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Norwegian Institute of Public Health

REPORT

2019

# HEALTH ECONOMIC EVALUATION:

## Disease modifying treatments for relapsing remitting multiple sclerosis

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Division for Health Services
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A health economic evaluation.
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En helseøkonomisk evaluering
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# Key Messages

The Norwegian Institute of Public health has previously assessed the efficacy, safety and cost effectiveness of drugs for relapsing remitting multiple sclerosis. In this report, three new drugs (cladribine, ocrelizumab and rituximab) are included. Effectiveness, safety and legal aspects are reported in a separate publication, as is ethical considerations. This report assesses the included drugs in light of the Norwegian priority setting criteria (benefit, resource use and disease severity).

- Relapsing remitting multiple sclerosis is a very severe disease, with an estimated absolute shortfall of 32 undiscounted quality adjusted life years (QALYs).
- In terms of health benefits, ocrelizumab is the treatment alternative that generates most health benefits (QALYs), while glatiramer acetate (40mg) generates the least.
- Ranked acording to decreasing health benefits, ocrelizumab, alemtuzumab, natalizumab, rituximab, dimethyl fumerate, fingolimod, cladribine, teriflunomide, glatiramer acetate (20 mg) og glatiramer acetate (40mg) generate respectively 8.29, 8.27, 8.15, 8.14, 8.11, 7.95, 7.92, 7.79, 7.65 and 7.36 discounted QALYs.
- Some of the differences between the treatments are large compared to what is common in other disease areas.
- In terms of resource use over a 20 year timeperiod, applying a broad healthcare perspective, natalizumab generates most costs and rituximab least costs based on net prices.
- Ranked by increasing cost, rituximab, cladribine, alemtuzumab, glatiramer acetate (20 mg), teriflunomide, glatiramer acetate (40mg), dimethyl fumerate, ocrelizumab, fingolimod and natalizumab generate respectively discounted NOK [redacted] and [redacted] based on net prices.
- Rituximab is more effective and less costly than cladribine (i.e. a dominant treatment strategy). Compared to alemtuzumab, rituximab is less effective, but also less costly.
- Ocrelizumab generates more health and more cost than cladribine, alemtuzumab and rituximab. Whether or not ocrelizumab can be considered a cost effective alternative, depend on assumed threshold value for cost effectiveness.

**Title:**
Disease modifying treatments for relapsing remitting multiple sclerosis- A health economic evaluation.

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**Type of publication:**
Health economic evaluation

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**Doesn't answer everything:**
This report is limited to relapsing remitting multiple sclerosis. The report only includes pharmacological treatment options.

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**Publisher:**
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# Hovedbudskap (Norwegian)

Folkehelseinstituttet har tidligere evaluert klinisk effekt, sikkerhet og kostnadseffektivitet av legemidler til behandling av relapserende remitterende multippel sklerose. I denne rapporten inkluderer vi tre nye legemidler (kladribin, okrelizumab og rituximab). Effekt, sikkerhet, og juridiske aspekter er publisert i en egen rapport, det samme gjelder etiske aspekter. I denne rapporten vurderer vi i hvilken grad de inkluderte legemidlene oppfyller de norske prioriteringskriteriene (nytte, ressursbruk og sykdommens alvorlighet).

- Relapserende remitterende multippel sklerose er en svært alvorlig sykdom med et estimert absolutt prognosetap på 32 udiskonterte livskvalitetsjusterte leveår (QALYs).
- Av de inkluderet behandlingene, så genererer ockelizumab mest og glatiramer acetate (40mg) minst helse målt i QALYs.
- Helseeffekten av ocrelizumab, alemtuzumab, natalizumab, rituximab, dimethyl fumerate, fingolimod, cladribine, teriflunomide, glatiramer acetate (20 mg) og glatiramer acetate (40mg) er henholdsvis 8,29, 8,27, 8,15, 8,14, 8,11, 7,95, 7,92, 7,79, 7,65 and 7,36 diskonterte QALYs.
- Noen av forskjellene i helseeffekt mellom legemidlene er store sammenlignet med forskjeller som er vanlige for andre sykdomsområder.
- I et bredt helsetjenesteperspektiv og over en tidsperiode på 20 år, genererer natalizumab mest og rituximab minst kostnader, basert på tilbuspriser.
- Rangert etter stigende kostnader genererer rituximab, kladribin, alemtuzumab, glatiramer acetate (20 mg), teriflunomide, glatiramer acetate (40mg), dimethyl fumerate, okrelizumab, fingolimod and natalizumab en diskontert ressursbruk på henholdsvis NOK [redacted] og [redacted] basert på tilbudspriser.
- Rituximab generer mer helse og mindre kostnader enn kladribin (er en dominant strategi). Sammenlignet med alemtuzumab, genererer rituximab mindre helse og også mindre kostnader.
- Ocrelizumab genererer større helseeffekter og også større kostnader enn kladribin, alemtuzumab og rituximab. Hvorvidt okrelizumab kan vurderes å være et kostnadseffektivt alternativ avhenger av antatt terskelverdi for kostnadseffektivitet.

**Tittel:**
Sykdomsmodifiserende behandling for relapserende remitterende multippel sklerose. En helseøkonomisk evaluering

**Publikasjonstype:**
Helseøkonomisk evaluering

**Svarer ikke på alt:**
Denne rapporten omhandler kun relapserende remitterende multippel sklerose. Rapporten ser kun på ulike legemidler, ikke andre typer behandling.

**Hvem står bak denne publikasjonen?**
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Bestillerforum RHF

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# Preface

**The Norwegian Institute of Public Health takes full responsibility for the content of this report. The clinical expert group, internal- and external reviewers hold no responsibility for the content of the report.**

The Norwegian Institute of Public Health supports transparency about health technology assessments and the basis for these. At the same time, the Institute is obliged by the Public Administration Act and must therefore prevent others from gaining access to certain information that can be commercially sensitive, such as technical devices and procedures, as well as operational or business matters which for competition reasons it is important to keep secret. As the Institute interprets the law, some information about price in this report is such confidential information.

The Norwegian Institute of Public Health received a commission from the Commissioning Forum in The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway on the 23.04.2018 to undertake a full Health Technology Assessment of drugs for relapsing remitting multiple sclerosis, including rituximab, cladribine, alemtuzumab, natalizumab, fingolimod, glatiramer acetate and ocrelizumab. This report contains the health economic evaluation of the included drugs. A report on effectiveness, safety, and legal aspects is published separately (1), as is ethical considerations (2). The three documents should be considered together. NIPH started the project on the 14th of May 2018.

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We would like to thank our excellent clinical expert group and reviewers.

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| **LOGG** | |
|---|---|
| Suggestion submitted for full HTA | 30.01.2018 |
| HTA report commissioned | 23.04.2018 |
| Start HTA | 15.05.2018 |
| Clinical experts contacted first time | 19.06.2018 |
| First meeting with clinical expert group | 19.06.2018 |
| Estimates of clinical effectiveness finalized | 05.06.2019 |
| Report sent to review | 13.06.2019 |
| Report delivered | 28.06.2019 |
| **Time** | |
| Number of days from commission to project start | 21 |
| Number of days from commission to delivery | 431 |

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# Introduction

## Health policy context

The Norwegian Institute of Public Health has previously assessed the efficacy, safety and cost effectiveness of drugs for the treatment of relapsing remitting multiple sclerosis (RRMS) (3).

