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Datum 16 januari 2018
Betreft GVS beoordeling cladribine (Mavenclad®)

Onze referentie
2018001350

Geachte heer Bruins,

In uw brief van 16 oktober 2017 (CIBG-17-05240) heeft uw voorgangster Zorginstituut Nederland (ZIN) verzocht om een inhoudelijke toetsing uit te voeren over de vraag of cladribine (Mavenclad®) onderling vervangbaar is met een middel dat is opgenomen in het GVS. Het Zorginstituut heeft, daarbij geadviseerd door de Wetenschappelijke Adviesraad (WAR), deze beoordeling inmiddels afgerond. De overwegingen hierbij treft u aan in de rapporten die als bijlage zijn toegevoegd.

Cladribine is geregistreerd voor de behandeling van volwassen patiënten met zeer actieve relapsing multipele sclerose (RMS), zoals gedefinieerd door klinische of beeldvormingskenmerken.

Cladribine (Mavenclad®) is beschikbaar in de vorm van tabletten. Elke tablet bevat 10 mg cladribine. Er zijn momenteel verpakkingen met 1, 4, 5, of 6 tabletten beschikbaar. De aanbevolen cumulatieve dosis van cladribine is 3,5 mg/kg lichaamsgewicht over een periode van 2 jaar, toegediend als 1 behandelingskuur van 1,75 mg/kg per jaar.

De fabrikant van cladribine vraagt vergoeding aan voor zeer actieve RMS bij volwassenen met 1 relapse in het voorafgaande jaar en tenminste 1 T1-Gd+-laesie of 9 of meer T2-laesies tijdens therapie met andere ziektemodificerende geneesmiddelen (eveneens tweede lijn of later). Daarmee kunnen dezelfde bijlage 2 voorwaarden van fingolimod ook gelden voor cladribine.

Therapeutische waarde
Middels indirecte vergelijkingen is de effectiviteit van cladribine vergeleken met de effectiviteit van fingolimod. Er is geen bewijs of aanwijzing dat de gunstige effecten van cladribine en fingolimod wezenlijk van elkaar verschillen bij de behandeling van patiënten met zeer actieve Relapsing (Remitting) Multiple Sclerose (R(R)MS). Bij patiënten met zeer actieve RRMS komen de gunstige effecten van cladribine dus overeen met die van fingolimod.

Indeling in GVS
Oraal cladribine (Mavenclad®) is onderling vervangbaar met oraal fingolimod, dat momenteel is opgenomen op Bijlage 1B in het GVS.

Zorginstituut Nederland
Zorg I

Datum
16 januari 2018

Onze referentie
2018001350

Fingolimod is met bijlage 2 voorwaarde opgenomen in het GVS. Volgens een voorstel van het Zorginstituut, gedaan bij brief van 19 oktober 2017 (ref: 2017035763) gaan deze luiden: *Uitsluitend voor een verzekerde van achttien jaar of ouder met zeer actieve relapsing-remitting multiple sclerose (RRMS) die niet heeft gereageerd op een behandeling met ten minste één ziektemodificerend geneesmiddel dat geregistreerd is voor de behandeling van MS* (kortom: tweede lijn of later).

Het Zorginstituut adviseert u om oraal cladribine op te nemen op bijlage 1A in een nieuw te vormen cluster met fingolimod. De standaarddosis voor cladribine kan vastgesteld worden op 0,19 mg.

Hoogachtend,

Arnold Moerkamp
Voorzitter Raad van Bestuur

Zorginstituut Nederland

GVS-rapport 18/02
Cladribine tabletten (Mavenclad®)

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Inhoud

1 Inleiding

In de brief van 16 oktober 2017 verzoekt de minister van Volksgezondheid, Welzijn en Sport Zorginstituut Nederland een inhoudelijke toetsing uit te voeren over het geneesmiddel cladribine (Mavenclad®).

1.1 Cladribine tabletten (Mavenclad®)

Samenstelling
Elke tablet bevat 10 mg cladribine. Er zijn verpakkingen met 1, 4, 5, 6, 7 of 8 tabletten beschikbaar. In Nederland zijn vooralsnog alleen de verpakkingen met 1, 4 of 6 tabletten verkrijgbaar.[1]

Geregistreerde indicatie
Voor de behandeling van volwassen patiënten met zeer actieve relapsing multipele sclerose (MS), zoals gedefinieerd door klinische of beeldvormingskenmerken.[2]

Dosering
De aanbevolen cumulatieve dosis van cladribine is 3,5 mg/kg lichaamsgewicht over een periode van 2 jaar, toegediend als 1 behandelingskuur van 1,75 mg/kg per jaar. Elke behandelingskuur bestaat uit 2 behandelingsweken: één week aan het begin van de eerste maand en één week aan het begin van de tweede maand van het respectievelijke behandelingsjaar. Elke behandelingsweek bestaat uit 4 of 5 dagen waarop een patiënt, afhankelijk van het lichaamsgewicht, 10 mg of 20 mg (één of twee tabletten) krijgt als een enkele dagelijkse dosis.[2]
Na voltooiing van de 2 behandelingskuren is er geen verdere behandeling met cladribine nodig in jaar 3 en 4. Er is geen onderzoek verricht naar het opnieuw starten van de therapie na jaar 4.[2]

1.2 Voorstel fabrikant opname GVS

De fabrikant van oraal cladribine (Mavenclad®) stelt dat cladribine onderling vervangbaar is met fingolimod, en daarom kan worden geplaatst op bijlage 1A van de Regeling zorgverzekering (Rzv), in een nieuw te vormen cluster samen met fingolimod.

2 Beoordeling onderlinge vervangbaarheid

Om de plaats van een geneesmiddel in het GVS te kunnen vaststellen, wordt eerst beoordeeld of het onderling vervangbaar is met reeds in het GVS opgenomen geneesmiddelen. Vervolgens wordt beoordeeld wat de therapeutische waarde van cladribine is ten opzichte van de standaard- of de gebruikelijke behandeling.

Voor de indicatie relapsing (remitting) multipele sclerose (R(R)MS) zijn verschillende geneesmiddelen in het GVS opgenomen:

- Parenterale MS middelen (1e lijn):
    - 0L03ABBP V: interferon bèta-1a, interferon beta-1b, peginterferon beta-1a, glatirameer en daclizumab
- Orale MS middelen (1e lijn):
    - 0N07XXCO V: dimethylfumaraat en teriflunomide
- Oraal MS middel (2e lijn (Bijlage 2 voorwaarde)):
    - Bijlage 1B: fingolimod

Alemtuzumab, natalizumab en fingolimod zijn alle drie middelen die net als cladribine worden voorgeschreven bij *zeer actieve* R(R)MS. De intramurale middelen alemtuzumab en natalizumab zijn vanwege de intraveneuze toedieningsvorm niet opgenomen in het GVS. Voor vergelijking komt daarom, gezien de huidige indeling in het GVS, in eerste instantie fingolimod in aanmerking, dat is opgenomen op Bijlage 1B van het GVS.

2.1 Beoordeling criteria onderlinge vervangbaarheid

2.1.1 Gelijksoortig indicatiegebied

Cladribine is geregistreerd voor de behandeling van volwassen patiënten met zeer actieve relapsing multipele sclerose (RMS), zoals gedefinieerd door klinische of beeldvormingskenmerken. De definitie van zeer actieve RMS is:

- Patiënten met 1 relaps in het voorafgaande jaar en ten minste 1 T1-Gd+-laesie of 9 of meer T2-laesies tijdens therapie met andere ziekte modificerende middelen;
- Patiënten met 2 of meer relapsen in het voorafgaande jaar, al dan niet tijdens behandeling met een ziekte modificerend middel.[2]

Fingolimod is geïndiceerd als enkelvoudige ziektemodificerende therapie bij zeer actieve *relapsing-remitting* multipele sclerose (RRMS) in de volgende patiëntengroepen:

- Patiënten met zeer actieve ziekte ondanks een volledige en adequate behandeling met ten minste één ziektemodificerend middel;
- Of patiënten met zich snel ontwikkelende ernstige RRMS, gedefinieerd door 2 of meer invaliderende schubs in één jaar en met 1 of meer gadolinium aankleurende laesies op de hersen-MRI of een significant toename van de lading van T2-leasies in vergelijking met een eerdere recente MRI.[3]

Op grond van het veiligheidsprofiel heeft de EMA de indicaties van fingolimod en cladribine ingeperkt tot hoofdzakelijk tweedelijnsgebruik.[2,3] Aangezien fingolimod en cladribine beiden in gerandomiseerde klinische onderzoeken breder als eerstelijnsmiddel bij RRMS zijn onderzocht[2,3], is RRMS voor beide geneesmiddelen de hoofdindicatie.

Conclusie: De hoofdindicatie van cladribine en fingolimod is RRMS. Het indicatiegebied van cladribine en fingolimod is daarom gelijksoortig.

2.1.2 Gelijke toedieningsweg

Cladribine en fingolimod zijn beiden bestemd voor orale toediening.[2,3]

Conclusie: Er is sprake van gelijke toedieningsweg.

2.1.3 Bestemd voor dezelfde leeftijdscategorie

Cladribine is net als fingolimod bestemd voor volwassenen.[2,3]

Conclusie: Cladribine en fingolimod zijn bestemd voor dezelfde leeftijdscategorie.

2.1.4 Klinische relevante verschillen in eigenschappen

De weging van het criterium klinisch relevante verschillen in eigenschappen berust met name op een beoordeling van de gunstige en ongunstige effecten van cladribine ten opzichte van fingolimod. Verschillen in de toepasbaarheid en het gebruiksgemak worden wel in de weging meegenomen maar hebben alleen een doorslaggevende rol indien dit tot een klinisch relevante verandering in (on)gunstige effecten leidt.

Gunstige effecten

Bij patiënten met RRMS is de effectiviteit van 3,5 mg/kg cladribine in een direct vergelijkende studie en één extensiestudie significant en klinisch relevant beter gebleken dan placebobehandeling.[4-7] Ten opzichte van placebo nam het geannualiseerd relapspercentage (ARR) af. Daarnaast verhoogde cladribine ten opzichte van placebo het percentage van patiënten dat gedurende 96 weken vrij bleef van relapsen. Ook voor alle MRI eindpunten, werd een statistisch significant verschil gevonden tussen actieve behandeling en placebo. Een effect op progressie van invaliditeit kon niet worden aangetoond. De behandeleffecten bereikt in de twee jaar durende CLARITY trial bleven behouden tijdens de twee jaar durende CLARITY Extension trial. Daaruit bleek dat er geen relevant voordeel is van additionele behandeling in jaar 3 en 4.
Post-hoc subgroep-analyses tonen aan dat cladribine effectiever is bij patiënten met hoge ziekte activiteit[A] voor zowel het geannualiseerd relapspercentage als tijd tot invaliditeitsontwikkeling (3 maanden en 6 maanden). Op de MRI eindpunten werd geen verschil aangetoond. Al met al suggereren de post-hoc subgroep analyses dat een groter effect wordt bereikt bij patiënten met zeer actieve RRMS. Daarnaast is het aannemelijk dat cladribine ook effectief is bij patiënten met zeer actieve secundair progressieve multipele sclerose (SPMS) met daarbovenop relapsen.[8] Vandaar dat cladribine (Mavenclad®) geregistreerd is voor patiënten met zeer actieve *relapsing* multipele sclerose (RMS[B]).

Middels indirecte vergelijkingen is de effectiviteit van cladribine vergeleken met de effectiviteit van fingolimod. Door verschillen in patiëntenpopulaties, uitkomstmaten en gebruik van post-hoc subgroep analyses is dit lastig. Er is geen bewijs of aanwijzing dat de gunstige effecten van cladribine en fingolimod wezenlijk van elkaar verschillen bij de behandeling van patiënten met zeer actieve R(R)MS.

Conclusie: Bij patiënten met zeer actieve RRMS komen de gunstige effecten van

[A] Zeer actieve RRMS is gedefinieerd als patiënten met 1 relaps in het voorafgaande jaar en ten minste 1 T1-Gd+-laesie of 9 of meer T2-laesies tijdens therapie met andere ziekte modificerende middelen of patiënten met 2 of meer relapsen in het voorafgaande jaar, al dan niet tijdens behandeling met een ziekte modificerend middel.
[B] *Relapsing* multiple sclerose is gedefinieerd als *relapsing remitting* multipele sclerose (RRMS) + secundaire progressieve multipele sclerose (SPMS) met daarbovenop relapsen.

cladribine overeen met die van fingolimod.

Ongunstige effecten
Het meest voorkomende ongunstige effect van cladribine was (ernstige) lymfopenie en daaraan gekoppeld een verhoogd risico op (ernstige) herpes zoster. Gezien het werkingsmechanisme van cladribine zijn ernstige en opportunistische infecties een belangrijk potentieel risico van cladribine, waaronder mogelijk progressieve multifocale leuko-encefalopathie (PML). Een ander potentieel ongunstig effect van cladribine zijn maligniteiten. Dit laatste wordt nader onderzocht.[2,8]

De meest voorkomende ongunstige effecten van fingolimod zijn griep, sinusitis, hoofdpijn, diarree, rugpijn, verhoogde leverenzymen en hoest. De meest ernstige ongunstige effecten van fingolimod waren infecties, macula-oedeem en voorbijgaande atrioventriculair blok bij aanvang van de behandeling.[3]

Conclusie: De ongunstige effecten van cladribine en fingolimod leiden niet tot een duidelijke voorkeur voor een van de twee middelen.

