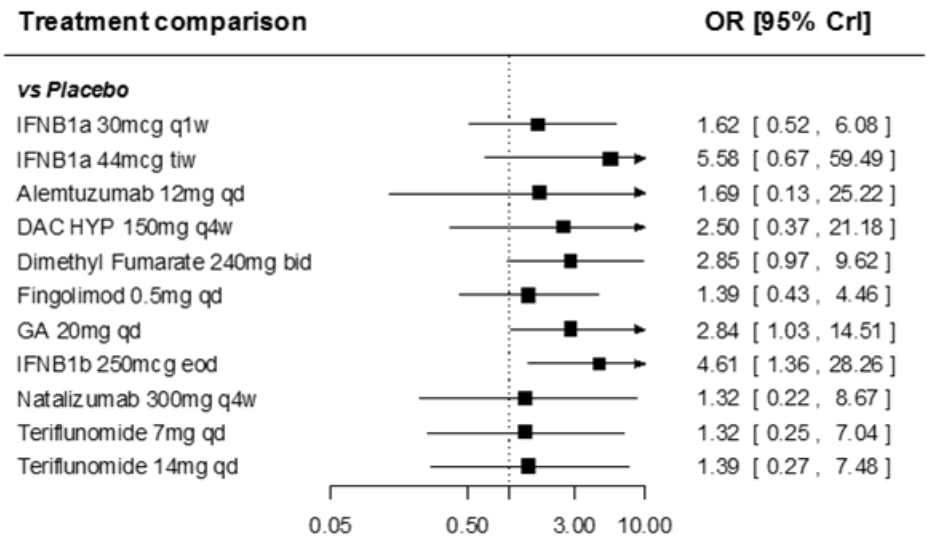
Figur 2 presents all pairwise comparisons of the Bayesian analysis versus placebo.

Figur 2: ***ARR – Pairwise treatment comparisons – Base case (vs Placebo)***



The results for adverse events from the MTC confirm the conclusions on the lack of robustness of the networks for adverse events. Results presented here are for adverse event discontinuation at 2 years only, as this is the larger network anyhow (Figur 3).

Figur 3: ***AE discontinuations – Pairwise treatment comparisons – Base case (vs Placebo)***



NoMA's assessment:

Results presented for ARR support the conclusion that DAC HYP is less effective than Alemtuzumab and Natalizumab. All other treatments show largely overlapping confidence intervals and in general there is little evidence to support significant differences compared to any of the active comparators.

Results for a fixed effects model were similar (not shown).

When compared to results presented in the Cochrane review there are clear numerical differences in the comparisons versus placebo (generally all treatments obtain better ARR in the Biogen analysis compared to Cochrane), yet qualitatively the ranking of treatments is comparable.

It is clear that these mixed comparisons cannot be directly compared due to differences already discussed earlier, yet there is reason to believe that certain elements in the study selection lead to potential overestimation of ARR in the Biogen MTC. In particular, the inclusion of studies with short term follow up, prone to overestimate the actual sustained response, is considered a shortcoming of the presented results.

In addition ARR is presented as a mix of 1 and 2-year data, so some data is imputed. Separate analyses for 1 and 2-year data have been provided and despite numerical differences and the fact that for some comparisons no data was available the overall conclusion is that this approach would not change the treatment ranking, rather that it potentially has influence on the absolute numerical ratios.

Despite the numerical difference to the Cochrane review, the qualitative results in terms of ranking are comparable. Alemtuzumab and Natalizumab are outperforming all other treatments. For all other treatments, there is no evidence for substantial differences in efficacy. Again, all provided sensitivity analyses support the primary finding.

The CPD6M results are considered little robust. The CPD3M data are derived from a better-informed network but as mentioned earlier, the methodology used to obtain the hazard ratios can be criticised. As for ARR the numerical results are considered less reliable than the qualitative ranking information provided. The result again support the conclusion that there is little indication of substantial differences between treatments with the exception of Alemtuzumab and Natalizumab.

As is indicated by the wide credibility intervals, even for the better informed 2 year network results must be interpreted with caution. No firm conclusions on differences in safety profiles for any of the drugs can be derived from these data. This is also supported by the sensitivity analyses that consistently show high variability and width in the credibility intervals.

Overall Conclusions:

The systamatic litterature review (SLR) is considered of good quality. Based on the research question, the selection criteria and the conduct of the review there is no reason to assume that relevant studies have not been assessed.

The MTC has not been assessed by the same authors than the SLR. Additional criteria for selection have been used that further reduced the number of studies included in the MTC. In addition have treatment arms of no interest been excluded. This is potentially a source of uncertainty

The study selection is the main driving force for the MTC results. Despite the similar scope, the MTC selection presented here is substantially different to that of the Cochrane review. In particularly the inclusion of short term follow up studies is considered problematic. Short term changes are not considered of value to the patient and tend to overestimate the effectiveness of rugs in this setting.

Several deviations from the protocol have been detected. The technical report provides neither an explanation nor does it discuss the potential impact of those deviations.

The MTC methodology has been described in detail and a number of sensitivity analyses are provided to allow the assessment of the impact of the statistical approach as well as potentially confounding factors present in the clinical studies.