Since that time, two new treatments have received marketing authorization (MA) for RRMS, namely cladribine and ocrelizumab. These two drugs have been assessed by single technology appraisals by the Norwegian Medicines Agency (NoMA) (4;5). Only cladribine has been included in routine public financing at the time of writing this report.

In the debate surrounding adoption of ocrelizumab, off-label use of rituximab for RRMS also became a topic of discussion (6). Rituximab does not hold a MA for RRMS, and a HTA for this indication has not been conducted. At the same time, some Norwegian health regions have included rituximab in routine clinical practice. Against this background, the Comissioning Forum for the Regional Health Authorities commissioned a HTA of drugs for the treatment of RRMS that included rituximab. While the HTA process was ongoing, rituximab was granted an exception from the rule that new treatments should not be used while undergoing HTA evaluation (7).

Currently, all MS drugs with a MA for RRMS that have also been apporoved for public financing are part of a national annual tender. Due to the presence of a national tender, the cost effectiveness of all MS drugs (e.g. cladribine and ocrelizumab) have not been assessed by NoMA. Instead NoMA has evaluated whether or not the new drugs could be considered to have similar efficacy as the ones already included in the tender.

The logic being that assuming all drugs have the same efficacy, ranking them on price only would ensure fulfilment of the priorization criteria. As long as the assumption of similar efficacy holds, this would be a valid approach. However, should this assumption

not hold true, one risks funding non cost effective treatment alternatives, thereby distorting funds away from interventions that would have improved population health.

While the present report assesses to what degree the included treaments fulfill the Norwegian priority setting criteria health benefits, resource use and disease severity. effectiveness, safety and legal aspects are assessed in another report (1), as is ehtical considerations (2).

## Priority setting criteria

There are three primary criteria for setting priorities in the Norwegian health care sector: the benefit criterion , the resource criterion, and the severity criterion (8-10).

### Benefit

According to the benefit criterion, priority increases with the size of the expected benefit of the intervention. The benefit criterion primarily refers to a technology's expected health effects: increased longevity and/or improved health-related quality of life. By combining these two types of health gains into a single outcome measure, the quality-adjusted life-year (QALY), it is possible to compare treatment outcomes across different diseases, patient groups and types of treatments.

### Resources

According to the resource criterion, priority increases, as fewer resources are needed for the intervention.

The resource criterion focuses on how the health sector uses its limited resources. Introducing a new technology creates demands for personnel, equipment, facilities, etc. that could have been used to provide treatments for other patients – a reality that is referred to as the "opportunity cost" of the new technology. The larger the quantity of resources allocated to a technology for one patient group, the fewer the resources available for treating others. In addition to resource use within the health sector, a technology may also engender costs for other parties.

**Severity of Disease**

According to the severity criterion, priority increases with expected future health loss resulting from the disease. Severity of disease is measured as "absolute shortfall", defined as the expected loss of future health (QALYs) associated with a specified diagnosis. For treatment of a diagnosed disease, severity is the average expected absolute shortfall for the relevant patient group given the current standard treatment.
Generally, the greater the absolute shortfall associated with a disease, the more resources per QALY gained the authorities may be willing to allocate.

**Cost-effectiveness**

In practice, the three priority setting criteria are taken into account by weighing costs against benefits in a cost-effectiveness analysis of the technology of interest. Resource use, measured as monetary costs, enters into the numerator of the cost-effectiveness ratio (see further description below), while the health effect enters in the denominator.

Norwegian policy documents indicate that weighting of resource use against health benefits should be based on the opportunity cost principle, and that priority should be further increased according to disease severity (absolute shortfall).

## Introduction to Economic Evaluation of Health Care Programmes

The aim of a health economic evaluation is to compare health effects and costs of the alternatives under consideration in an incremental analysis, one in which the differences in health effects are compared with differences costs. Results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

The health care sector, similarly to society in general, is restricted by limited resources and budget constraints. Therefore, economic evaluations are important tools for decision makers facing questions of how to prioritize treatments and maximize health benefits using scarce resources. . The ICER must be compared to a threshold of cost effectiveness to decide if the intervention is cost effective or not. According to the report to the

Parliament "Verdier i pasientenes helsetjeneste" should this threshold be based on an estimate of the opportunity cost of the intervention (10).

$$\frac{\Delta C}{\Delta E} < \lambda ,$$

where λ equals the threshold value (opportunity cost). An ICER below that threshold suggests that the intervention represents good value for money. Because the ICER has poor statistical properties, ICERs are often re-arranged to express either incremental net monetary benefit (INMB) or incremental net health benefit (INHB), which yields the following decision rules related to INMB or INHB.

*INMB: $\lambda \bullet \Delta E - \Delta C > 0$*

*INHB: $\Delta E - (\Delta C/\lambda) > 0$*

In other words, an intervention can be considered cost-effective if it yields a positive INHB or INMB.

Economic evaluations are often based on decision models (such as decision trees or Markov models) that calculate results based on various input parameters in the model. Because there are always uncertainties related to the values of these parameters, sensitivity analysis is an important feature of any economic evaluation based on a decision model framework. In short, sensitivity analysis illustrates how much the results vary when model parameters are changed.

Probabilistic sensitivity analysis (PSA) is a kind of sensitivity analysis. The advantage of PSA is that it makes it possible to take the uncertainties of all of the model-parameters into account simultaneously. The basic approach in PSA is to assign appropriate probability distributions to the model-parameters, which makes it possible to replace the "fixed" values of the parameters with values generated by random draws from the distributions. Doing this repeatedly, with a specified number of iterations, makes it possible to estimate the probabilities that alternative interventions are cost-effective subject to different ceiling values of WTP. The calculation is based on the alternative that renders the highest values of NMB or NHB. Results from PSAs are often presented as scatter plots,

which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and also as cost-effectiveness acceptability curves (CEACs), which show the probability of the alternatives being cost-effective subject to changing values of threshold value.

# Objectives

The health economic part of this report is set up to serve the following objectives:

1. To assess the cost effectiveness of rituximab
2. To assess the cost effectiveness of ocrelizumab
3. To assess the cost effectiveness of all included treatments

# Methods

### General Method

We performed a cost-utility analysis (CUA). Relevant costs were expressed in Norwegian kroner (NOK) and effects were expressed in quality-adjusted life years (QALYs). The analysis was made from a broad health care perspective. Both costs and effects were discounted with an annual discount rate of 4%. Time perspective for analysis is 20 year. Patients are 30 years old at start of analysis.

The results are expressed in incremental cost-effectiveness ratios (ICERs), which means extra costs for additional unit of health effects, compared to an alternative. Conclusions on the cost-effectiveness can not be made without assuming a cost effectiveness threshold value, except in the case that either

a. Intervention is both more effective and less costly than comparator (i.e. intervention is a dominant treatments alternative) or
b. Intervention is both less effective and more costly than comparator (i.e. intervention is an inferior treatment alternative)

### Health economic model

The health economic decision model used is this report is fully described in our previous report and following peer-reviewed publication (3;11). Unless otherwise described, all structural assumptions and input are the same as in the previous report.