Ervaring
De ervaring met cladribine is beperkt (2017).[2] De ervaring met fingolimod is voldoende (2011).[3]

Toepasbaarheid
Er zijn geen grote verschillen wat betreft de contra-indicaties, toepasbaarheid bij specifieke groepen en interacties. Wel is het, vanwege het bijzondere doseringsregime van cladribine, voor (partners van) patiënten mogelijk gedurende een vierjarige cladribinebehandeling zwanger te worden, terwijl bij vierjarige behandeling met fingolimod de behandeling gestaakt dient te worden. Daarnaast zijn de vereiste controles bij fingolimod uitgebreider dan de controles bij cladribine.[2,3]

Gebruiksgemak
Op basis van toedieningsfrequentie is het gebruiksgemak van cladribine gunstiger dan het gebruiksgemak van fingolimod.[2,3]

Conclusie: Cladribines voordelen in gebruiksgemak en toepasbaarheid leiden niet tot klinische relevante veranderingen in gunstige en/of ongunstige effecten. Daarom kan geconcludeerd worden dat er geen klinisch relevante verschillen in eigenschappen zijn tussen cladribine en fingolimod.

2.2 Conclusie onderlinge vervangbaarheid

Oraal cladribine (Mavenclad®) is onderling vervangbaar met oraal fingolimod, dat momenteel is opgenomen op Bijlage 1B in het GVS.

Fingolimod is met bijlage 2 voorwaarde opgenomen in het GVS: Uitsluitend voor een verzekerde van achttien jaar of ouder met zeer actieve relapsing-remitting multiple sclerose (RRMS) die niet heeft gereageerd op een behandeling met ten minste één ziektemodificerend geneesmiddel dat geregistreerd is voor de behandeling van MS (kortom: tweede lijn of later). De fabrikant van cladribine vraagt vergoeding aan voor zeer actieve RMS bij volwassenen met 1 relapse in het voorafgaande jaar en tenminste 1 T1-Gd+-laesie of 9 of meer T2-laesies tijdens therapie met andere ziektemodificerende geneesmiddelen (eveneens tweede lijn of later). Daarmee kunnen dezelfde bijlage 2 voorwaarden van fingolimod ook gelden voor cladribine.

2.3 Standaarddosis

Er is geen DDD vastgesteld voor cladribine. In de SmPC van Mavenclad® wordt een dosering aanbevolen van 3,5 mg cladribine per kg lichaamsgewicht over een periode van twee jaar, toegediend als één behandelkuur van 1,75 mg/kg per jaar. Dit wordt gevolgd door een behandelingsvrije periode van nog eens twee jaar.[2]

Voor de gemiddelde patiënt met een lichaamsgewicht van 70 kg zijn over een totale periode van vier jaar 28 tabletten van 10 mg nodig (twee keer zeven tabletten van 10 mg in het eerste jaar én twee keer zeven tabletten van 10 mg in het tweede jaar [zie Tabel 1 in de SmPC van cladribine[2]]). Omgerekend betekent dit voor cladribine een standaarddosis van 0,19 mg [280 mg/(4*365) dagen].

Aangezien fingolimod tot nu toe op Bijlage 1B is opgenomen, is hiervoor nog geen standaarddosis vastgesteld. De vastgestelde DDD door de WHO is 0,5 mg voor fingolimod. De standaarddosis kan daarmee worden vastgesteld op 0,5 mg. De berekende standaarddosis van cladribine (0,19 mg) valt binnen de doseringsrange en kan daarmee worden gesteld op 0,19 mg.

2.4 Conclusie plaatsing op lijst 1A

Oraal cladribine (Mavenclad®) kan op bijlage 1A worden geplaatst in een nieuw te vormen cluster met fingolimod. De Bijlage 2 voorwaarden van fingolimod zijn ook van toepassing op cladribine: Uitsluitend voor een verzekerde van achttien jaar of ouder met zeer actieve relapsing-remitting multiple sclerose (RRMS) die niet heeft gereageerd op een behandeling met ten minste één ziektemodificerend geneesmiddel dat geregistreerd is voor de behandeling van MS.

3 Conclusie plaatsing in GVS

Oraal cladribine kan op bijlage 1A worden geplaatst in een nieuw te vormen cluster met fingolimod. De standaarddosis voor cladribine kan vastgesteld worden op 0,19 mg.

De Bijlage 2 voorwaarde van fingolimod geldt ook voor cladribine: Uitsluitend voor een verzekerde van achttien jaar of ouder met zeer actieve relapsing-remitting multiple sclerose (RRMS) die niet heeft gereageerd op een behandeling met ten minste één ziektemodificerend geneesmiddel dat geregistreerd is voor de behandeling van MS.

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Pharmacotherapeutic assessment using the rapid relative effectiveness assessment format

CLADRIBINE TABLETS (MAVENCLAD®) FOR THE TREATMENT OF ADULT PATIENTS WITH HIGHLY ACTIVE RELAPSING REMITTING MULTIPLE SCLEROSIS (MS) AS DEFINED BY CLINICAL OR IMAGING FEATURES, DESPITE A FULL AND ADEQUATE COURSE OF TREATMENT WITH AT LEAST ONE DISEASE MODIFYING THERAPY.

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Disclaimer

The assessment represents a consolidated view of the National Health Care Institute (ZIN) and is in no case the official opinion of EUnetHTA.

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Consultation of the draft Rapid Assessment

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Conflict of interest

All authors and dedicated reviewers involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of interest and confidentiality undertaking of interest (DOICU) statement form.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Annualised Relapse Rate
CHMP	Committee for Medicinal Products for Human use
CNS	Central Nervous System
DCK	Deoxycytidine kinase
DMD	Disease Modifying Drug
DOICU	Declaration of interest and confidentiality undertaking
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	Euro Quality of Life 5 Dimensions
FDA	Food and Drug Administration
Gd+	Gadolinium-enhancing
HAD	High Disease Activity
ICD	International Classification of Diseases
MeSH	Medical Subject Headings
MRI	Magnetic Resonance Imaging
MSQOL-54	Multiple Sclerosis Quality of Life-54
OR	Odds ratio
PASS	Post Authorization Safety Study
PML	Progressive multifocal leukoencephalopathy
RCT	Randomised Controlled Trial
REA	Relative Effectiveness Assessment
RMS	Relapsing Multiple Sclerosis (RRMS + SPMS with superimposed relapses)
RR	Relative Risk
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Severe Adverse Event
SAG	Scientific Advisory Group
SmPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
VEP	Visual Evoked Potentials
WAR	Wetenschappelijke Adviesraad; Scientific Advisory Board, The Netherlands
ZIN	Zorginstituut Nederland; National Health Care Institute, The Netherlands

SUMMARY OF RELATIVE EFFECTIVENESS OF ORAL CLADRIBINE VS. FINGOLIMOD

Please note that the population in the scope of this assessment report differs from the registered indication of cladribine (see question [B0002] on p.14 for an explanation).

We examined effectiveness of oral cladribine compared to fingolimod for adults with highly active relapsing remitting multiple sclerosis (MS) as defined by clinical or imaging features, despite a full and adequate course of treatment with at least one disease modifying therapy. Although alemtuzumab and natalizumab are comparators as well, we chose to limit the comparison to cladribine and fingolimod and to extrapolate the findings to alemtuzumab and natalizumab. Previously, in the assessment report of alemtuzumab, the National Health Care Institute of the Netherlands (ZIN) concluded that alemtuzumab, natalizumab and fingolimod have a comparable therapeutic value.[1] This conclusion was drawn based on a network meta-analysis executed on request of the National Health Care Institute of The Netherlands (ZIN).[2]

Cladribine tablets administered as monotherapy at the approved dose of 3.5 mg/kg increases the probability of being relapse-free at 96 weeks compared to placebo in RRMS patients. The annualised relapse rate favoured cladribine 3.5 mg/kg compared to placebo. These benefits were confirmed with disease measures defined by MRI scans. However, there was no clinically relevant difference of cladribine at 3.5 mg/kg on preventing disability worsening. The treatment effect obtained in CLARITY was maintained in CLARITY Extension. There is no relevant added benefit of additional treatment courses in year 3 and 4.

High disease activity (HDA) patients had more pronounced effects than non-HDA patients for both annualized relapse rate and time to disability progression (3 months and 6 months), but not for MRI endpoints, where there was no difference. Altogether, subgroup analyses suggested a larger effect size in HDA patients with relapsing remitting multiple sclerosis (RRMS).
Annualized relapse rate, participants free from relapse, participants free from disability and participants free from MRI Gd+ lesions did not differ significantly between cladribine and fingolimod treated patients. Therefore, we conclude there is no difference in efficacy between cladribine and fingolimod in (highly active) RRMS patients.

The main safety issues of oral cladribine are related to the risks of prolonged severe lymphopenia and infections including reactivation of latent infections (herpes zoster) and opportunistic infections. These adverse events are considered to be acceptable when used in accordance with the conditions defined in the SmPC. Furthermore, there are remaining uncertainties pertaining to the increased rate of malignancies seen with cladribine. Further data are gathered in the post-marketing setting.
Safety profiles of oral cladribine and fingolimod partly overlap. Both drugs are accompanied by (potential) serious adverse events that need monitoring, although cladribine's monitoring burden is lower. There are no clinically relevant differences in incidences in serious adverse events or withdrawals due to adverse events between cladribine and fingolimod treated patients. Individual patient characteristics determine which interventional strategy is most appropriate.

The National Health Care Institute of the Netherlands (ZIN) concludes oral cladribine and fingolimod have a comparable therapeutic value. This conclusion also applies to alemtuzumab and natalizumab, given the earlier conclusions drawn in the assessment report of alemtuzumab on the basis of a network meta-analysis.[1,2]

1 SCOPE (PICOT)

Description	Project scope
Population	***Please note that the population in the scope differs from the registered indication of cladribine (see question [B0002] on p.14 for an explanation).*** Adult patients with *highly active relapsing remitting multiple sclerosis (MS)* as defined by clinical or imaging features, despite a full and adequate course of treatment with at least one disease modifying therapy.[3] International Classification of diseases (ICD)-10 code: G35
Intervention	Cladribine 3.5 mg/kg body weight over 2 years, administered as 1 oral treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4.[3]
Comparison	Fingolimod 0.5 mg capsule taken once daily. Alemtuzumab and natalizumab are comparators as well. However, since the National Health Care Institute concluded in the assessment report of alemtuzumab that alemtuzumab, natalizumab and fingolimod have a comparable therapeutic value[1,2], we chose to limit the comparison to the oral drugs cladribine and fingolimod.
Outcomes	The outcomes for treatments intended to modify the natural course of the disease are described in the CHMP's Guideline on clinical investigation of medicinal products for the treatment of MS.[4] Relapsing multiple sclerosis (patients with RRMS or SPMS with superimposed relapses): **Crucial endpoints** • Relapses: Annual relapse rate (ARR) and/or the time to relapse (other possibilities: frequency of moderate/severe relapses, proportion of patients free from relapses at a given time, proportion of subjects receiving recue therapy); • Disability; • Safety (incidence of serious adverse events and withdrawals due to adverse events). **Important endpoints** • MRI derived parameters; • Patient reported outcomes.

Description	Project scope
Study design	The preferred study design for treatments intended to modify the natural course of the disease is described in the CHMP's Guideline on clinical investigation of medicinal products for the treatment of MS.[4] Efficacy should be established by means of randomised double-blind (double dummy if needed) controlled parallel group trials. The preferred approach would be a development showing superiority versus placebo or an active comparator. All possible efforts should be done to keep the design double blind. Criteria to refer the patient to evaluation of a relapse should be established *a priori* in the protocol to avoid selective referral. If a development aims at RMS as the intended indication, it should provide for separate conclusions at the time of the benefit/risk assessment on the efficacy and safety in patients both with low and highly active MS. The recommended approach will be that data on efficacy and safety are generated for both populations. In any case it has to be made possible to conclude that any efficacy as observed in the patients with low disease activity also translates into efficacy in the population with more active disease An effect on relapses poorly correlates to prevention of disability. For a distinct claim on disability large-scale long-term parallel group trials will be required to establish clinically relevant treatment effects on disease progression. Such a study may need to last ~3 years. In order to address maintenance of the effect and to gather information on the long-term course of patients under treatment, an extended follow-up either blinded or open label should performed.

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

The assessment team consisted of employees of Zorginstituut Nederland (ZIN; National Health Care Institute, The Netherlands). ZIN received comments from the Scientific Advisory Board (WAR, The Netherlands) and stakeholder (Merck B.V.). ZIN assessed all comments and incorporated relevant changes.

2.2 Search

The MEDLINE and the Cochrane Library databases where searched. The search was adapted for each database.

MEDLINE
Search #1 CLADRIBINE:
"*Multiple Sclerosis*"[Mesh] AND (*cladribine*)
Article type: Clinical Trial, Meta-Analysis
The search was performed on November 30, 2017 and resulted in 33 hits.

Search #2 FINGOLIMOD:
"*Multiple Sclerosis*"[Mesh] AND (*fingolimod*)
Article type: Clinical Trial, Meta-Analysis.
Publication date: From 2016/02/15 to 2017/12/31 (because a Cochrane review is included that searched for literature till February 15, 2016).
The search was performed on November 30, 2017 and resulted in 16 hits.