Every MTC is only as good as the underlying data and is driven by the selection of the included studies. The sheer numerical differences presented in this MTC can be questioned, in particular if compared to the numbers reported in the Cochrane review that has been conducted in the same period and a very similar scope. The most important conclusion is that the qualitative ranking of treatments is comparable between both MTC's. Alemtuzumab and Natalizumab are considered more effective, all other treatments can be considered of comparable relative effectiveness.

APPENDIX 2: KORT OM HELSEØKONOMI OG BEGREPER I RAPPORTEN

Legemiddelverket har i flere år vurdert kostnadseffektivitet av legemidler som søker opptak til forhåndsgodkjent refusjon. Slike vurderinger baserer seg på "Forskrift om stønad til dekning av utgifter til viktige legemidler mv. (blåreseptforskriften)".

Følgende faglige kriterier vurderes:

- Om legemidlet skal brukes til behandling av alvorlige sykdommer eller av risikofaktorer som med høy sannsynlighet vil medføre eller forverre alvorlig sykdom
- Om sykdommen eller risiko for sykdom som nevnt i punktet over medfører behov eller risiko for gjentatt behandling over en langvarig periode
- Om legemidlet har en vitenskapelig godt dokumentert og klinisk relevant virkning i en definert, aktuell pasientpopulasjon
- Om kostnadene ved bruk av legemidlet står i et rimelig forhold til den behandlingsmessige verdi og til kostnader forbundet med alternativ behandling.

Produsenten av legemiddelet utarbeider en legemiddeløkonomisk analyse for å dokumentere at disse kriteriene er oppfylt hvorpå Legemiddelverket kritisk vurderer den innsendte analysen med tilhørende dokumentasjon.

Legemiddelverket har fra 2013 fått i oppdrag fra Helse-og omsorgsdepartementet å vurdere kostnadseffektiviteten av legemidler som vurderes innført i spesialisthelsetjenesten. Vurderingen baseres i hovedsak på legemiddeløkonomiske analyser utarbeidet av legemiddelprodusenten etter tilsvarende mal som for blåreseptsaker.

Vurdering av kostnadseffektivitet kan bidra til at samfunnet kan velge de tiltakene som maksimerer nytte gitt hensyn til fordeling m.m.

For lettere å forstå innholdet i rapporten gis det nedenfor en kort innføring i helseøkonomiske begreper som også i denne saken vil kunne forekomme.

Legemiddeløkonomisk evaluering – er en helseøkonomisk evaluering der intervensjonene som evalueres er legemidler

Intervensjon – er det behandlingsalternativet/legemidlet som vurderes og som er utgangspunkt for analysen.

Komparator – er det behandlingsalternativet/legemidlet som sannsynligvis vil fortrenges dersom intervensjonen tas i bruk.

ICER – er en måleenhet for kostnader i forhold til effekt, for vurdering av kostnadseffektivitet. ICER står for incremental cost-effect ratio, og angir den inkrementelle kostnads-effekt raten (IKER på norsk):

$$\text{ICER} = \frac{\text{Kostnader Intervensjon - Kostnader Komparator}}{\text{Helseeffekt Intervensjon - Helseeffekt Komparator}}$$

Dette betyr at ICER påvirkes av både kostnader og effekter. Usikkerheter rundt en eller begge av disse, kan ha stor betydning for ICER. I analysene inngår legemiddelkostnader, men også kostnader til sykehusinnleggelser, primærhelsetjenesten m.m. knyttet til de to behandlingene (intervensjon og komparator). ICER angir således netto merkostnad per vunnet enhet helseeffekt for den nye behandlingen sammenliknet med komparator, for eksempel merkostnader per vunne kvalitetsjusterte leveår (QALYs).

Kostnadseffektivitet – en intervensjon vurderes gjerne som kostnadseffektiv (sammenliknet med komparator) dersom ICER er lavere enn det man er villig til å betale for helseeffekten som oppnås. Betalingsvilligheten kan variere med alvorlighetsgrad, effektstørrelse m.m.

Modeller – For vurdering av kostnadseffektivitet brukes ofte helseøkonomiske beregningsmodeller. Dette fordi datagrunnlaget fra kliniske studier ofte er for begrenset til å vurdere alle relevante helseeffekter og kostnader over tilstrekkelig lang tidsperiode. I modellene kombineres best mulig informasjon fra ulike kilder matematisk for å anslå forventede effekter på helse, livskvalitet og kostnader av ulike behandlinger.

QALY – er et mål på størrelsen av helsegevinster. QALY står for quality adjusted life year, og angir effekt både på levetid og helserelatert livskvalitet. Til beregningene benyttes QALY-vekter (også kalt nyttevekter) for ulike helsetilstander, fra 0 ved død til 1 ved full helse. Ett år med perfekt helse tilsvarer 1 QALY. Dersom et tiltak øker levetiden til en pasient med 1 år, men at kvaliteten på dette året vurderes som lavere enn perfekt helse, vil denne gevinsten få en lavere verdi enn 1. Også effekten av tiltak som ikke er livsforlengende kan måles i QALY, i det de kan bedre helsetilstanden til pasienten i en gitt periode.