## Included comparators

Structural changes made for this project includes exclusion of interferons and inclusion of rituximab, ocrelizumab and cladribine.

## Effectiveness of treatments

Effectiveness estimates driving the health economic model are annualized relapse rate and disability progression. Of the two, disability progression is the estimate with most impact on results. Effectiveness estimates were taken from NIPHs systematic review (1). Estimates are reported in Table 1.

***Table 1: Effectiveness estimates and confidence intervals included in the health economic model. All estimates are against placebo***

| | Annualized relapse rate (RR) | Disability progression (RR) |
|---|---|---|
| Dimethyl fumerate (2xday, first dosage 120mg, later 240 mg)) | 0.51 (0.37 - 0.71) | 0.61 (0.36 -1.02) |
| Fingolimod 0.5 mg | 0.44 (0.33 - 0.60) | 0.69 (0.42 -1.14) |
| Glatimer acetate 20 mg | 0.71 (0.54 - 0.93) | 0.83 (0.50 -1.38) |
| Glatimer acetate 40 mg | 0.65 (0.45 - 0.94) | 0.97 (0.49 -1.93) |
| Alemtuzumab 12 mg* | 0.27 (0.19 - 0.40) | 0.54 (0.28 -1.04) |
| Cladribine 3.5 mg | 0.42 (0.30 - 0.60) | 0.70 (0.40 -1.21) |
| Natalizumab 300 mg | 0.32 (0.23 - 0.45) | 0.60 (0.36 -1.01) |
| Ocrelizumab 600 mg | 0.34 (0.23 - 0.50) | 0.53 (0.27 -1.05) |
| Rituximab (first dose 1000mg, later doses 500 mg) | 0.43 (0.22 - 0.85) | 0.54 (0.19 -1.55) |
| Teriflunomide 14 mg | 0.66 (0.48 - 0.90) | 0.75 (0.43 -1.30) |

*Alemtuzumab is under investigation from EMA https://www.ema.europa.eu/en/documents/press-release/use-multiple-sclerosis-medicine-lemtrada-restricted-while-ema-review-ongoing_en.pdf and its use is currently restricted. Some may not consider alemtuzumab a relevant comparator while this limitation is in place

**Cost of interventions**

We preformed analyses based on both list and net prices of included drugs without value added tax (VAT). Included annual drug cost are shown in Table 2. Most drugs will be administered every year and will have the same drug cost each year under treatment. The exceptions in this case are cladribine and alemtuzumab. For cladribine, the summary of product characteristics (SPC) (12) indicates that treatment is for two years. For alemtuzumab, the SPC indicates that treatment fis or up to four years (13). Based on discussion with our clinical expert group who largely considered such short treatment periods to be unrealistic, we assumed that 26% of patients would be treated with alemtuzumab in year 3 and 12% in year four, for cladribine the corresponding percentages are 12.5% and 12.5%. In the following years, 10% of patients are assumed to require treatment, for both treatments. We want to highlight that these percentages are very uncertain due to lack of data and are based purely on educated guesses.

***Table 2: Annual drug cost based on list and net prices excluding VAT***

| | **Annual drug cost based on list prices** | **Annual drug cost based on net prices** |
|---|---|---|
| Dimethyl fumerate (2xday) | 117 213 | [redacted] |
| Fingolimod 0.5 mg | 181 850 | [redacted] |
| Glatimer acetate 20 mg | 69 086 | [redacted] |
| Glatimer acetate 40 mg | 180 892 | [redacted] |
| Alemtuzumab 12 mg* | 307 679 (yr1), 184 608 (yr2), 48 219 (yr 3), 22 504 (yr 4) | [redacted] |
| Cladribine 3.5 mg* | 119 707 (yr 1), 119 721 (yr 2) | [redacted] |
| Natalizumab 300 mg | 169 636 | [redacted] |
| Ocrelizumab 600 mg | 217 295 | [redacted] |
| Rituximab | 29 559 (yr 1), 19 706 (yr2) | [redacted] |
| Teriflunomide 14 mg | 86 030 | [redacted] |

* In the following years, 10% of patients are assumed to require treatment.

### State cost

We updated state cost based on a recent publication (14).

### Administration cost

We retrieved administrative costs, i.e. costs associated with infusion and injections, from a micro-costing analysis of societal costs of nine biologics for the treatment of rheumatoid arthritis (RA) (15). This micro-costing analysis was conducted at the outpatient clinic at Diakonhjemmet hospital in Oslo (2016). We assume that administration of infusion and injection for rheumatoid arthritis in this study could be transferable to administration of MS treatments. More specific, we used costs for administration of infliximab (Remicade, Remsima and Inflectra).

The administrative costs included were related to pre-treatment medication, pre-treatment laboratory tests (urine sample and blood tests), capital equipment needed for infusion, consumables (pre-treatment consumables for venous cannulas, procedure consumables and disposable anaphylaxis emergency consumables) accounted for 10% wastage, personnel (nurse, physicians, bioengineer, nursing assistant, secretary and coordinator), and overhead (costs of building space, electricity, heating, and cleaning, and 20% added to the sum to account for other overhead costs such as administration, clothing, and IT equipment/service).

We assume costs incurred in one education or introduction session with nurse of patients starting self-administration of injections or oral treatment. We used a co-payment tariffs of 345 Norwegian kroner per infusion multiplied by 2, and per education and introduction session with nurse (16). Drug administration costs per treatment are shown in Table 3, and annual drug administration costs are presented in Table 4, 5 and 6.

**Table 3. Drug administration costs expressed in NOK[a] per treatment according to administration form[d]**

| | Infusion | Injection year 1[b] (Injection year 2+)[b] | Oral year 1[b] (oral year 2+) [b] |
|---|---|---|---|
| **Pre-treatment laboratory tests** | 105 | 0 (0) | 0 (0) |
| **Pre-treatment medication[c]** | 15 | 0 (0) | 0 (0) |
| **Capital equipment** | 280 | 0 (0) | 0 (0) |
| **Consumables** | 675 | 0 (0) | 0 (0) |
| **Personell** | 1,003 | 370 (31) | 370 (0) |
| **Overhead** | 392 | 230 (0) | 230 (0) |
| **Total administration cost per treatment** | 2,471 | 600 (31) | 600 (0) |

[a]NOK: Norwegian kroner. [b]Year 1 included one education session/introduction session with nurse of patients starting self-administration of injections and oral treatment. Year 2 excluded education/introduction session with nurse. [c] We assumed 5% of patients receive pre-medication prior to the infusions. [d]For detailed calculation we refer to the micro-cost analysis "Societal costs of nine biologics for the treatment of rheumatoid arthritis" (15).

### Monitoring and travel costs

Monitoring costs associated with the use of drugs included in the health economic evaluation are mainly in accordance with the previous report from the Norwegian Institute of Public Health, which was related to analyses of neutralizing antibodies (NAB-analyses), eye examinations, observation at start-up, medical consultations, magnetic resonance imaging (MRI), and blood tests (3). In addition, we have included a cost for electrocardiogram (ECG) at start-up (17). We did not include costs incurred of testing for JCV-testing because of absence of data. Travel expenses were also taken from the previous HTA-report, and multiplied with the number of infusions or medical consultations (3). We assumed infusions, educational/introduction session with nurse of starting self-administration of injections, medical consultations, analyses, and MRI were done at the same day (except first year of treatment when MRI will require on additional visit) . First and second year of treatment, costs were based on estimates from the Norwegian Drug Procurement Cooperation (3). Costs beyond the second year was based on information from clinical experts (Table 4, 5 and 6). For patients who end their treatment with alemtuzumab in year 3 we have excluded administration cost related to infusion including co-payments and travel costs.