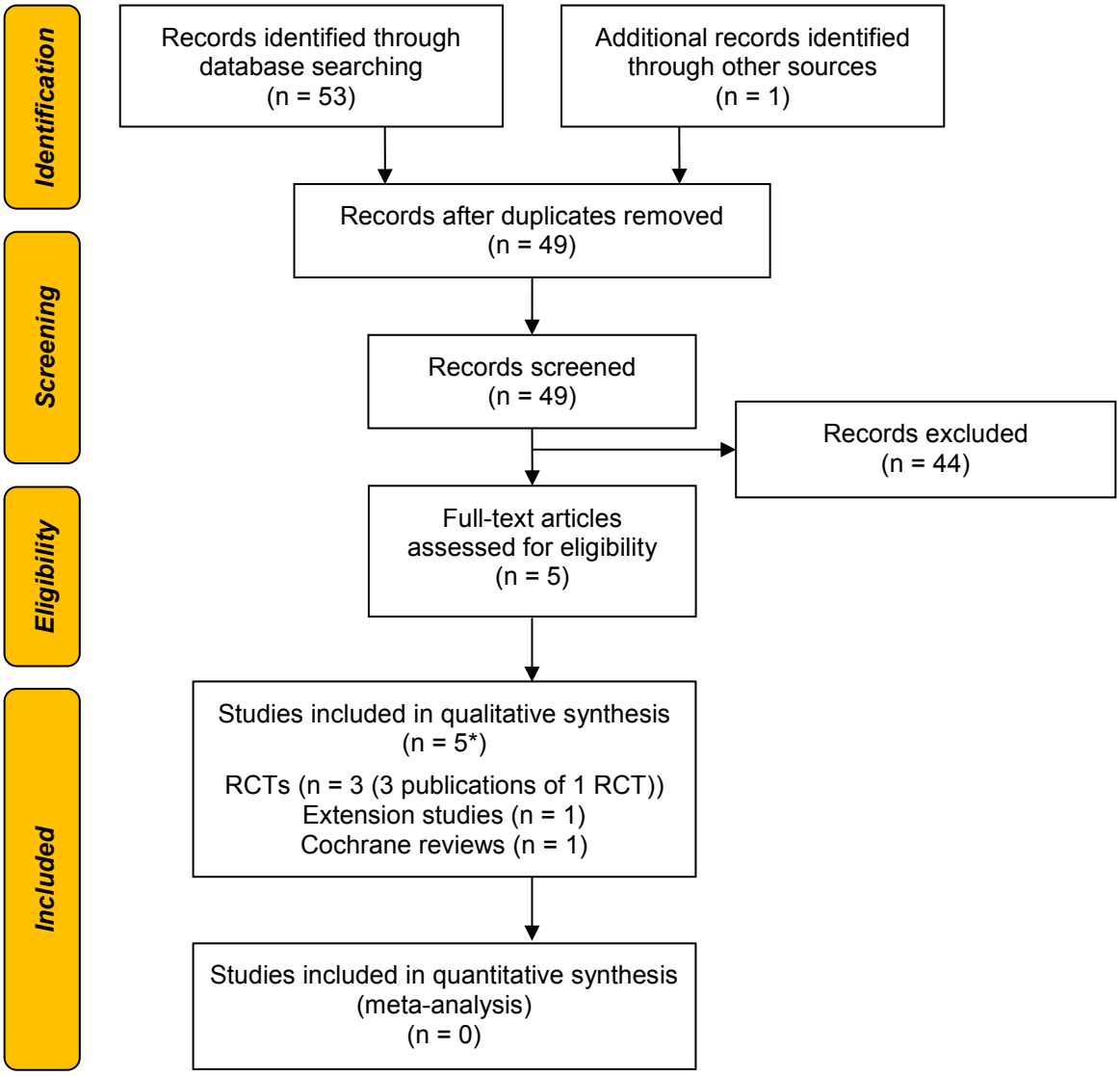
Cochrane Library
Search #1 CLADRIBINE:
"*multiple sclerosis*" AND *cladribine (both in title, abstract and keywords)*
Limits: Trials and Cochrane reviews
The search was performed on November 30, 2017 and resulted in 1 hit.

Search #2 FINGOLIMOD:
"*multiple sclerosis*" AND *fingolimod (both in title, abstract and keywords)*
Limits: Trials and Cochrane reviews
Online Publication Date from Feb 2016 to Nov 2017 (because a Cochrane review is included that searched for literature till February 15, 2016).
The search was performed on November 30, 2017 and resulted in 12 hits.

In total the searches resulted in 50 unique hits.

2.3 Study selection

Figure 2.1: Flow chart



* See paragraph 2.5 for the main characteristics of the included studies.

2.4 Quality rating

We assessed the quality of identified trials and outcomes. We used the Cochrane risk of bias tool to assess internal validity (see Appendix 1: Risk of bias table). We assessed external validity using GRADE (Grading of Recommendations, Assessment, Development and Evaluation, www.grade-workinggroup.org) for the following outcomes: annualized relapse rate, participants free from relapse, participants free from disability worsening, patients free from T1 Gd+ lesions and withdrawals due to adverse events. The GRADE method involves an evaluation of factors influencing our confidence in the reported estimates. Results are as far as possible presented in absolute and relative terms. Finally, the overall quality, or confidence in the estimate was categorized as high, moderate, low or very low.

2.5 Main characteristics of studies included

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/ or safety domain
CLADRIBINE					
CLARITY Publications: Giovannoni, 2010[5] (effectiveness) Comi, 2013[6] (effectiveness) Cook, 2011[7] (safety)	Multicentre, double-blind, placebo-controlled, RCT [ITT] Follow-up: 96 weeks	1326	Placebo (n=437) 3,5 mg/kg cladribine (n=433) 5,25 mg/kg cladribine (n=456)	**Primary:** rate of relapses at 96 weeks **Key secondary:** proportion of patients who were relapse-free, time to sustained progression of disability **Other:** time to the first relapse, proportion of patients receiving rescue therapy with interferon beta-1a, MRI end points, safety	Clinical effectiveness and safety
CLARITY EXTENSION Publication: Giovannoni, 2017[8] (effectiveness and safety)	Multicentre, double-blind, placebo-controlled, randomised extension study of CLARITY trial Follow-up: another 96 weeks followed by a 24-week "supplemental follow-up"	867	**Placebo-recipients from CLARITY:** • 3,5 mg/kg cladribine (PC 3.5) (n=244) **Cladribine-recipients from CLARITY re-randomised 1:2:** Placebo (P) • *3,5 mg/kg cladribine* (CP 3.5) (n=98)* • 5,25 mg/kg cladribine (CP 5.25) (n=92) Or 3,5 mg/kg cladribine (3,5C) • 7 mg/kg cladribine (CC 7) (n=186) • 8,75 mg/kg cladribine (CC 8.75) (n=186)	Amongst others annualized relapse rate, proportion of patients free of qualifying relapses, time to first qualifying relapse, time to confirmed Expanded Disability Status Scale (EDSS) progression and safety	Clinical effectiveness and safety

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/ or safety domain
FINGOLIMOD					
META-ANALYSE Publication: La Mantia, 2016[9] (effectiveness and safety)	Meta-analyse (Cochrane reivew) The aim is to assess the safety and the benefits of fingolimod versus placebo or other disease-modifying drugs, in reducing disease activity in people with RRMS. Follow-up: mean 13 months (range: 6 months till 2 years)	5152 patients from 6 trials 1621 controls (treated with placebo or with other disease modifying drugs) 3551 treated with fingolimod at different doses (2061 with 0.5 mg)	Placebo Fingolimod Interferon-beta 1a	**Primary:** number of participants: **-** relapse-free at 6, 12 and 24 months after randomisation and at the end of follow-up; **-** free from disability worsening at 12, 24 and 36 months after randomisation and at the end of follow-up; **-** who withdrew from the study due to: **--** adverse events; **--** serious adverse events. **Secondary:** annualised relapse rate at 6, 12 and 24 months after randomisation and at the end of follow-up; number of participants free from MRI gadolinium-enhancing lesions at 6, 12 and 24 months after randomisation and at the end of follow-up; mean change of total MRI T2 weighted lesion load at 12 and 24 months after randomisation and at the end of follow-up; quality of life measurement by validated questionnaires	Effectiveness and safety

Abbreviations: * The registered treatment schedule.

Sources: **CC 7:** cladribine tablets 3.5 mg/kg in CLARITY followed by cladribine 3.5 mg/kg in CLARITY Extension; **CC 8.75:** cladribine tablets 5.25 mg/kg in CLARITY followed by cladribine tablets 3.5 mg/kg in CLARITY Extension; **CP 3.5:** cladribine tablets 3.5 mg/kg in CLARITY followed by placebo in CLARITY Extension; **CP 5.25:** cladribine tablets 5.25 mg/kg in CLARITY followed by placebo in CLARITY Extension; **ITT:** intention to treat; **PC 3.5:** placebo in CLARITY followed by cladribine tablets 3.5 mg/kg in CLARITY Extension;

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is cladribine and the comparators?
A0020	For which indication has cladribine received marketing authorisation?
B0002	What is the claimed benefit of cladribine in relation to the comparators?

3.2 Results

Features of the technology and comparators

[B0001] – What is cladribine and the comparators?

Cladribine

Cladribine (2-chloro-2'-deoxyadenosine, 2-Cda) is a nucleoside analogue of deoxyadenosine. It is a prodrug, which is activated after intracellular phosphorylation to 2-chlorodeoxyadenosine triphosphate (CdATP). This is particularly efficiently achieved in lymphocytes, due to their constitutively high deoxycytidine kinase (DCK) and relatively low 5'-nucleotidase levels. Cladribine through its active metabolite exerts reversible selective depletion of lymphocytes, which are thought to underlie the autoimmune processes involved in MS pathophysiology.[10]

Cladribine was first developed for treatment of leukaemia and used for many years with parenteral formulations in patients with hairy cell leukaemia. An oral formulation (10 mg tablets) was later developed for the treatment of MS.[10]

Comparators (alemtuzumab, fingolimod and natalizumab)

Currently fingolimod, alemtuzumab and natalizumab are approved treatment options for patients with relapsing(-remitting) multiple sclerosis. In this assessment only fingolimod is used as comparator. Previously, the National Health Care Institute concluded in the assessment report of alemtuzumab that alemtuzumab, natalizumab and fingolimod have a comparable therapeutic value as second-line treatments for highly active RRMS.[1] A network meta-analysis was executed to base this conclusion on.[2]

Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. Animal studies have shown that this redistribution reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 cells, into the CNS, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also act via interaction with S1P receptors on neural cells.[11]

The features of cladribine and the comparator fingolimod are presented in **Table 3.1**.

Table 3.1: Features of the intervention and comparators

	Cladribine[3]	**Fingolimod[11]**
Proprietary name	Mavenclad®	Gilenya®
Active substance	Cladribine	Fingolimod as hydrochloride
ATC code	L04AA40 Antineoplastic and immunomodulating agents: selective immune-suppressants	L04AA27 Antineoplastic and immunomodulating agents: selective immunosuppressants
Administration mode	Oral, tablet	Oral, capsule
Recommended duration of treatment	Cladribine is administered over 2 years in 2 treatment courses. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days. Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied.	Fingolimod is administered daily.
Dosing	3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. On each treatment day, the patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight.	0,5 mg once daily.

[A0020] – For which indication has cladribine received marketing authorisation?

Cladribine

Oral cladribine is indicated for treatment of adult patients with highly active relapsing multiple sclerosis (RMS) as defined by clinical or imaging features.

- High disease activity (HDA4) = Patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs (DMDs) AND/OR patients with 2 or more relapses in the previous year, whether on treatment or not. (Effectiveness of cladribine in HDA4 patients was determined via post-hoc analyses. Results of these post-hoc analyses are presented in the EPAR, see also page 21 of this report)[10].
- RMS = RRMS or SPMS with superimposed relapses.

Cladribine tablets under the tradename Movectro® were approved in Russia and Australia in 2010.[12] In 2010 the CHMP had given a negative opinion. The CHMP had concerns about the medicine's safety, and these concerns were not resolved during a re-examination procedure in 2011.

After this second opinion Merck Serono Europe Limited withdrew. The company informed the CHMP that it intended to continue clinical trials with cladribine.[13] Also the FDA rejected cladribine in 2011, due to a suspected increase in cancer risk. In 2017, the EMA decided that Mavenclad's® benefits are greater than its risk in patients with highly active disease and recommended that it should be approved for use in the EU. In addition, the fact that Mavenclad® is given by mouth, and requires only 2 short courses 12 months apart, offers an advantage to patients.

Comparator fingolimod

Fingolimod is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient 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.[11]

The European Commission approved fingolimod (Gilenya®) on 17 March 2011.[14]

[B0002] – What is the claimed benefit of the technology in relation to the comparator(s)?

For reasons of ease of possible clustering with fingolimod, the applicant applies for reimbursement of cladribine tablets for patients with highly active relapsing multiple sclerosis with 2 or more relapses in the previous year or 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs. Patients with highly active relapsing multiple sclerosis with 2 or more relapses in the previous year while not on therapy with other disease modifying drugs, are excluded from the reimbursement request. This reimbursement claim of cladribine corresponds to fingolimod's 'Bijlage 2 voorwaarde' in the Netherlands, which states that fingolimod is only reimbursed for patients with highly active relapsing-remitting multiple sclerosis who did not respond to at least one other disease modifying drug registered for MS (Bijlage 2 voorwaarde[15]).

According to the applicant, cladribine's therapeutic value is comparable to fingolimod's therapeutic value.

Treatment burden

Cladribine leads to selective depletion of T and B cells.[3] Fingolimod blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes.[11] This difference in mechanism of action has implications for user-friendliness: reduced drug intake during cladribine treatment compared to fingolimod treatment (see **Table 3.1**). The applicant claims that reduced drug intake supports compliance.