LYG – er en måleenhet som angir helseeffekten i vunne leveår (life years gained). Denne måleenheten kobles ofte opp mot kostnaden for en behandling og uttrykkes som merkostnad per vunne leveår. I motsetning til QALY tar LYG ikke hensyn til livskvaliteten i de vunne leveårene.

TTO – er en måte å måle QALY på. TTO står for ”time trade off”, og går ut på at man enten beskriver en helsetilstand for et individ, eller spør en pasient med tilstanden man ønsker å undersøke, om hvordan han verdsetter tilstanden. Dette gjøres ved at individet blir bedt om å angi hvor mye tid i perfekt helse, av en fremtidig periode på 10 år, individet er villig til å oppgi for å unngå 10 år i tilstanden man vil verdsette.

SG – er en måte å måle QALY på. SG står for ”standard gamble”, og går ut på at man enten beskriver en helsetilstand for et individ, eller spør en pasient med tilstanden man ønsker å undersøke, om hvordan han verdsetter tilstanden. Dette gjøres ved at individet blir presentert for to alternativer: Alternativ 1 er å leve

resten av livet med tilstanden man vil verdsette; alternativ 2 er en fiktiv intervensjon som enten vil gjøre individet frisk fra tilstanden for resten av individets levetid eller være dødelig. Individet blir så spurt om hvor liten sannsynlighet for overlevelse ved intervensjonen individet vil være villig til å akseptere, og fortsatt takke ja til intervensjonen. Er tilstanden veldig alvorlig og lite ønskelig, vil pasienten være villig til å risikere livet i større grad og akseptere en lavere sannsynlighet for å overleve intervensjonen.

Analyseperspektiv – angir hvilket perspektiv analysen har. Her skiller man gjerne mellom helsetjenesteperspektiv og samfunnsperspektiv. Mens helsetjenesteperspektivet kun tar hensyn til effekter og kostnader i helsetjenesten vil man i et samfunnsperspektiv i tillegg også inkludere andre gevinster/kostnader utenom spesialisthelsetjenesten som endringer i produktivitetstap, spart tid osv.

Ekstrapolering – innebærer framskrivning av data utover tidsperioden med konkrete studiedata. Dette vil si en form for modellering av sannsynligheten for fremtidige hendelser basert på tilgjengelige data. Dette gjøres for eksempel i analyser hvor det kun finnes studiedata for en kortere periode. Sannsynligheten for overlevelse vurderes da utover tidsperioden dekket av tilgjengelige studiedata, og man lager en prognose på bakgrunn av dette. En slik ekstrapolering vil kunne brukes som grunnlag for et tidsperspektiv som er lengre enn det finnes studiedata for.

Diskontering – er en metode som benyttes for å kunne sammenlikne og summere helseeffekter og kostnader som oppstår i ulike år. De årlige helse- og kostnadsvirkninger omregnes til en nåverdi og i en slik nåverdiberegning blir både helseeffekter og kostnader diskontert med en rate som i skrivende stund er 4 prosent per år. Dette antas å gjelde de fleste tiltak innen helsesektoren. Nåverdien regnes ut etter følgende formel hvor P er nåverdi, F er kostnaden (eller helseeffekten), t er tiden og r er diskonteringsraten:

$$P = \frac{F}{(1+r)^t}$$

Deterministisk sensitivitetsanalyse (DSA) – er en usikkerhetsmåling som brukes for å undersøke robustheten av analysen. DSA tar utgangspunkt i en deterministisk hovedanalyse. I den deterministiske hovedanalysen bruker man en fastsatt verdi for hver parameter uten å ta hensyn til usikkerheten rundt parameteren. I en deterministisk *sensitivitets*analyse endrer man en og en eller kun et mindre antall variabler om gangen. Ved å gjøre dette får man se effekten en bestemt variabel har på utfallet.

Probabilistisk sensitivitetsanalyse (PSA) – er en usikkerhetsmåling som brukes for å undersøke robustheten av analysen. De enkelte parametre i den økonomiske beregningsmodellen tilordnes en sannsynlighetsfordeling. I en probabilistisk sensitivitetsanalyse utføres en rekke (f.eks. 2000) simuleringer med modellen. I hver simulering trekkes en verdi for hver parameter ut ifra sannsynlighetsfordelingene. Modellen simuleres så med disse parameterverdiene. Hver simulering gir et anslag på kostnader og effekt. En kan derfor si at i en PSA endrer man en rekke gitte variabler innenfor et forhåndsbestemt

intervall samtidig i hver simulering. Resultatene av simuleringene presenteres gjerne som en «sky» i et diagram med merkostnader og mereffekt på hver akse.

Cost effect acceptability curve (CEAC) – er en kurve som viser sammenhengen mellom betalingsvillighet og sannsynligheten for kostnadseffektivitet (dvs at ICER er lavere enn ulike nivåer for betalingsvillighet). Kurven er basert på probabilistiske simuleringer og brukes for å vurdere om et tiltak er kostnadseffektivt eller ikke avhengig av hvor tiltaket kan plasseres, over eller under CEAC.