***Table 4. Drug administration, monitoring and travel costs expressed in NOK[a] (quantity) associated with each of the drugs (1. year)***

| **Drug** ***Administration form*** | **Alemtuzumab** ***Infusion*** | **Dimethyl fumarate** ***Oral*** | **Fingolimod** ***Oral*** | **Glatiramerace-tat 40 mg and 20 mg** ***Injection*** | **Natalizumab** ***Infusion*** | **Teriflunomide** ***Oral*** | **Cladribine** ***Oral*** | **Ocrelizumab** ***Infusion*** | **Rituximab** ***Infusion*** |
|---|---|---|---|---|---|---|---|---|---|
| **Administration cost[c] (number of infusions)** | 15,804 (5) | 1,290 (0) | 1,290 (0) | 1,290 (0) | 41,092 (13) | 1,290 (0) | 1,290 (0) | 9,483 (3) | 6,322 (2) |
| **NAB-analyses** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1,987 (2) | 0 (0) | 0 (0) | 0 (0) | 994 (1) |
| **MRI** | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) |
| **Eye examinations** | 0 (0) | 0 (0) | 2,700 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Medical consultations** | 7,938 (4) | 5,954 (3) | 5,954 (3) | 3,969 (2) | 7,938 (4) | 5,954 (3) | 5,954 (3) | 7,938 (4) | 7,938 (4) |
| **Blood tests** | 1,452 (12) | 484 (4) | 484 (4) | 242 (2) | 605 (5) | 1,089 (9) | 363 (3) | 484 (4) | 484 (4) |
| **Start-up** | 0 (0) | 0 (0) | 4,794 (observation + ECG[b]) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Travel** | 2,592 | 1,728 | 1,728 | 1,296 | 6,048 | 1,728 | 1,728 | 2,160 | 2,160 |
| **Total[d]** | 30,594 | 12,264 | 19,758 | 9,605 | 60,478 | 12,868 | 12,143 | 22,872 | 20,705 |

[a]NOK: Norwegian kroner. [b]Start-up includes observation for 6 hours, and according to the Ministry of Health and Care Services ECG-tariffs corresponds to 372 Norwegian kroner which we multiplied with 2 (17). [c]Administration cost includes patient co-payments using a tariffs of 345 Norwegian kroner multiplied with 2 (16). [d] We have not included costs for JCV-testing which are likely to increase the total cost.

***Table 5. Drug administration, monitoring and travel costs expressed in NOK[a] (quantity) associated with each of the drugs (2. year)***

| **Drug** ***Administration form*** | **Alemtuzumab** ***Infusion*** | **Dimethyl fumarate** ***Oral*** | **Fingolimod** ***Oral*** | **Glatirameracetat 40 mg (20 mg)** ***Injection*** | **Natalizumab** ***Infusion*** | **Teriflunomide** ***Oral*** | **Cladribine** ***Oral*** | **Ocrelizumab** ***Infusion*** | **Rituximab** ***Infusion*** |
|---|---|---|---|---|---|---|---|---|---|
| **Administration cost[b] (number of infusions)** | 9,483 (3) | 0 (0) | 0 (0) | 0 (0) | 41,092 (13) | 0 (0) | 0 (0) | 6,322 (2) | 6,322 (2) |
| **NAB-analyses** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **MRI** | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) |
| **Eye examinations** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Medical consultations** | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) |
| **Blood tests** | 1,452 (12) | 484 (4) | 242 (2) | 181 (1-2) | 484 (4) | 726 (6) | 242 (2) | 242 (2) | 242 (2) |
| **Start-up** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Travel** | 1,296 | 864 | 864 | 864 | 5,616 | 864 | 864 | 864 | 864 |
| **Total[c]** | 19,007 | 8,125 | 7,883 | 7,822 | 53,968 | 8,367 | 7,883 | 14,205 | 14,205 |

[a]NOK: Norwegian kroner. [b]Administration cost includes patient co-payments using a tariffs of 345 Norwegian kroner multiplied with 2 (16). [c] We have not included costs for JCV-testing which are likely to increase the total cost.

***Table 6. Drug administration, monitoring and travel costs expressed in NOK[a] (quantity) associated with each of the drugs (beyond 2. year)***

| **Drug** *Administration form* | **Alemtuzumab** [b] *Infusion* | **Dimethyl fumarate** *Oral* | **Fingolimod** *Oral* | **Glatirameracetat 40 mg (20 mg)** *Injection* | **Natalizumab** *Infusion* | **Teriflunomide** *Oral* | **Cladribine** *Oral* | **Ocrelizumab** *Infusion* | **Rituximab** *Infusion* |
|---|---|---|---|---|---|---|---|---|---|
| **Administration cost**[c] **(number of infusions/ injections)** | 9,483 (3) | 0 (0) | 0 (0) | 0 0 | 41,092 (13) | 0 (0) | 0 (0) | 6,322 (2) | 6,322 (2) |
| **NAB-analyses** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **MRI** | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) | 2,808 (1) |
| **Eye examinations** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Medical consultations** | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) | 3,969 (2) |
| **Blood tests** | 1,391 (11-12) | 242 (2) | 242 (2) | 181 (1-2) | 484 (4) | 726 (6) | 121 (1) | 242 (2) | 242 (2) |
| **Start-up** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Travel** | 1,296 | 864 | 864 | 864 | 5,616 | 864 | 864 | 864 | 864 |
| **Total**[f] | 18,947 | 7,883 | 7,883 | 7,822 | 53,968 | 8,367 | 7,762 | 14,205 | 14,205 |

[a]NOK: Norwegian kroner. [b]Just some patients will require treatment in following years. [c]Administration cost includes patient co-payments using a tariff of 345 Norwegian kroner multiplied with 2(16). [d]We have not included costs for JCV-testing which are likely to increase the total cost.

### Disease severity

Disease severity was calculated as absolute shortfall, following the methodology as described by the Norwegian Medicines agency (18).

### Probabilistic sensitivity analysis

We assigned probability distributions to all uncertain parameters following the method described by Briggs and co-workers (19). We performed a Monte Carlo simulation with 1,000 random draws from these distributions, generating 1,000 different potential ICERs. These 1,000 ICERs were plotted on the cost effectiveness plane, and we calculated the percentages of the simulations falling within in each quadrant. The probability that the intervention can be considered cost effective can only be calculated using a

cost effectiveness threshold. Without assuming such a threshold, we were not able to calculate the probability that rituximab or ocrelizumab could be considered cost effective.

### Budget impact

We have not assessed the budget impact of uptake of rituximab or ocrelizumab, as the Norwegian Medicines agency (NoMA) previously has provided an estimate (20).