Furthermore, due to cladribine's reduced drug-intake with long-term effect, the patient('s partner) is able to become pregnant during a 4 year treatment period with cladribine.[3] During a continuous treatment period with fingolimod, on the other hand, women should not become pregnant. After stopping fingolimod, immunosuppresive effectivity is stopped as well (short-term effect).[11]

Monitoring burden

Less safety controls (and less hospital monitoring costs) are necessary with cladribine compared to fingolimod.[3,11] See also **Table 6.5** in Chapter 6: Safety.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0004	What is the natural course highly active relapsing multiple sclerosis?
A0005	What are the symptoms and the burden of disease or health condition for the patient?
A0025	How is multiple sclerosis currently managed according to published guidelines and practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

4.2 Results

Overview of the disease or health condition

[A0002] – What is the disease or health condition in the scope of this assessment?

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) resulting in neurological impairment and severe disability.[10] The neuropathology of the disease is marked by an aberrant activation of specific T and B cells that recognize self-antigens (i.e., myelin) expressed in the CNS. MS relapses are considered the clinical expression of acute inflammatory focal lesions associated with an influx of inflammatory T cells and B cells into the CNS, leading to breakdown of the blood-brain barrier, followed by entry of innate immune cells including B cells and monocytes and macrophages. This leads to oligodendrocyte loss, demyelination, axonal damage, and neuronal loss.[10] In addition, disease progression irrespective of relapses can occur, which is considered due likely to a neurodegenerative process associated with demyelination, impaired remyelination, axonal loss and neuronal loss independent of CNS inflammation.[10]

Approximately 85% of all MS patients present '***relapsing-remitting MS (RRMS)***', which is characterised by unpredictable acute episodes of neurological dysfunction named relapses, followed by variable recovery and periods of clinical stability.[4] Approximately 30-45 percent of MS patients currently have RRMS.[16] The other patients developed SPMS.

- Within ten years more than 50% of patients who suffer from a relapsing-remitting form eventually develop sustained disability with or without superimposed relapses. This form is called the '***secondary progressive multiple sclerosis (SPMS)***'.[4] Approximately 30-45 percent of MS patients currently have SPMS.[16]
- The term '***relapsing MS (RMS)***' applies to those affected patients either with a RRMS or SPMS *with* superimposed relapses. Patients with RMS, in spite of suffering from different MS forms, constitute a common target for current treatment options.[4]

Around 15% of patients develop a sustained deterioration of their neurological function early: i.e. '***primary progressive MS (PPMS)***'.

- Some patients who start with a progressive deterioration may experience series of unresolved relapses with time and this form is called '***progressive relapsing multiple sclerosis***'.
- In others the deterioration occurs in the absences of relapses.

The term '*clinically isolated syndrome (CIS)*' refers to the first clinical event that can be attributed to a demyelinating event but does not comply with the diagnostic criteria for definite MS i.e. dissemination of demyelinating events in time and space either observed clinically or radiographically.[4]

Besides these main types of disease a '***benign variety of MS***' refers to a relapsing remitting form with only few relapses and no significant disability after several years of evolution. Conversely, the term '***malignant MS***' applies to a very aggressive form leading to severe disability or death in a few years after the onset of the disease.[4]

Cladribine is indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (RRMS or SPMS with superimposed relapses) as defined by clinical or imaging features.[3] Cladribine intends to modify the natural course of the disease.

Patients with high disease activity included:

- Patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs;
- Patients with 2 or more relapses in the previous year, whether on disease modifying drugs or not.[3]

For reasons of ease of possible clustering with fingolimod, the scope of this assessment is for the treatment of **adult patients with highly active RRMS as defined by clinical or imaging features, despite a full and adequate course of treatment with at least one disease modifying therapy.** See question [B0002] on p.14 for an explanation.

[A0003] – What are the known risk factors for the disease or health condition?

While the exact cause of MS unknown, an autoimmune process has been implicated involving both a genetic predisposition and environmental triggers.[10]

MS is known to occur more frequently in areas that are farther from the equator. Growing evidence suggests that vitamin D plays an important role. People who live closer to the equator are exposed to greater amounts of sunlight year-round. The evidence is also growing that smoking plays an important role in MS. Since viruses are well-recognized as causes of demyelination and inflammation, it is possible that a virus or other infectious agent is the triggering factor in MS, but none have been definitively proven to trigger MS. While MS is not hereditary, having a first-degree relative such as a parent or sibling with MS does significantly increase an individual's risk of developing the disease. Therefore, some researchers theorize that MS develops because a person is born with a genetic predisposition to react to some environmental agent that, upon exposure, triggers an immune-mediated response.[17]

[A0004] – What is the natural course of the disease or health condition?

Approximately 85% of all MS patients present RRMS. Within ten years more than 50% of patients who suffer from a relapsing-remitting form eventually develop sustained disability with or without superimposed relapses: SPMS.[4]

In general, the course of multiple sclerosis with respect to disability is slow. Apart from cases of severe MS, which are rare, the prognosis for longevity is generally good. The course of the disease is highly variable. MS causes damage in the CNS. Therefore, nearly any function can be adversely affected. Symptoms of MS are unpredictable and vary in type and severity from one person to

another and in the same person over time. Symptoms may disappear or remit completely or they may persist and may worsen over time.[17]

[A0005] – What are the symptoms and the burden of disease or health condition for the patient?

Because MS causes damage in the CNS, nearly any function can be adversely affected. However, the most common symptoms are overwhelming fatigue, visual disturbances, altered sensation and difficulties with mobility.[17]

Symptoms of MS are unpredictable, and vary in type and severity from one person to another and in the same person over time. Symptoms may disappear or remit completely or they may persist and may worsen over time.[17]

Two-thirds of people who have MS remain able to walk, though many will need an aid, such as a cane or crutches, and some will use a scooter or wheelchair because of fatigue, weakness, balance problems, or to assist with conserving energy.[17]

MS is the most common cause of serious neurological disability in young adults. According to the Global Burden of Disease Study 2010 of the WHO, the estimated disability weights of mild MS, moderate MS and severe MS are respectively 0.198 (95% CI: 0.137–0.278), 0.445 (95% CI: 0.303–0.593) and 0.707 (95% CI: 0.522–0.857).[18]

Current clinical management of the disease or health condition

[A0025] – How is the disease or health condition currently managed according to published guidelines and in practice?

Diagnosing MS can be a challenging process. In early MS, symptoms may be non-specific and suggestive of several disorders of the nervous system. Early symptoms that come and go may be ignored. While no single laboratory test is yet available to prove or rule out MS, magnetic resonance imaging (MRI) is a great help in reaching a definitive diagnosis. Diagnostic criteria that incorporate MRI findings have been developed and revised by experts in the field and have helped providers make an accurate and timely diagnosis.[17]

The Revised McDonald Criteria, published in 2010 by the International Panel on the Diagnosis of Multiple Sclerosis, include specific guidelines for using MRI, visual evoked potentials (VEP) and cerebrospinal fluid analysis to speed the diagnostic process.
Diagnostic criteria for definite MS are dissemination of demyelinating events in time and space either observed clinically or radiographically:

- There must be evidence of damage in at least two separate areas of the CNS AND
- There must be evidence that the damage occurred at least one month apart AND
- All other possible diagnoses must be ruled out.

The current therapeutic approach involves symptomatic treatment, treatment of acute relapses, and disease modifying therapies.[4] Cladribine and fingolimod are both disease modifying therapies, which aim to prevent relapses and ultimately intend to decrease the rate of accumulation of disability.

Disease modifying drug treatments in the Netherlands
In the Netherlands, therapy of patients with RRMS is usually initiated with treatments with modest effect and more benign safety profile (interferon-beta, glatiramer, teriflunomide, dimethylfumarate, daclizumab).[16] If the treatment response is unsatisfactory, treatment alternatives with high efficacy and a more unfavourable safety profile can be used such as alemtuzumab, natalizumab or fingolimod.[16] These treatments are also authorised and used to initiate treatment in patients with high disease activity (HDA).[11,19,20] In the Netherlands, however, only alemtuzumab is reimbursed as first- and second-line treatment. Natalizumab and fingolimod are only reimbursed as second-line treatments, due to their less favourable safety profiles.[16]

The reimbursement claim for cladribine tablets is for the treatment of adult patients with highly active RRMS as defined by clinical or imaging features, despite a full and adequate course of treatment with at least one disease modifying therapy. Therefore, comparators of cladribine should be alemtuzumab, natalizumab and fingolimod. In this assessment report only fingolimod is used as comparator, according the rationale given in the Scope.

Target population

[A0007] – What is the target population of this assessment?

For reasons of ease of possible clustering, the applicant seeks reimbursement of cladribine tablets for patients with highly active relapsing multiple sclerosis with 2 or more relapses in the previous year or 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs (second-line treatment). Patients with highly active relapsing multiple sclerosis with 2 or more relapses in the previous year, while not on therapy with other disease modifying drugs, are excluded from the reimbursement request (first-line treatment). This reimbursement claim of cladribine corresponds to fingolimod's 'Bijlage 2 voorwaarde' in the Netherlands, which states that fingolimod is only reimbursed for patients with highly active relapsing-remitting multiple sclerosis who did not respond to at least one other disease modifying drug registered for MS (Bijlage 2 voorwaarde[15]).

[A0023] – How many people belong to the target population?

MS is the most common cause of serious neurological disability in young adults. It is estimated that more than 2.3 million people have MS worldwide.[10] In the Netherlands the incidence of multiple sclerosis was approximately 1.800 in the year 2007. In 2007, the annual prevalence of multiple sclerosis was 16.200 (95% CI:11.400–23.600).[1]

MS typically begins between the ages of 20 to 40 years. Overall, women are affected approximately twice as often as men, except in individuals with the primary-progressive form of the disease, where there is no gender prevalence difference.[10]

The applicant seeks reimbursement of cladribine tablets for patients with highly active relapsing multiple sclerosis with 2 or more relapses in the previous year or 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs (second-line treatment). Patients with highly active relapsing multiple sclerosis with 2 or more relapses in the previous year, while not on disease modifying drugs, are excluded from the reimbursement request (first-line treatment). The chance that a patient had 2 or more relapses in the

previous year, while not treated with a disease modifying drug, however, is thought to be (very) small, due to an earlier start of MS treatment which is caused by more stringent diagnostic criteria.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of cladribine on mortality?
D0005	How does cladribine affect symptoms and findings (severity frequency) of highly active relapsing MS?
D0006	How does cladribine affect progression of highly active relapsing MS?
D0011	What is the effect of cladribine on patients' body functions?
D0012	What is the effect of cladribine on generic health-related quality of life?
D0013	What is the effect of cladribine on disease-specific quality of life?

5.2 Results

Included studies

Direct evidence is available on the clinical effectiveness of oral cladribine compared to placebo (see Paragraph 2.5).[5-8] The choice of comparator, fingolimod, is justified in Chapter 3 ´Description and technical characteristics of the technology´. The indirect evidence for the relevant comparator patient group consists of a Cochrane review (see Paragraph 2.5).[9]

Cladribine

CLARITY study (Giovannoni, 2010[5]; Cook, 2011[7]; Comi, 2013[6])

Efficacy and safety of oral cladribine were evaluated in a multicentre, double-blind, placebo-controlled, randomised clinical trial (CLARITY) in 1326 patients with RRMS. The study included patients who had at least one relapse within 12 months before study entry, and had a score of no more than 5,5 on the Kurtzke Expanded Disability Status Scale (EDSS). Patients were amongst others excluded from the study if two or more previous disease-modifying therapies had failed or if they had received immunosuppressive therapy at any time before study entry or cytokine-based therapy, intravenous immune globulin therapy, or plasmapheresis within 3 months before study entry. For any patient who had received a disease-modifying drug for multiple sclerosis, a washout period of at least 3 months before study entry was required.

The median age was 39 years (range 18 to 65), and the female to male ratio was approximately 2:1. Patients received either placebo (n=437), or a cumulative dose of cladribine of 3,5 mg/kg (n=433) or 5,25 mg/kg body weight (n=456) over the 96-week study period in 2 treatment courses. Patients randomised to the 3,5 mg/kg cumulative dose received a first treatment course at weeks 1 and 5 of the first year and a second treatment course at weeks 1 and 5 of the second year. Patients randomised to the 5,25 mg/kg cumulative dose received additional treatment at weeks 9 and 13 of the first year. After week 24, rescue therapy with subcutaneous interferon beta-1a was available if a patient had more than one relapse or a sustained increase in the EDSS score. Relapses could be treated with intravenous corticosteroids at the discretion of the treating physician.

The primary end point was the rate of relapse at 96 weeks[A]. Key clinical secondary efficacy end points were the proportion of patients who were relapse-free and the time to sustained progression of disability[B]. Patients who completed the 2-year study period were eligible for the CLARITY Extension study if they had normal lymphocyte count and other normal haematological results within 28 days of the first planned dose.

Post-hoc subgroup analyses[10]

The EPAR describes *post-hoc* analyses in patients with High Disease Activity (HDA). The HDA definition was developed in line with a CHMP scientific advice using the definitions for highly active disease previously agreed for other DMDs, considering a number of clinical relapses in a previous year as well as a number of T1 Gd+ or T2 lesions as criteria to build this definition. The resulting HDA subgroups are presented in **Table 5.1**.

Table 5.1: Definitions of different subgroups of patients with High Disease Activity (HDA)

Definition	HDA 1 A and/or C	HDA 2 D	HDA 3 B and D	HDA 4 A and/or D
A. Subjects with ≥1 relapse in previous year while on DMD therapy and ≥1 T1 Gd+ or ≥9 T2 lesions	X			X
B. ≥1 T1 Gd+ or ≥9 T2 lesions			X	
C. Subjects with ≥2 relapses (no prior use of DMD at any time in subject's history or duration of previous DMD therapy <1 year)	X			
D. Subjects with ≥2 relapses in previous year regardless of treatment status		X	X	X

N.B. Cladribine is registered for subgroup HDA 4: Subjects with ≥1 relapse in previous year while on DMD therapy and ≥1 T1 Gd+ or ≥9 T2 lesions (definition A) AND/OR subjects with ≥2 relapses in previous year regardless of treatment status (definition D).[3]

DMD: Disease Modifying Drug; **HDA:** High Disease Activity.

CLARITY Extension study (Giovannoni, 2017[8])

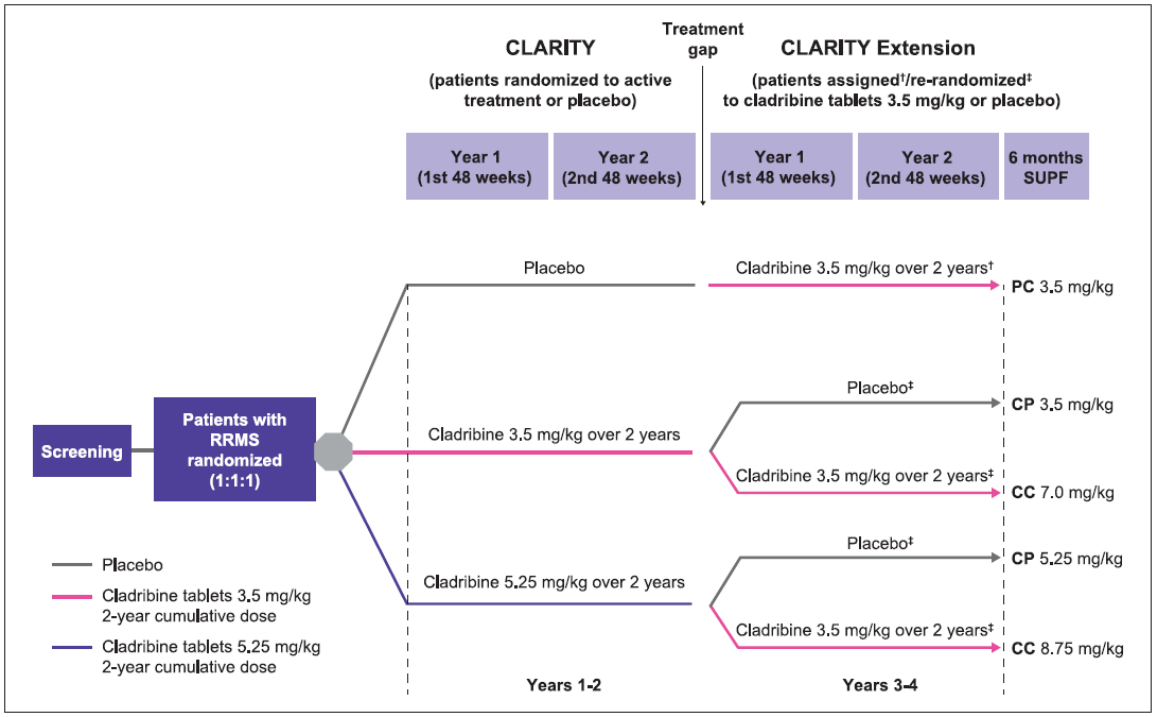
CLARITY Extension was not a pre-planned study, and as a consequence after completing CLARITY, there was a variable gap period before patients entered the Extension. Gap duration was similar across treatment groups and the median gap duration for the overall population was 40.3 weeks. Patients who had received interferon beta or glatiramer acetate during the gap period had to discontinue their disease-modifying drug therapy ≥3 months before the first study day of the Extension. Patients who received placebo in CLARITY were assigned to cladribine tablet 3.5 mg/kg, and patients treated with cladribine tablets in CLARITY were re-randomized (2:1) to cladribine tablets 3.5 mg/kg or placebo (see **Figure 5.1**). All patients treated with cladribine tablets during the Extension received a cumulative dose of 3.5 mg/kg, administered in Weeks 1, 5, 48 and 52 (only patients with

[A] A relapse was defined as an increase of 2 points in at least one functional system of the EDSS or an increase of 1 point in at least two other functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement.

[B] The time to sustained progression was defined as the time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0.

Grade 0 or 1 lymphocyte counts were retreated at Weeks 48 and 52). The Extension (96 weeks) was followed by a 24-week "supplemental follow-up" during which patients did not receive treatment with cladribine tablets but could receive disease-modifying drugs. The blind was maintained from CLARITY in all treatment arms during the Extension. Clinical endpoints included the annualized relapse rate (ARR), the proportion of patients free of qualifying relapses, time to first qualifying relapse, and time to confirmed Expanded Disability Status Scale (EDSS) progression. The ITT population comprised patients randomized or assigned to treatment in the Extension. The safety population included patients who received ≥one dose of study medication and had follow-up safety data. Patients who had completed CLARITY but were not eligible for treatment in the Extension were followed for safety only.

Figure 5.1: Study design of CLARITY (Extension)



Each short course of treatment comprised one or two 10-mg cladribine tablets taken once daily for four or five consecutive days or an equivalent number of matching placebo tablets. There was a variable interval between the treatment periods in the CLARITY and Extension studies. **CP 3.5 mg/kg:** cladribine tablets 3.5 mg/kg in CLARITY followed by placebo in CLARITY Extension; **CP 5.25 mg/kg:** cladribine tablets 5.25 mg/kg in CLARITY followed by placebo in CLARITY Extension; **CC 7 mg/kg:** cladribine tablets 3.5 mg/kg in CLARITY followed by cladribine 3.5 mg/kg in CLARITY Extension; **CC 8.75 mg/kg:** cladribine tablets 5.25 mg/kg in CLARITY followed by cladribine tablets 3.5 mg/kg in CLARITY Extension; **PC 3.5 mg/kg:** placebo in CLARITY followed by cladribine tablets 3.5 mg/kg in CLARITY Extension; **RRMS:** relapsing-remitting MS; **SUPF:** supplemental follow-up.

Fingolimod

Meta-analysis (La Mantia, 2016[9])

The aim of the Cochrane meta-analysis is to assess the safety and benefits of fingolimod in reducing disease activity in people with relapsing-remitting multiple sclerosis (RRMS). Fingolimod was compared to placebo (main comparison) or other disease modifying drugs. In total six studies were included, comprising a total of 5152 participants suffering from RRMS. The treatment duration was six months in three studies, 12 months in one study and 24 months in two studies. Participants were affected by relapsing-remitting multiple sclerosis in all studies, and secondary progressive multiple sclerosis in a small percentage in two studies. Primary outcomes were number of participants relapse-free at 6, 12 and 24 months after randomisation and at the end of follow-up; number of participants free from disability worsening at 12, 24 and 36 months after randomisation and at the end of follow-up; and number of participants who withdrew from the study due to (serious) adverse events. GRADE considerations were used to assess the quality of the body of evidence.

Confirmed relapse was defined as the occurrence of new symptoms, or worsening of previously stable or improving symptoms, and signs not associated with fever, lasting more than 24 hours. Symptoms had to appear at least 30 days after the onset of a preceding relapse (two out of six included studies), and had to be accompanied by an increase of at least half a point in the EDSS score (four out of six included studies) or one point in at least one of the functions in the Kurtzke Functional System score (excluding bowel-bladder and mental systems) (one out of six included studies) or one point in each of two functions in the Kurtzke Functional Systems score, or two points in one of the functions in the Kurtzke Functional System score (excluding bowel-bladder or cerebral systems) (four out of six included studies). Disability worsening is defined as at least one point Expanded Disability Status Scale (EDSS) increase, or a 0.5 point increase if the baseline EDSS was ≥5.5, confirmed during two subsequent neurological examinations separated by at least 6 months 'interval free of relapses.

Post-hoc subgroup analysis (Derfuss, 2015[21])
Post-hoc analysis of the two phase 3 trials were performed according to the population specified by the EMA in the label for fingolimod: Patients who had received treatment in the previous year and had (1) ≥1 relapse in the previous year and either ≥1 gadolinium (Gd) enhancing T1 lesion or ≥9 T2 lesions at baseline and/or (2) as many or more relapses in the year before baseline as in the previous year (as per fingolimod's EU label). The included trials correspond to the trials included in the Cochrane review.

Mortality

[D0001] – What is the expected beneficial effect of cladribine on mortality?

Apart from cases of severe MS, which are rare, the prognosis for longevity is generally good. Therefore no beneficial effect of cladribine on mortality is expected and no results of cladribine on mortality are presented.

Morbidity

[D0005] – How does 3.5 mg/kg cladribine affect relapses of patients with active relapsing multiple sclerosis compared to placebo and fingolimod?

Annualized relapse rate

In the CLARITY trial, oral cladribine reduced the annualized relapse rate significantly as compared with the placebo group (0.14 vs. 0.33, respectively). The relative reduction was 57.6% in the cladribine 3.5 mg group (p<0.001).[5] Corresponding rate ratio was 0.424. HDA4[C] patients treated with cladribine 3.5 mg/kg had a relapse rate of 0.16 (95% CI:0.12-0.22) compared to 0.47 (95% CI:0.40-0.57) in HDA4-patients treated with placebo. The relative risk was 0.33 (95% CI:0.23-0.48; p<0.001). In non-HDA4 patients the relapse rate was 0.14 (95% CI:0.11-0.18) for patients receiving cladribine 3.5 mg/kg compared to 0.29 (95% CI:0.24-0.34) for placebo. The relative risk was 0.49 (95%-CI: 0.37-0.65; p<0.001). The difference between HDA4 and non-HDA4 did not reach statistical significance.[10]

The treatment effect of 3.5 mg/kg cladribine obtained in CLARITY was maintained during CLARITY Extension when these patients were treated with placebo. Annualized relapse rate was 0.15 (95% CI: 0.09-0.21). There were no obvious differences in annualized relapse rate between subgroups defined by gap duration (before entering CLARITY Extension).[8]

According to the Cochrane review of La Mantia (2016), fingolimod 0.5 mg reduced the annualized relapse rate significantly as compared with placebo at 24 months. The rate ratio was 0.50 (95% CI: 0.40 to 0.62).[9] Subgroup analysis showed that HDA patients treated with fingolimod had an annualised relapse rate of 0.24. In the placebo group the annualised relapse rate was 0.46. The corresponding rate ratio is 0.52 (95% CI: 0.40-0.69).[21]

Results of Annualized relapse rate are shown in **Table 5.2** and **Table 5.3**.

Participants free from relapse

79.7% of subjects in the cladribine 3.5 mg/kg group, and 60.9% of subjects in the placebo group remained relapse-free at Week 96. There was a statistically significant increase in the risk of participants free from relapse compared to placebo in 3.5 mg/kg cladribine treated patients (OR=2.53; 95% CI:1.87-3.43; p<0.001).[5] Corresponding RR=1.30 (95% CI: 1.19-1.43; p<0.001). Participants free from relapse in HDA subgroups were not reported in the EPAR.[10]

75.6% of subjects who were treated with 3.5 mg/kg cladribine during CLARITY remained relapse free during the 2-year CLARITY Extension study while treated with placebo.[8]

There was a statistically significant increase in the risk of participants free from relapse in patients treated with fingolimod 0.5 mg compared to placebo at 24 months (RR=1.44; 95% CI: 1.28-1.63; p-value not reported).[9]

Results of Participants free from relapse are shown in **Table 5.4**.

[C] HDA4 = Subjects with ≥1 relapse in previous year while on DMD therapy and ≥1 T1 Gd+ or ≥9 T2 lesions AND/OR subjects with ≥2 relapses in previous year regardless of treatment status.

[D0006] – How does cladribine affect progression of disability in patients with active relapsing multiple sclerosis compared to fingolimod?

Time to sustained progression of disability

Time to sustained progression of disability increased significantly in 3.5 mg/kg cladribine treated patients compared to placebo (13.6 vs. 10.8 months; HR=0.67; 95% CI:0.48 to 0.93; *p*=0.02).[5] Post-hoc analyses, defining the time-frame of sustained disease progression at 6 months resulted in a HR compared with placebo of 0.53 (95% CI:0.36-0.79; *p*=0.002).[10] With regards to 3 months confirmed disease progression in HDA4 subjects treated with cladribine 3.5 mg/kg, the HR was 0.28 (95% CI:0.15-0.54), compared to 0.8 (95% CI:0.55-1.17) in non-HDA4 patients (*p*=0.008). For time to 6-months confirmed disease progression, the HR was 0.18 (95% CI:0.07-0.43) for HDA4 patients and 0.82 (95% CI:0.51-1.30) for non-HDA4 patients (*p*=0.004).[10]

Time to sustained progression of disability was not reported in CLARITY Extension[8] and in fingolimod's Cochrane review[9].

Participants free from disability worsening

Participants free from 3-mo sustained change in EDSS score increased significantly in the 3.5 mg/kg cladribine (85.7%) group compared to placebo (79.4%) (OR=1.55; 95% CI:1.09 to 2.22; *p*=0.02).[5] Corresponding RR is 1.08 (95% CI: 1.01-1.15; *p*=0.015).