[redacted]

# Results

## Calculated severity of disease

As disease severity is calculated based on prognosis in terms of undiscounted QALYs for patients receiving current treatment. Estimates vary marginally with what treatment you assume to represent current clinical practice and also with what you assume is the current average age of patients. If we assume that patients are 30 years old, these patients would have a quality adjusted life expectancy of approximately 11.0 QALYs.

A 30 years old person, not suffering from RRMS, has a quality adjusted life expectancy of 43.1 QALY (21). Compared to the normal population, a patient 30 years old receiving current treatment would have a loss of 43.1-11-0=32.1 years in good health (QALYs).

## Cost effectiveness

### Most relevant comparators for cost effectiveness

Results for all treatments with MA for RRMS and routine public financing (except alemtuzumab) treatments compared to placebo and using net prices are shown in Table 7. Placebo is not a relevant treatment option, but represents a common comparator. In instances where there is uncertainty as to whether current practice reflects a cost effective alternative, including  a comparison to placebo is recommended (18). Since alemtuzumab has a temporarily limited label, we consider cladribine to be the most relevant comparator for both rituximab and ocrelizumab. However, if alemtuzumab were to end up without a restricted label, alemtuzumab would be the most relevant comparator from a cost effectiveness perspective.

From a cost effectiveness perspective, glatimer acetate 20 and 40 mg, teriflunomide and fingolimod should be excluded from the analysis on the basis that they are less effective and more costly than alternative treatment strategies (i.e. are dominated).

*Table 7: All treatments currently included in routine public financing compared to placebo based on net prices*

| All referencing no treatment (placebo) | Cost | Incremental Cost | Eff | Incremental QALY | ICER | Dominance |
|---|---|---|---|---|---|---|
| No treatment | 718 885 | | 7.0861 | | | undominated |
| Cladribine | [redacted] | [redacted] | 7.9148 | 0.8287 | [redacted] | undominated |
| Glatiramer acetate 20mg | [redacted] | [redacted] | 7.6464 | 0.5603 | [redacted] | dominated* |
| Teriflunomide 14 mg | [redacted] | [redacted] | 7.7938 | 0.7077 | [redacted] | dominated* |
| Glatiramer acetate 40 mg | [redacted] | [redacted] | 7.3636 | 0.2774 | [redacted] | dominated* |
| Dimethyl fumarate 240 mg | [redacted] | [redacted] | 8.1122 | 1.0261 | [redacted] | undominated |
| Fingolimod | [redacted] | [redacted] | 7.9454 | 0.8592 | [redacted] | dominated* |
| Natalizumab | [redacted] | [redacted] | 8.1533 | 1.0672 | [redacted] | undominated |

*That a treatment is dominated means that it is inferior, i.e. that it both is less effective and more costly than another treatment.

### Cost effectiveness of rituximab

Compared to cladribine, rituximab generates more health in terms of QALYs. Based on net prices, rituximab will likely lead to a cost saving of NOK [redacted]. Being both more effective and less costly, rituximab is a dominant strategy and thus clearly a cost effective alternative compared to cladribine based on net prices.

Compared to alemtuzumab, rituximab generates less health in terms of QALYs, not considering potential side effect of either drug. In terms of costs, rituximab will lead to a cost saving of NOK [redacted]. Whether or not rituximab can be considered cost effective compared to alemtuzumab depends on assumed threshold value for cost effectiveness.

**Table 8. Cost effectiveness of rituximab relative to cladribine and alemtuzumab**

| | QALY | Incremental QALY | Cost | Incremental Cost | ICER |
|---|---|---|---|---|---|
| Rituximab | 8.136685 | | [redacted] | | |
| Cladribine | 7.914814 | | [redacted] | | |
| Alemtuzumab | 8.273765 | | [redacted] | | |
| Rituximab vs cladribine | | 0.221871 | | [redacted] | [redacted] |
| Rituximab vs alemtuzumab | | -0.13708 | | [redacted] | [redacted] |

## Cost effectiveness of ocrelizumab

Compared to cladribine, ocrelizumab generates more health in terms of QALYs, a gain of 0.3717. Ocrelizumab also generates large increases in cost, based on net prices. Whether or not ocrelizumab can be considered cost effective compared to cladribine depends on assumed estimate of opportunity cost (i.e. threshold value for cost effectiveness).

Ocrelizumab generates more health in terms of QALYs than alemtuzumab, a gain of 0.0127. Ocrelizumab also generates large increases in cost. Whether or not ocrelizumab can be considered cost effective compared to alemtuzumab depends on assumed estimate of threshold value for cost effectiveness.

**Table 9 Cost effectiveness of ocrelizumab relative to cladribine and alemtuzumab**

| | QALY | Incremental QALY | Cost | Incremental Cost | ICER |
|---|---|---|---|---|---|
| Ocrelizumab | 8.286529 | | [redacted] | | |
| Cladribine | 7.914814 | | [redacted] | | |
| Alemtuzumab | 8.273765 | | [redacted] | | |
| Ocrelizumab vs cladribine | | 0.371715 | | [redacted] | [redacted] |
| Ocrelizumab vs alemtuzumab | | 0.012764 | | [redacted] | [redacted] |

### Cost effectiveness of ocrelizumab vs rituximab

Compared to rituximab, ocrelizumab is more effective in term of QALYs. However, ocrelizumab also generates a much higher incremental cost. Whether or not ocrelizumab can be considered a cost effective alternative to rituximab, depends on assumed threshold value for cost effectiveness.

**Table 10 Cost effectiveness of ocrelizumab vs rituximab**

| | QALY | Incremental QALY | Cost | Incremental Cost | ICER |
|---|---|---|---|---|---|
| Ocrelizumab | 8.286529 | | [redacted] | | |
| Rituximab | 8.136685 | | [redacted] | | |
| Ocrelizumab vs. rituximab | | 0.149844 | | [redacted] | [redacted] |

### Cost effectiveness of all included interventions

Results for all treatments compared to cladribine is shown in Table 11. Please note that a negative ICER may result from either a negative cost and a positive health benefit (a very desirable situation), but also from a positive cost and a negative health benefit (a very undesirable situation).

***Table 11 Cost effectiveness of all included treatments relative to cladribine***

| All referencing cladribine | Costs NOK | Incremental costs NOK | QALYs | Incremental QALYs | ICER NOK/QALY |
|---|---|---|---|---|---|
| Cladribine | [redacted] | | 7.9148 | | |
| Alemtuzumab 12 mg | [redacted] | [redacted] | 8.2738 | 0.359 | [redacted] |
| Glatiramer acetate 20mg | [redacted] | [redacted] | 7.6464 | -0.2684 | [redacted] |
| Glatiramer acetate 40 mg | [redacted] | [redacted] | 7.3636 | -0.5512 | [redacted] |
| Teriflunomide 14 mg | [redacted] | [redacted] | 7.7938 | -0.121 | [redacted] |
| Dimethyl fumarate 240 mg | [redacted] | [redacted] | 8.1122 | 0.1974 | [redacted] |
| Fingolimod | [redacted] | [redacted] | 7.9454 | 0.0306 | [redacted] |
| Natalizumab | [redacted] | [redacted] | 8.1533 | 0.2385 | [redacted] |
| Rituximab | [redacted] | [redacted] | 8.1366 | 0.2218 | [redacted] |
| Ocrelizumab | [redacted] | [redacted] | 8.2865 | 0.3717 | [redacted] |

Assuming rituximab were to be included in routine public financing for RRMS, results for all treatments compared to rituximab are shown in Table 12. Note that both glatimer acetate 20 and 40 mg, teriflunomide, dimethyl fumerate, fingolimod and cladribine would generate less health benefits than rituximab, while alemtuzumab, natalizumab and ocrelizumab would generate more.