In CLARITY Extension 72.4% remained free of confirmed 3-month EDSS progression in patients treated with 3.5 mg/kg cladribine during CLARITY followed by placebo in year 3 and 4 during CLARITY Extension. The gap-interval did not seem to influence the time to 3-month confirmed EDSS progression.[8]

The number of participants free from disability worsening increased significantly in fingolimod treated patients compared to placebo (RR=1.07; 95% CI: 1.02 to 1.11; *p*-value not reported).[9]

Results of Participants free from disability worsening are shown in **Table 5.5**.

[D0011] – What is the effect of the technology on patients' body functions?

Patients free from T1 Gd+ lesions
86.8% of patients treated with cladribine 3.5 mg/kg were free from MRI Gd+ lesions, compared to 48.3% in placebo. The OR for this comparison is 7.57 (95% CI:5.37-10.67). The RR is 1.80 (95% CI:1.62-2.00).[6]
89% of patients treated with fingolimod 0.5 mg were free from MRI Gd+ lesions, compared to 65% in placebo. The OR is 4.14 (95% CI:3.08-5.58). The RR for this comparison is 1.36 (95% CI:1.27-1.45).[9]

Active T2 lesions
61.7% of patients treated with cladribine 3.5 mg/kg were free from active T2 lesions, compared to 28.4% in placebo. The OR for this comparison is 4.17 (95% CI:3.13-5.55).[6]

Combined unique lesions

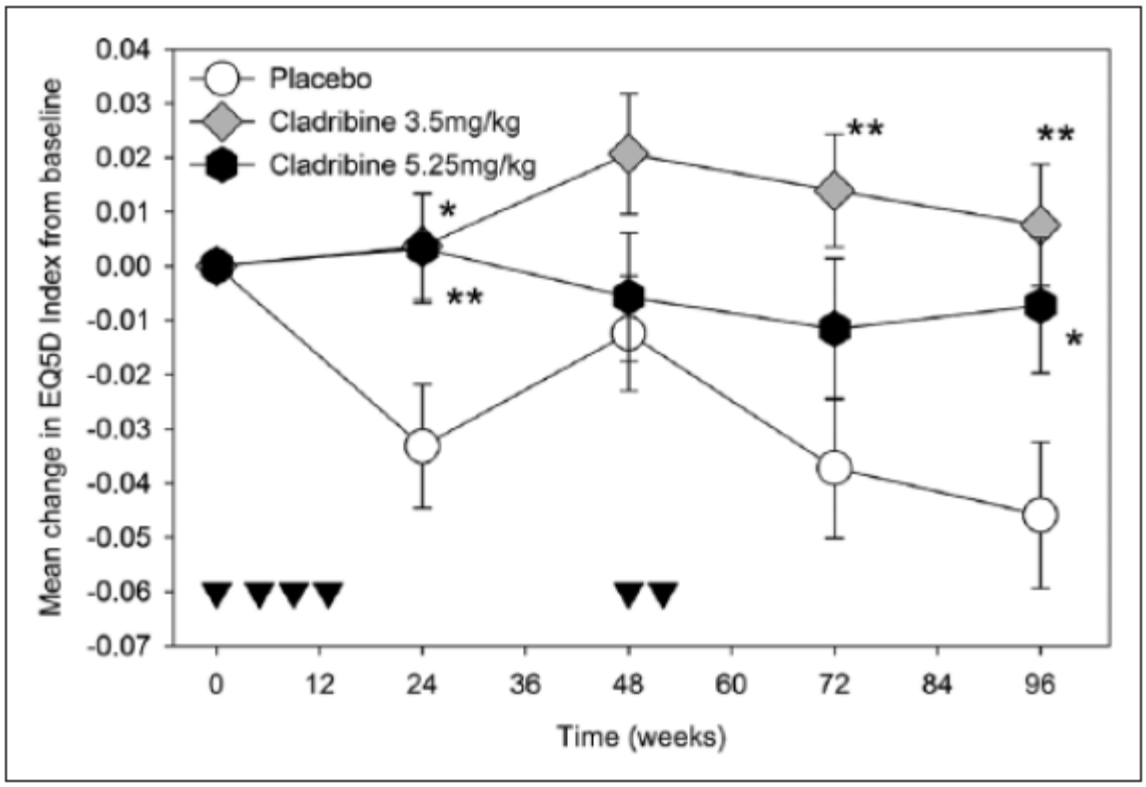
59.6% of patients treated with cladribine 3.5 mg/kg were free from combined unique lesions, compared to 26.1% in placebo. The OR for this comparison is 4.27 (95% CI:3.20-5.71).[6]

Health-related quality of life

[D0012] – What is the effect of cladribine on generic health-related quality of life?

Quality of life data was not reported in the publication of the CLARITY trial. However, Afolabi et al. (2017) acquired quality of life data from the CLARITY trial from the European Medicines Agency through Freedom of Information and published the analysed results.[22] After 96 weeks patients with RMS taking 3.5 mg/kg cladribine reported significantly improved Euro Quality of Life 5 Dimension (EQ-5D) index scores compared with placebo (*p*=0.001) (**Figure 5.2**).

Figure 5.2: The impact of cladribine on EQ-5D[22]



Based on data from the North American Research Committee on MS (NARCOMS) registry, the EQ-5D-3L minimal clinically important difference was between 0.050 and 0.084.[22]

According to fingolimod's Cochrane review, no differences in quality of life (EQ-5D scale) were found between fingolimod and placebo after 24 months.[9]

[D0013] – What is the effect of cladribine on disease-specific quality of life?

Quality of life data was not reported in the publication of the CLARITY trial.
Positive, yet non-significant, differences were detected in Multiple Sclerosis Quality of Life-54 (MSQOL-54) scores between cladribine and placebo.[22]

5.3 Discussion

Efficacy of 3.5 mg/kg oral cladribine in patients with highly active RRMS

The CLARITY trial along with its 2-year extension study has been conducted to support the initially claimed indication (RRMS). The annualised relapse rate was 0.14 for patients receiving cladribine 3.5 mg/kg and 0.33 for the placebo group (p<0.001). The relative reduction of the annualised relapse rate was 57.6%.[5] According to the CHMP this was clinically relevant.[10] Also the difference between the active and placebo arm was statistically significant and considered relevant, with regards to the time to 3-months sustained disability progression (HR=0.67).[8,10] Post-hoc analysis of time to 6-month sustained change in EDSS showed similar results in favour of active treatment (HR=0.53).[10] There was a small absolute difference of cladribine 3.5 mg/kg on preventing disability worsening (OR=1.55; 95% CI:1.09-2.22 or RR=1.08; 95% CI:1.01-1.15).[5] However, this difference was not considered clinically relevant. EQ-5D data showed significant improvements for cladribine 3.5 mg/kg as well[22], although also this difference was not considered clinically relevant[4] For all imaging endpoints, a statistically significant difference between active treatment and placebo was found (p<0.001 for all comparisons).[8] Results for the tertiary endpoints supported the findings for the primary and secondary endpoints.[10]

In general, RRMS patients recruited in CLARITY were relatively mildly affected, which is reflected in the low annualised relapse rate in the placebo group (0.33), which was in fact somewhat lower compared to the annualised relapse rates in placebo groups of clinical trials with recently approved MS treatments.[10] During the assessment the EMA consulted additional experts. These SAG members noted the rather low disease activity as a limitation of the clinical trial program. This decreases reliability of indirect comparison to other disease modifying drugs, such as fingolimod. The CLARITY trial, however, also included a limited subset of patients with highly active RRMS.[5] In line with a CHMP Advice in December 2014, *post-hoc* subgroup analyses were performed in patients with high disease activity (HDA). HDA-patients were defined taking into account clinical and MRI criteria as previously used for disease modifying drugs approved in MS patients with HDA (fingolimod and natalizumab) and included patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other DMDs or patients with 2 or more relapses in the previous year, whether on DMD treatment or not.[10] A greater effect of cladribine in HDA patients compared to non-HDA patients was observed for annualised relapse rate, time to 3 months or 6 months disease progression, but not for MRI endpoints, where there was no difference. Overall, the CLARITY study showed a clinically relevant effect of cladribine in the treatment of adult patients with RRMS and subgroup analyses support a trend for a greater benefit of cladribine in HDA patients.[10]

The CLARITY Extension trial was not initiated immediately but only after 54% of the patients had completed CLARITY. Of the 1184 patients who competed CLARITY, only 883 patients were enrolled into CLARITY Extension.[8] Overall, the baseline demographic characteristics were similar for all treatment groups and resembled the baseline demographic characteristics in CLARITY. Notably, baseline EDSS score in the placebo treated patients had not changed at the time of entry into the CLARITY Extension study compared to enrolment in CLARITY i.e. for two years there was no worsening in disability despite absence of treatment. This again speaks for a mildly affected study population.[10]

[4] Based on data from the North American Research Committee on MS (NARCOMS) registry, the EQ-5D-3L minimal clinically important difference was between 0.050 and 0.084.[22]

Overall, the efficacy results from the study should be interpreted with caution, given the exploratory nature of the analyses. However, the majority of clinical efficacy results suggested that there was no relevant added benefit of additional treatment courses beyond year 2 and that the treatment effect obtained in CLARITY was maintained. The extensive list of MRI parameters, however, had been predefined, which increases the likelihood of chance-findings. The gap-interval did not seem to influence the annualized relapse rate. The need for re-treatment beyond 4 years has not been studied. The applicant therefore agreed to further investigate recurrence of disease activity and the need for re-treatment as secondary objective in the planned long-term cohort post-authorisation study.[10]

With regards to patients with high disease activity in CLARITY Extension, the applicant presented *post-hoc* analyses for patients treated with 3.5 mg/kg cladribine in year 1 and 2 followed by placebo treatment in year 3 and 4. According to the EPAR there were no meaningful differences in the annualised relapse rate, T1 Gd+ lesions, or active T2 lesions during CLARITY Extension between these patients fulfilling either HDA or non-HDA definitions.[10]

Efficacy of 3.5 mg/kg cladribine in patients with highly active SPMS with superimposed relapses

Since the population in the scope of this assessment report does not include patients with highly active SPMS with superimposed relapses, this patient group – that is also indicated for cladribine – is not relevant for this assessment report. Nevertheless, study results from the supportive ONWARD study (results only published in the EPAR[10]) and a post-hoc analysis of a mixed cohort including CLARITY and ONWARD patients suggest that efficacy on relapses in RRMS may also be extrapolated to efficacy on relapses in SPMS. Therefore, the CHMP was of the view that a more appropriate target population for cladribine would be patients with highly active RMS (RRMS + SPMS with superimposed relapses) instead of RRMS.[10]

Additional expert consultation (Scientific Advisory Group (SAG))

SAG members agreed that a clear beneficial effect of cladribine in the treatment of (R)RMS has been shown. The SAG noted that the patient population recruited in the CLARITY trial (main study) had overall rather low disease activity, therefore we downgraded for indirectness in the indirect comparison with fingolimod. Other limitations of the clinical trial program for cladribine include the lack of an active comparator and that the evidence in HDA patients was derived from a *post-hoc* subgroup analysis, therefore we downgraded for risk of bias in the direct comparisons of cladribine vs. placebo and fingolimod vs. placebo. Nevertheless, the experts considered the evidence convincing.[10]

Efficacy of 3.5 mg/kg cladribine vs. 0.5 mg fingolimod

In RRMS patients, regardless of treatment status, oral cladribine 3.5 mg/kg has a comparable beneficial effect compared to oral fingolimod 0.5 mg. Quality of the evidence is low or very low for different outcomes. This is due to the indirect comparison, which is hampered by differences in terms of study characteristics (diagnostic criteria), the patient populations recruited (mean relapses in prior year, disease duration, treatment history (previously treated vs. treatment naïve)) and definitions of outcomes. This is, amongst others, demonstrated by differences in placebo group values. Furthermore study populations (mild to highly active RRMS) do not match the target population

(highly active RRMS). The indirect comparison with HDA patients is also limited by variations in the definitions of HDA across studies. Nevertheless, we conclude effectiveness of cladribine 3.5 mg/kg is comparable to effectiveness of fingolimod 0.5 mg. This conclusion is supported by two recently published studies, a Systematic Literature Review and Network Meta-Analysis of Cladribine Tablets versus alternative Disease-Modifying Treatments for Relapsing-Remitting Multiple Sclerosis[23] and a pairwise propensity score–matched analyses.[24]

5.4 Conclusion

Cladribine tablets administered as monotherapy at the approved dose of 3.5 mg/kg increases the probability of being relapse-free at 96 weeks compared to placebo in RRMS patients. The annualised relapse rate favoured cladribine 3.5 mg/kg compared to placebo. These benefits were confirmed with disease measures defined by MRI scans. However, there was no clinically relevant added value of cladribine at 3.5 mg/kg on preventing disability progression. The treatment effect obtained in CLARITY was maintained in CLARITY Extension. Or, in other words, there is no relevant added benefit of additional treatment courses in year 3 and 4.

Across all subgroups, HDA patients had more pronounced effects than non-HDA patients for both annualized relapse rate and time to disability progression (3 months and 6 months), but not for MRI endpoints, where there was no difference. Altogether, subgroup analyses suggested a larger effect size in patients with high disease activity.

Annualized relapse rate, participants free from relapse, participants free from disability and participants free from MRI Gd+ lesions did not differ significantly between cladribine and fingolimod treated patients. Therefore, we conclude there is no difference in efficacy between cladribine and fingolimod in highly active RRMS patients.

Table 5.2: Annualized relapse rate – indirect comparison

Quality assessment							Effect				Quality	Importance
							Absolute		Relative			
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other consider-ations	Annualized relapse rate (95% CI)	Annualized relapse rate (95% CI)	Cladribine 3.5 mg/kg vs. placebo	Fingolimod 0.5 mg vs. placebo		
Cladribine 3.5 mg/kg vs. placebo: Annualized relapse rate (follow-up: 96 weeks ~ 24 months)												
1	Randomised trial	Not serious	Not serious	Serious[A]	Not serious	Not found	**Cladribine 3.5 mg/kg** 0.14 (0.12-0.17)	**Placebo** 0.33 (0.29-0.38)	**Rate ratio (95% CI):** 0.42* (not known)		⊕⊕⊕◯ MODERATE	CRUCIAL
Fingolimod 0.5 mg vs. placebo: Annualized relapse rate (follow-up: 24 months)												
2	Meta-analysis with two random-ised trials (see appendix)	Not serious	Not serious	Serious[A]	Not serious	Not found	**Fingolimod 0.5 mg** not reported	**Placebo** not reported		**Rate ratio (95% CI)** 0.50 (0.40-0.62)	⊕⊕⊕◯ MODERATE	CRUCIAL
Indirect comparison cladribine 3.5 mg/kg vs. fingolimod 0.5 mg: Annualized relapse rate (follow-up ~24 months)												
3	Indirect compari-son with a ran-domised trial (cladribine) and a meta-analysis (fingolimod)	Not serious	Not serious	Very serious[A,B]	Not serious	Not found	**Cladribine 3.5 mg/kg** 0.14 (0.12-0.17)	**Fingolimod 0.5 mg** not reported	**Rate ratio (95% CI):** 0.42* (not known)	**Rate ratio (95% CI)** 0.50 (0.40-0.62)	⊕⊕◯◯ LOW	CRUCIAL

See page 34 for annotations.

Table 5.3: Annualized relapse rate in HDA patients – indirect comparison

Quality assessment							Effect				Quality	Importance
							Absolute		Relative			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Annualized relapse rate in HDA patients (95% CI):	Annualized relapse rate in HDA patients (95% CI):	Cladribine 3.5 mg/kg vs. placebo	Fingolimod 0.5 mg vs. placebo		
Cladribine 3.5 mg/kg vs. placebo in HDA patients: Annualized relapse rate (follow-up: 96 weeks ~ 24 months)												
1	Subgroup analysis from a randomised trial	Serious[C]	Not serious	Not serious	Not serious	Not found	**Cladribine 3.5 mg/kg** 0.16 (0.12-0.22)	**Placebo** 0.47 (0.40-0.57)	**Rate ratio (95% CI)** 0.33 (0.23-0.48)		⊕⊕⊕◯ MODERATE	CRUCIAL
Fingolimod 0.5 mg vs. placebo in HDA patients: Annualized relapse rate (follow-up: 24 months)												
2	Pooled subgroup analyses from 3 randomised trials	Serious[C]	Not serious	Not serious	Not serious	Not found	**Fingolimod 0.5 mg/kg** 0.24 (0.19-0.30)	**Placebo** 0.46 (0.39-.055)		**Rate ratio (95% CI)** 0.52 (0.40-0.69)	⊕⊕⊕◯ MODERATE	CRUCIAL
Indirect comparison cladribine 3.5 mg/kg vs. fingolimod 0.5 mg in HDA patients: Annualized relapse rate (follow-up ~24 months)												
3	Indirect comparison of subgroup analyses from a randomised trial (cladribine) and 3 randomised trials (fingolimod)	Serious[C]	Not serious	Not serious[D]	Not serious	Not found	**Cladribine 3.5 mg/kg** 0.16 (0.12-0.22)	**Fingolimod 0.5 mg/kg** 0.24 (0.19-0.30)	**Rate ratio (95% CI)** 0.33 (0.23-0.48)	**Rate ratio (95% CI)** 0.52 (0.40-0.69)	⊕⊕⊕◯ MODERATE	CRUCIAL

See page 34 for annotations.

Table 5.4: Participants free from relapse – indirect comparison

Quality assessment							Effect				Quality	Im-portance
							Absolute		Relative			
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Other consider-ations	Participants free from relapse:	Participants free from relapse:	Cladribine 3.5 mg/kg vs. placebo	Fingolimod 0.5 mg vs. placebo		
Cladribine 3.5 mg/kg vs. placebo: Participants free from relapse (follow-up: 96 weeks ~ 24 months)												
1	Randomised trial	Not serious	Not serious	Serious[A]	Serious[E]	Not found	**Cladribine 3.5 mg/kg** 345/433 (79.7%)	**Placebo** 266/437 (60.9%)	**OR (95% CI)** 2.53 (1.87-3.43) **RR (95% CI)** 1.30 (1.19-1.43)*		⊕⊕◯◯ LOW	CRUCIAL
Fingolimod 0.5 mg vs. placebo: Participants free from relapse (follow-up: 24 months)												
2	Meta-analysis with two ran-domised trials (see appendix)	Not serious	Not serious	Serious[A]	Not serious	Not found	**Fingolimod 0.5 mg/kg** 555/783 (71%)	**Placebo** 378/773 (49%)		**OR (95% CI)** 2.54 (2.06-3.13)* **RR (95% CI)** 1.44 (1.28-1.63)	⊕⊕⊕◯ MODERATE	CRUCIAL
Indirect comparison cladribine 3.5 mg/kg vs. fingolimod 0.5 mg: Participants free from relapse (follow-up ~24 months)												
3	Indirect compari-son with a ran-domised trial (cladribine) and a meta-analysis (fingolimod)	Not serious	Not serious	Very serious[A,B]	Serious[E]	Not found	**Cladribine 3.5 mg/kg** 345/433 (79.7%)	**Fingolimod 0.5 mg/kg** 555/783 (71%)	**Cladribine 3.5 mg/kg vs. fingolimod 0.5 mg** **RR (95% CI)** 1.12 (1.05-1.20)*		⊕◯◯◯ VERY LOW	CRUCIAL

See page 34 for annotations.

Table 5.5: Participants free from disability worsening – indirect comparison

Quality assessment							Effect				Quality	Importance
							Absolute		Relative			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Participants free from disability worsening:	Participants free from disability worsening:	Cladribine 3.5 mg/kg vs. placebo	Fingolimod 0.5 mg vs. placebo		
Cladribine 3.5 mg/kg vs. placebo: Participants free from disability worsening (follow-up: 96 weeks ~ 24 months)												
1	Randomised trial	Not serious	Not serious	Serious[A]	Not serious	Not found	**Cladribine 3.5 mg/kg** 371/433 (85.7%)	**Placebo** 347/437 (79.4%)	**OR (95% CI)** 1.55 (1.09-2.22) **RR (95% CI)** 1.08 (1.01-1.15)*		⊕⊕⊕◯ MODERATE	CRUCIAL
Fingolimod 0.5 mg vs. placebo: Participants free from disability worsening (follow-up: 24 months)												
2	Meta-analysis with two randomised trials (see appendix)	Not serious	Not serious	Serious[A]	Not serious	Not found	**Fingolimod 0.5 mg/kg** 681/783 (87%)	**Placebo** 631/773 (82%)		**OR (95% CI)** 1.50 (1.14-1.98)* **RR (95% CI)** 1.07 (1.02-1.11)	⊕⊕⊕◯ MODERATE	CRUCIAL
Indirect comparison cladribine 3.5 mg/kg vs. fingolimod 0.5 mg: Participants free from disability worsening (follow-up ~24 months)												
3	Indirect comparison with a randomised trial (cladribine) and a meta-analysis (fingolimod)	Not serious	Not serious	Very serious[A,B]	Not serious	Not found	**Cladribine 3.5 mg/kg** 371/433 (85.7%)	**Fingolimod 0.5 mg/kg** 681/783 (87%)	**Cladribine 3.5 mg/kg vs. fingolimod 0.5 mg** **RR (95% CI)** 0.93 (0.87-0.98)*		⊕⊕◯◯ LOW	CRUCIAL

See page 34 for annotations.

Annotations
A: RRMS patients, including highly active RRMS patients, instead of only highly active RRMS patients: -1 for indirectness.
B: Patients in CLARITY are relatively mildly affected. It was a main point according to the SAG. It decreases the possibility for a valid indirect comparison with other DMDs: -1 for indirectness (intransitivity, see Puhan et al., 2014[25]).
C: Post-hoc subgroup analyses, not predefined: -1 for risk of bias.
D: There is a minor difference in definitions of High Disease Activity (HDA) between studies. However, we do not downgrade for indirectness because of intransitivity. **HDA4 in CLARITY trial:** Subjects with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions AND/OR subjects with 2 or more relapses in the previous year (regardless of previous treatment status). **HDA in fingolimod trials:** Subjects who had received treatment in the previous year and had ≥1 relapse in the previous year and either ≥1 Gd+ T1 lesion or ≥9 G T2 lesions at baseline AND/OR as many or more relapses in the year before baseline as in the previous year (as per fingolimod's EU label).
E: The 95% confidence interval of the relative risk crosses the 1.25 border of clinical relevance: -1 for imprecision.
***:** RRs calculated using a relative risk calculator (bron). ORs calculated using a odds ratio calculator.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is cladribine in relation to the comparators?
C0002	Are the harms related to dosage or frequency of applying cladribine?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of cladribine?

6.2 Results

Included studies

SmPC cladribine

The most clinically relevant adverse reactions reported in MS patients who received cladribine tablets at the recommended cumulative dose of 3.5 mg/kg over 2 years in clinical studies were lymphopenia and herpes zoster. The incidence of herpes zoster was higher during the period of grade 3 or 4 lymphopenia (<500 to 200 cell/mm^3 or <200 cell/mm^3) compared to the time when the patients were not experiencing grade 3 or 4 lymphopenia (See **Table 6.1**).[3]

Study results (CLARITY trial: Cook, 2010[7] and CLARITY Extension trial: Giovannoni, 2017[8])

73.3% and 80.7% of patients reported adverse events (Grade 1-5) in the placebo group and cladribine 3.5 mg/kg group, respectively.[7] In CLARITY Extension 75.5% treated with cladribine 3.5 mg/kg reported adverse events.[8] 3.5 mg/kg cladribine predominantly increased the risk for lymphopenia (1.8% vs. 21.6%), leukopenia (0.7% vs. 5.6%) and decreased lymphocyte counts (0% vs. 3.0%).[7] During CLARITY Extension lymphopenia and leukopenia occurred in 9.2% and 1.0% of patients, respectively.[8] Adverse events with the possibility of a dose-relationship were lymphopenia, leukopenia, lymphocyte count decreased, vertigo, tinnitus and hypoesthesia.

In the placebo and cladribine 3.5 mg/kg groups, respectively, 6.4% and 8.4% of patients experienced serious adverse events (RR=1.30; 95% CI: -0.81 – 2.09; **Table 6.3**).[7] In CLARITY Extension 16.3% of patients experienced serious adverse events.[8] Grade 3-4 lymphopenias occurred in 0.5% and 25.6% of patients in the placebo and cladribine 3.5 mg/kg groups, respectively, during the study.[7] And in 5.1% in the cladribine 3.5 mg/kg groups of CLARITY Extension.[8]

Treatment withdrawals due to adverse events occurred in 2.1% and 3.5% of patients in the placebo and cladribine 3.5 mg/kg groups, respectively (RR=1.68; 95% CI:0.74-3.80; **Table 6.2**)[7] (not reported in Extension). The most common adverse events leading to treatment discontinuation were lymphopenia and lymphocyte count decreased/abnormal and involved 0.9% of the patients in the cladribine 3.5 mg/kg group. None of the patients treated with placebo and also none of the patients treated with 3.5 mg/kg cladribine during CLARITY Extension withdrew from treatment due to lymphopenia. Reasons for treatment discontinuation included infections and infestations (0.5% vs. 0.6%), hepatobiliary disorders (0.2% vs. 0.3%), neoplasms – benign, malignant and unspecified (0 vs. 0.5%) and skin and subcutaneous disorders (0 vs. 0.5%).

Causes of death during the study were suicide (placebo), hemorrhagic stroke (placebo) and acute myocardial infarction (cladribine 3.5 mg/kg). Cause of death following study withdrawal was metastatic pancreatic carcinoma (cladribine 3.5 mg/kg).

During weeks 0-48, infections occurred in 34.3% and 38.4% of patients, respectively, compared to 23.4% and 32.8% of patients, respectively during weeks 48-96. Most infection events (~99% in each treatment group) were rated by investigators as mild or moderate. Cases of herpes zoster occurred in 1.9% in the 3.5 mg/kg group. There were no cases of herpes zoster in the placebo group.

Three cases of malignancy across different organ systems were reported during the study in patients treated with cladribine treatment (3.5 mg/kg and 5.25 mg/kg dose).

SmPC fingolimod

The most serious adverse reactions on fingolimod 0,5 mg were infections, macular oedema and transient atrioventricular block at treatment initiation. The most frequent adverse reactions (incidence ≥10%) on fingolimod 0,5 mg were influenza, sinusitis, headache, diarrhoea, back pain, hepatic enzyme increased and cough. The most frequent adverse reaction reported for fingolimod 0,5 mg leading to treatment interruption was ALT elevations (2.2%) (See **Table 6.1**).[11]

Study results Cochrane review

94.4%-97.8% of patients treated with fingolimod 0.5 mg for the duration of 24 months reported an adverse event compared to 92.6%-96.6% in the placebo group. Infections, hypertension and abnormal liver tests were more frequent in the fingolimod group than in the placebo group. Serious adverse events were reported in 10.1%-14.8% of fingolimod treated patients and in 12.7%-13.4% of patients in the placebo group (RR=0.94; 95% CI: 0.72 – 1.22, **Table 6.3** and see Appendix for Forest Plots). Particularly herpes virus infection, basal-cell carcinoma, first-degree atrioventricular block and second-degree atrioventricular block are significantly elevated serious adverse events in fingolimod treated patients.[9]

The number of participants who withdrew from the study because of adverse events with 0.5 mg fingolimod compared to placebo during the first 24 months of treatment was RR 1.42 (95% CI: 0.89 – 2.24)[9] (**Table 6.2**).