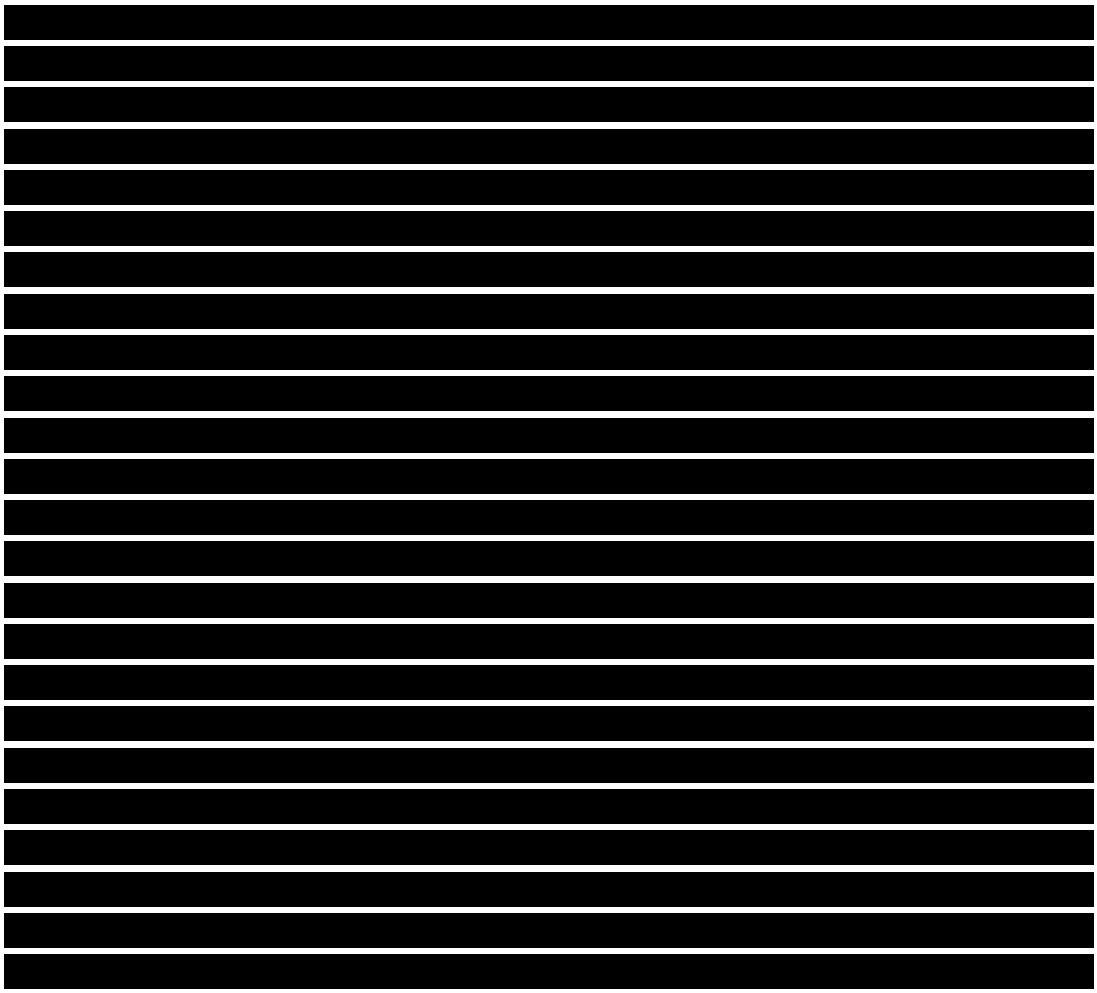
***Table12 Cost effectiveness rankings relative to rituximab***

| All referencing rituximab | Costs NOK | Incremental cost | QALYs | Incremental QALYs | ICER NOK/QALY |
|---|---|---|---|---|---|
| Rituximab | [redacted] | | 8.1366 | | |
| Alemtuzumab 12 mg | [redacted] | [redacted] | 8.2738 | 0.1372 | [redacted] |
| Glatiramer acetate 20mg | [redacted] | [redacted] | 7.6464 | -0.4902 | [redacted] |
| Glatiramer acetate 40 mg | [redacted] | [redacted] | 7.3636 | -0.773 | [redacted] |
| Teriflunomide 14 mg | [redacted] | [redacted] | 7.7938 | -0.3428 | [redacted] |
| Dimethyl fumarate 240 mg | [redacted] | [redacted] | 8.1122 | -0.0244 | [redacted] |
| Fingolimod | [redacted] | [redacted] | 7.9454 | -0.1912 | [redacted] |
| Natalizumab | [redacted] | [redacted] | 8.1533 | 0.0167 | [redacted] |
| Ocrelizumab | [redacted] | [redacted] | 8.2865 | 0.1499 | [redacted] |
| Cladribine | [redacted] | [redacted] | 7.9148 | -0.2218 | [redacted] |

**Probabilistic sensitivity analysis results rituximab**

The probabilistic analysis (illustrated in Figure 1) indicated a probability of 67% of rituximab generating more QALYs than cladribine and a probability of 66% of being less costly than cladribine. There was a probability of 49% for rituximab being both more effective and less costly than cladribine, 18% probability that rituximab was more effective and more costly and a 16% probability that rituximab was less effective and more costly than cladribine.

***Figure 1 Incremental cost effectiveness scatterplot of rituximab vs cladribine (top) and alemtuzumab (bottom), analyses based on net prices***



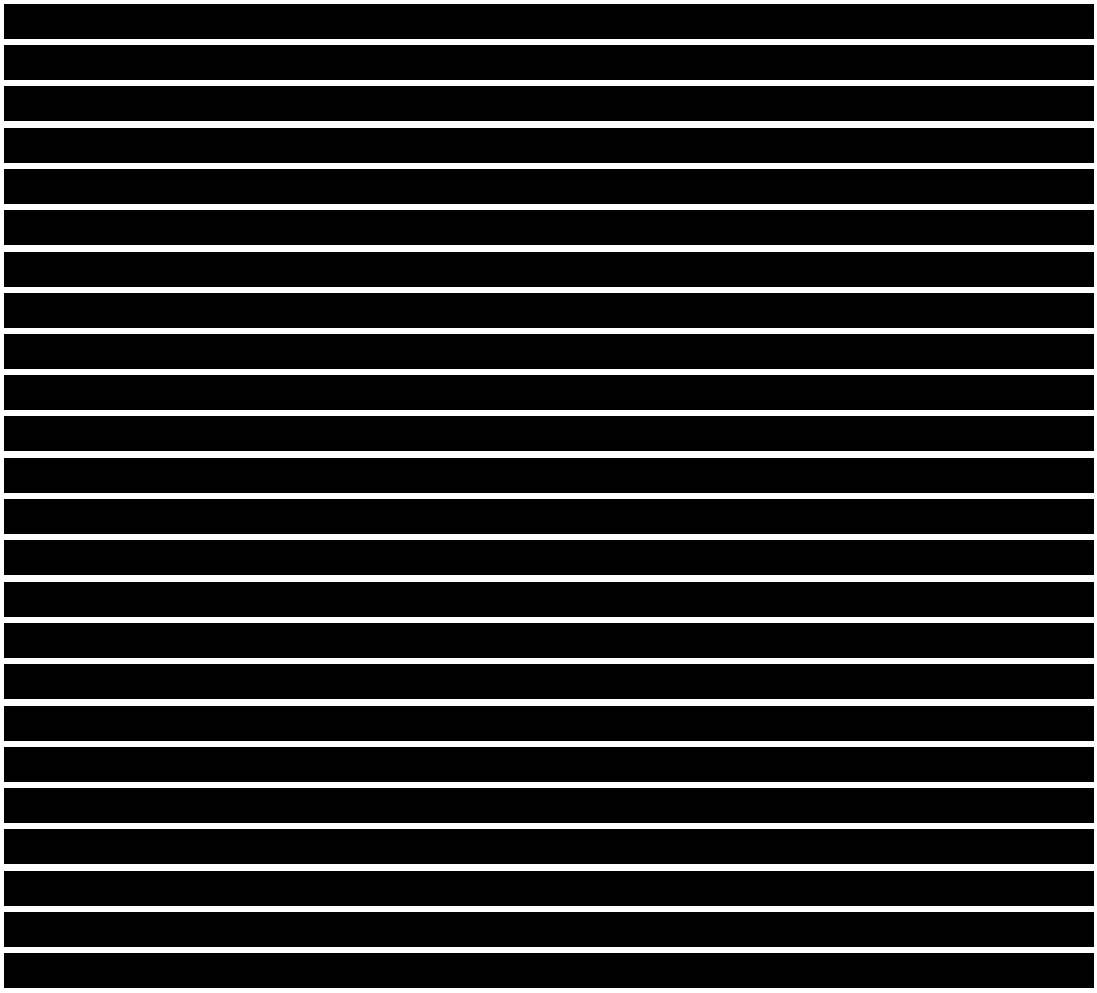
Compared to alemtuzumab, rituximab had a probability of 52% of generating more QALYs and a probability of 76% of being less costly. There is a probability of 43% that rituximab is both more effective and less costly than alemtuzumab, a probability of 33% that rituximab is less effective and less costly and a probability of 15% that rituximab is less effective and more expensive.

Due to the position on the cost effectiveness plane, conclusions on the cost effectiveness of rituximab compared to cladribine and compared to alemtuzumab are both largely insensitive to any assumed cost effectiveness threshold value. For this reason, we did not show cost effectiveness acceptability curves for these comparisons.

**Probabilistic sensitivity analysis results ocrelizumab**

Compared to cladribine, ocrelizumab has a probability of 73% of generating more health in terms of QALYs. Ocrelizumab also has a probability of 0% of being less costly than cladribine. Ocrelizumab has a probability of 73% of being more effective and more costly than cladribine and a probability of 27 % of being less effective and more costly.

***Figure 2 Incremental cost effectiveness scatterplot of ocrelizumab vs cladribine (top) and alemtuzumab (bottom), analyses based on net prices***

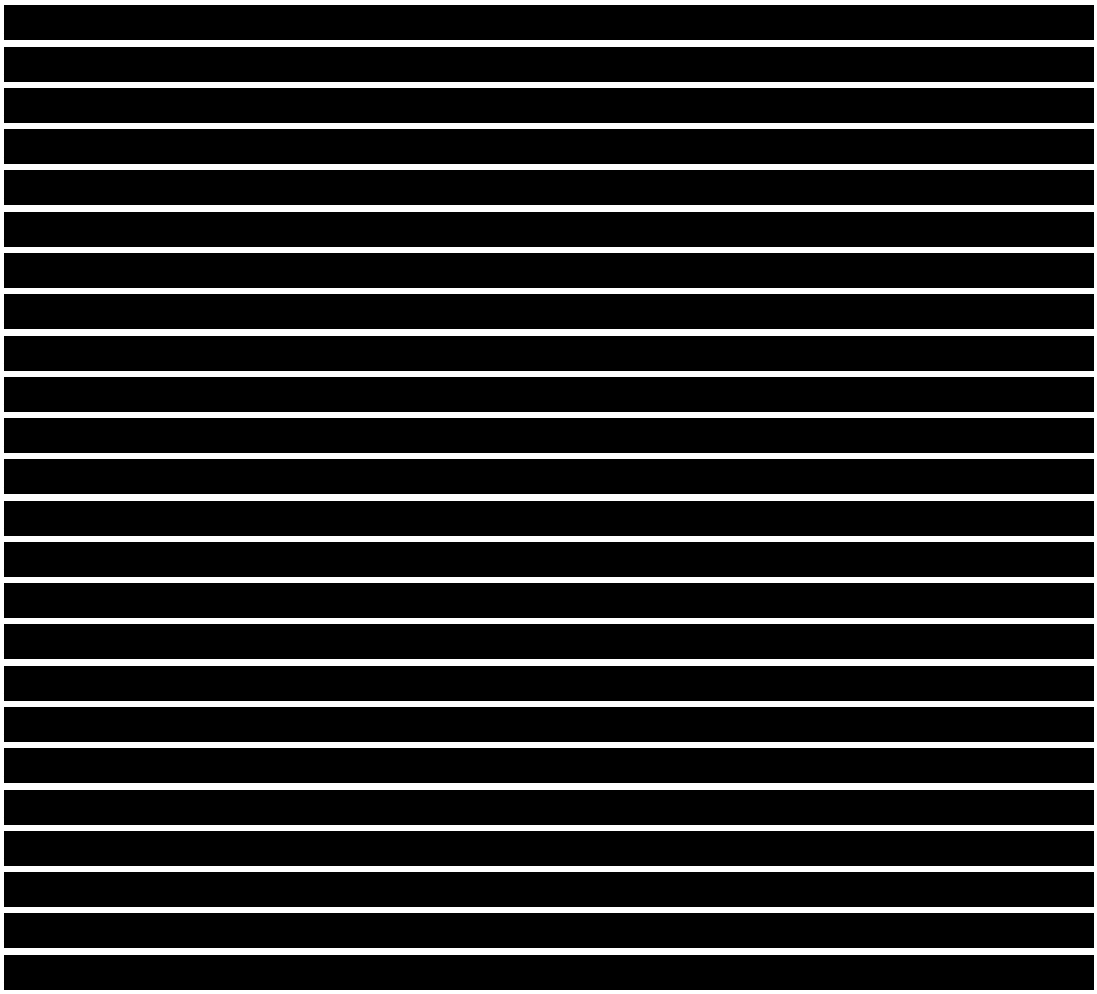


Compared to alemtuzumab, ocrelizumab has a probability of 50% of generating more health (QALYs). Ocrelizumab has a probability of 0% of being less costly than alemtuzumab. There is a probability of 50% of ocrelizumab generating less health and

being more costly than alemtuzumab. There is a 50% probability of ocrelizumab being more effective and more costly than alemtuzumab.

For the comparison ocrelizumab vs cladribine, a conclusion regarding cost effectiveness will depend on the assumed threshold value for cost effectiveness. In the comparison to alemtuzumab, the conclusion is more robust to changes assumed cost effectiveness threshold value, c.f. Figure 3.

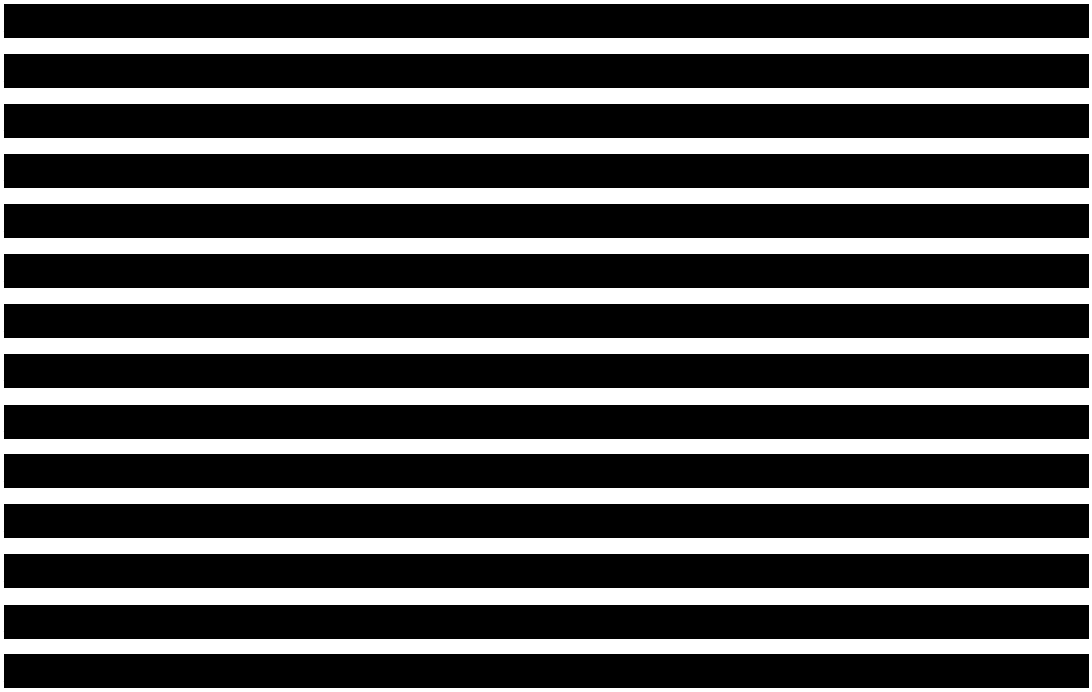
***Figure 3: Cost effectiveness acceptability curve, ocrelizumab vs cladribine (top) and alemtuzumab (bottom), based on (net prices***



***Probabilistic sensitivity analysis results ocrelizumab vs rituximab***

Compared to rituximab, there is a probability of 54% that ocrelizumab will generate more health as measured in QALYs. There is 0% probability that ocrelizumab is less costly than rituximab.

***Figure 4: Incremental cost effectiveness ocrelizumab vs rituximab (net prices)***



Ocrelizumab has a 54% likelihood of being more effective and more costly than rituximab and a likelihood of 46% of being less effective and more costly.

The sensitivity for the conclusion on cost effectiveness of ocrelizumab vs rituximab to changes in assumed cost effectiveness threshold is shown in Figure 5.

*Figure 5: Cost effectiveness acceptability curve, ocrelizumab vs rituximab (net prices)*

# Discussion

Conclusions on the cost effectiveness of the included drugs depend on the choice of comparator and on the choice of assumed cost effectiveness threshold value.

Whether or not the new proposed treatments represent good value for money is partly a value judgement. Rituximab will likely result in more health and less costs compared to cladribine, based on current tender prices. However, note that compared to alemtuzumab, rituximab could lead to both less health and cost saved. Whether or not it would be considered acceptable to offer a less effective, but also cost saving intervention is a judgement call.

Ocrelizumab generates more health and more cost than cladribine, alemtuzumab and rituximab. Note, however, that alemtuzumab has a temporarily limited label, while rituximab has been used off label and has not yet been included in routine public financing for RRMS.

Differences between drugs in terms of health gains (incremental QALYs) may seem small, ranging from 0.0127 to 0.3717. To put these numbers in context, the average difference between treatment strategies found when reviewing all published health economic evaluations from one year was 0.07 (22). The average found for lifestyle interventions was 0.03, while the average for cardiovascular and oncology interventions was 0.07. From this perspective, some of the differences found between the different MS drugs may be considered substantial.

There is uncertainty regarding what percentage of patients treated with cladribine and alemtuzumab require treatment in later years, i.e. after year two and after year four. In the label, cladribine is recommended used for two years (12). For alemtuzumab, the label recommends treatment for up to four years (13). Currently, there is a scarcity of data regarding the percentage of patients needing additional treatment. Members of our clinical expert group had very diverging opinions on this. The assumed percentages influence treatment cost to a large degree. The fewer years of treatment required, the more beneficial the cost profile of cladribine and alemtuzumab become.

We retrieved our drug administration costs from a micro-costing analysis, which enables precise, actual estimation of costs. On the other hand, these costs were related to administration of RA drugs that we assumed are applicable for administration of MS drugs. Further, drug administration costs may be over- or under-estimated as some of the calculations are based on the number of RA patients treated, such as personnel and overhead costs. However, these costs do not have the greatest impact on our results.

One limitation with our analysis is that we were not able to retrieve the cost of testing for JC virus. Our clinical expert group has pointed out that some doctors may choose to test patients before initiating and during treatment with all "potent" drugs, despite the fact that only natalizumab has a label requiring JCV testing before treatment initiation. Inclusion of additional costs related to JCV testing would make results for natalizumab less favourable.

We have excluded adverse events in our analyses, which can have an impact on differences in resource use when estimating monitoring costs associated with each of the treatment strategies. Inclusion of adverse events could also affect the estimated number of QALYs. In the previous MS report, we did include the possibility of developing progressive multifocal leukoencephalopathy (PML) following treatment with natalizumab. Inclusion of PML in the previous analysis made little impact on the results. Preparing this report, we did consider including possible autoimmune thyroid disease as a possible side effect of alemtuzumab. Before the analysis was final, our clinical expert group made us aware that alemtuzumab was under investigation by the European Medicines Agency (EMA) for "immune-mediated conditions (caused by the body's defence system not working properly) and problems with the heart and blood vessels with the medicine, including fatal cases. " All included drugs are likely to have some, but different, side effects. Exclusion of side effects or potential adverse events can be viewed as a simplification required, as a health economic model needs to be as simple as possible, while also capturing the most important consequences of included interventions (23;24). As most serious side effects of drugs are very rare (have a low incidence rate), they will often have little impact on the estimated expected costs and number of QALY. However, considering the inclusion of side effects in the health economic modelling of MS has been recommend by some researchers (25).

We have not accounted for any added value of oral administration, although there is some evidence that oral administration may represent a benefit to patients (26).

There is lack of documentation regarding the long-term efficacy and safety of the newer drugs. Further research could change current estimates and consequently the health economic results.

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