Table 6.1: Common adverse events; cladribine vs. fingolimod

	Cladribine[3]	Fingolimod[11]
Very common adverse events (≥10%)	**lymphopenia**	influenza, sinusitis headache cough diarrhoea back pain increased hepatic enzyme (ALT, gamma glutamyl-transferase, aspartate transaminase)
Common adverse events (≥1% to <10%)	**oral herpes**, **dermatomal herpes zoster** **decrease in neutrophil count** **rash**, **alopecia**	**herpes viral infections**, bronchitis, tinea versicolor basal cell carcinoma **lymphopenia**, **leukopenia** depression dizziness, migraine blurred vision bradycardia, atrioventricular block hypertension dyspnoea **eczema**, **alopecia, pruritus** asthenia increased blood triglycerides
Serious adverse events		infections macular oedema transient atrioventricular block at treatment initiation

Table 6.2: Withdrawals due to adverse events – indirect comparison

Quality assessment							Effect				Quality	Importance
							Absolute		Relative			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdrawals due to adverse events:	Withdrawals due to adverse events:	Cladribine 3.5 mg/kg vs. placebo	Fingolimod 0.5 mg vs. placebo		
Cladribine 3.5 mg/kg vs. placebo: Withdrawals due to adverse events (follow-up: 96 weeks ~ 24 months)												
1	Randomised trial	Not serious	Not serious	Not serious	Serious[A]	Not found	**Cladribine 3.5 mg/kg** 15/433 (3.5%)	**Placebo** 9/437 (2.1%)	**RR (95% CI)** 1.68 (0.74-3.80)*		⊕⊕⊕◯ MODERATE	CRUCIAL
Fingolimod 0.5 mg/kg vs. placebo: Withdrawals due to adverse events (follow-up: 24 months)												
2	Meta-analysis with two randomised trials (see appendix)	Not serious	Serious[B]	Not serious	Serious[A]	Not found	**Fingolimod 0.5 mg/kg** 104/783 (13%)	**Placebo** 71/773 (9%)		**RR (95% CI)** 1.42 (0.89-2.25)	⊕⊕◯◯ LOW	CRUCIAL
Indirect comparison cladribine 3.5 mg/kg vs. fingolimod 0.5 mg: Withdrawals due to adverse events (follow-up ~24 months)												
3	Indirect comparison with a randomised trial (cladribine) and a meta-analysis (fingolimod)	Not serious	Serious[B]	Serious[C]	Serious[A]	Not found	**Cladribine 3.5 mg/kg** 376/433 (86.8%)	**Fingolimod 0.5 mg/kg** 565/638 (89%)	**Cladribine 3.5 mg/kg vs. fingolimod 0.5 mg** **RR (95% CI)** 0.98 (0.94-1.03)*		⊕◯◯◯ VERY LOW	CRUCIAL

See page 40 for annotations.

Table 6.3: Serious adverse events – indirect comparison

Quality assessment							Effect				Quality	Importance
							Absolute		Relative			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Withdrawals due to adverse events:	Withdrawals due to adverse events:	Cladribine 3.5 mg/kg vs. placebo	Fingolimod 0.5 mg vs. placebo		
Cladribine 3.5 mg/kg vs. placebo: Serious adverse events (follow-up: 96 weeks ~ 24 months)												
1	Randomised trial	Not serious	Not serious	Not serious	Serious[A]	Not found	**Cladribine 3.5 mg/kg** 36/430 (8.4%)	**Placebo** 28/435 (6.4%)	**RR (95% CI)** 1.30 (0.81-2.09)*		⊕⊕⊕◯ MODERATE	CRUCIAL
Fingolimod 0.5 mg vs. placebo: Serious adverse events (follow-up: 24 months)												
2	Meta-analysis with two randomised trials (see appendix)	Not serious	Not serious	Not serious	Serious[A]	Not found	**Fingolimod 0.5 mg/kg** 96/783 (12.3%)	**Placebo** 101/773 (13.1%)		**RR (95% CI)** 0.94 (0.72-1.22)*	⊕⊕⊕◯ MODERATE	CRUCIAL
Indirect comparison cladribine 3.5 mg/kg vs. fingolimod 0.5 mg: Serious adverse events (follow-up ~24 months)												
3	Indirect comparison with a randomised trial (cladribine) and a meta-analysis (fingolimod)	Not serious	Not serious	Serious[C]	Very serious[A,D]	Not found	**Cladribine 3.5 mg/kg** 36/430 (8.4%)	**Fingolimod 0.5 mg/kg** 96/783 (12.3%)	**Cladribine 3.5 mg/kg vs. fingolimod 0.5 mg** **RR (95% CI)** 0.68 (0.47-0.98)*		⊕◯◯◯ VERY LOW	CRUCIAL

See page 40 for annotations.

Annotations:
A: The 95% confidence interval of the relative risk crosses the 0.75 or 1.25 border of clinical relevance in fingolimod and cladribine trials: -1 for imprecision.
B: Unexlpained heterogenity in fingolimod Cochrane review: -1 for inconsistency. I^2=61%. Calebresi, 2014: fingolimod 0.5 mg: 66/358 vs. placebo: 37/355; RR=1.77 (95% CI: 1.22–2.57). Kappos, 2010: fingolimod 0.5 mg: 38/425 vs. placebo: 34/418; RR=1.10 (95% CI: 0.71-1.71).[9]
C: Placebo groups in cladribine and fingolimod trials are not comparable. This might be caused by differences in study population. A main point according to the SAG was that patients in the cladribine trial are relatively mildly affected in comparison to patients in trials of other DMDs, such as fingolimod: -1 for indirectness.
D: The 95% confidence interval of the relative risk of the indirect comparison crosses the 0.75 or 1.25 border of clinical relevance: -1 for imprecision.
* RRs not reported. Calculated using RevMan (See also Appendix) or a relative risk calculator.

Patient safety

[C0008] – How safe is the technology in relation to (the) comparator(s)?

Safety profiles of oral cladribine and oral fingolimod partly overlap. There is no clinically relevant difference in incidence of serious adverse events or withdrawal due to adverse events. See Grade evidence profiles (**Table 6.2 and 6.3**).

[C0002] – Are the harms related to dosage or frequency of applying the technology?

5.25 mg/kg dose of cladribine is associated with higher harms (results not reported in this assessment report).[7] Also additional treatment during year 3 and 4 is associated with higher harms (results not reported in this assessment report).[8] Therefore, the EMA decided to register 2 years of 3.5 mg/kg cladribine therapy followed by 2 years of no treatment. This does not affect efficacy.[8,10]

[C0004] – How does the frequency or severity of harms change over time or in different settings?

Lymphopenia developed within weeks (nadir at week 16 after start of treatment in year 1) and persisted for a prolonged period of time (mean duration of Grade ≥3 lymphopenia in the cladribine 3.5 mg/kg groups in CLARITY was 5.4 weeks) with signs of gradual recovery in most patients. In a small subset of patients, however, values remained well below baseline even after 240 weeks of follow-up. In case of Grade 2-3-4 lymphopenia, retreatment in year 2 should be delayed for up to six months.[3] Since the gap-interval between CLARITY and CLARITY Extension did not seem to influence annualized relapse rate, there is some support that if drug administration needs to be interrupted for lymphopenia between the first and second treatment course, cladribine's effectiveness on the long-term will not be affected.[10]

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

Cladribine treatment should not be initiated in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppresive therapy. Furthermore, pregnant and breast-feeding women should not be treated with cladribine. Other contraindications are listed in **Table 6.4**. These contraindications are comparable to contraindications for fingolimod (See **Table 6.4**).

Table 6.4: Contraindications for cladribine vs. fingolimod

Cladribine[3]	*Fingolimod*[11]
Infection with human immunodeficiency virus (HIV)	Known immunodeficiency syndrome
Active chronic infection (tuberculosis or hepatitis)	Severe active infections, active chronic infections (hepatitis, tuberculosis)
Initiation of cladribine treatment in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy	Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies)
Active malignancy	Known active malignancies

Moderate or severe renal impairment (creatinine clearance <60 mL/min) (safety and efficacy have not been established these patients)	
	Severe liver impairment (Child-Pugh class C)
Pregnancy and breast-feeding (Fe)male patients must take precautions to prevent pregnancy (of their partner) during cladribine treatment and for at least 6 months after the last dose.	Pregnancy and breast-feeding Patients must take precautions to prevent pregnancy during fingolimod treatment and for at least 2 months after the last dose.

Due to insufficient data, caution is recommended when cladribine is used in elderly patients. Furthermore, in the absence of data, cladribine is not recommended in patients with moderate or severe hepatic impairment. Fingolimod is associated with more special groups compared to cladribine. Fingolimod is particularly not recommended in patients with a history of cardiovascular or cerebrovascular problems, and those who are taking other medicines that lower the heart rate, considering that particularly these patients have an increased risk of cardiovascular problems after initiating treatment with fingolimod.

See also **Table 6.5**.

Table 6.5: Special populations for cladribine vs. fingolimod

Cladribine[3]	*Fingolimod*[11]
In the absence of data, cladribine is contraindicated in patients with moderate or severe renal impairment	
In the absence of data, cladribine is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh score>6).	Fingolimod should not be used in patients with severe hepatic impairment (Child-Pugh C) and caution should be exercised when initiating treatment with mild or moderate hepatic impairment. Caution in the use of fingolimod should be exercised in patients with a history of significant liver disease.
Caution is recommended when cladribine is used in elderly patients, due to insufficient data.	Caution is recommended when fingolimod is used in elderly patients, due to insufficient data.
	Fingolimod should be used with caution in diabetic patients.
	Special care is indicated if patients with uncontrolled hypertension are treated with fingolimod. Initiation of fingolimod decreases heart rate (bradyarrhythmia) (see section monitoring). Due to the risk of serious rhythm disturbances, fingolimod should not be used in patients with cardiac arrhythmia, known ischemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea.
	Fingolimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease.

[C0007] – Are the technology and comparator(s) associated with user-dependent harms?

In patients who require blood transfusion, irradiation of cellular blood components is recommended prior to administration of cladribine to prevent transfusion-related graft-versus-host disease.[3] Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes by fingolimod.[11]
Cladribine and fingolimod are both associated with interactions with other medicinal products and other forms of interaction. These interactions are presented in **Table 6.6**.

Table 6.6: Interactions of cladribine vs. fingolimod

Cladribine[3]	*Fingolimod*[11]
It is recommended that administration of any other oral medicinal product be separated from that of Mavenclad® by at least 3 hours during the limited number of days of cladribine administration.	
Cladribine in combination with other disease-modifying treatments for MS is not recommended.	Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered. Caution should be exercised when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone.
Additive haematological adverse reactions may be expected if cladribine is administered prior to or concomitantly with other substances that affect the haematological profile.	
Vaccination with live or attenuated live vaccines should be avoided within 4 to 6 weeks before, during and after cladribine treatment as long as the patient's blood cell counts are not within normal limits.	During and for up to two months after treatment with fingolimod vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.
It is recommended that co-administration of potent ENT1, CNT3 or BCRP inhibitors be avoided during the 4- to 5-day cladribine treatment.	Fingolimod is metabolised mainly by CYP4F2. Other enzymes like CYP3A4 may also contribute to its metabolism. Caution should be exercised with substances that may inhibit or induce CYP3A4.
	Treatment with fingolimod should not be initiated in patients receiving beta blockers, or other substances which may decrease heart rate because of the potential additive effects on heart rate.

[B0010] – What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

Monitoring is necessary and described in the SmPC[3]. Compared to fingolimod treatment[11], monitoring is less frequently needed. See **Table 6.5**.

Table 6.5: Most important special warnings and precautions (safety controls) for use of cladribine vs. fingolimod

	Cladribine[3]	**Fingolimod[11]**
Haematological monitoring	X	X
Screening for (virus) infections before starting the treatment	X	X
Varicella zoster virus vaccination of antibody-negative patients prior to initiation of treatment	X	X
ECG measurement		X
Heart rate and blood pressure measurement		X
Baseline MRI	X	X
Liver transaminase and bilirubin measurement		X
Ophthalmological evaluation		X
Viligance for skin lesions (basal cell carcinoma)		X
Pregnancy test	X	X

6.3 Discussion

Most frequently reported related treatment emergent adverse events were lymphopenia, leukopenia, lymphocyte count decreased, neutropenia and herpes zoster. The majority of events were mild or moderate in severity. Lymphopenia was the only severe adverse event that occurred more frequently on cladribine 3.5 mg/kg than on placebo.[7] Data presented for HDA patients gave no indication of different adverse event profiles by HDA groups as compared to non-HDA patients.[10] Additional treatment with cladribine tablets in years 3 and 4 (7.0 mg/kg cladribine in total), following the initial courses received in years 1 and 2 of CLARITY (3.5 mg/kg cladribine in total) was accompanied by a more disadvantageous safety profile (data not shown in this assessment report).[8] Overall, the risk of lymphopenia was considered manageable based on the implementation of haematological criteria for (re-)treatment and with screening for latent infections, and instigation of anti-herpes prophylaxis in case of Grade 4 lymphopenia (see SmPC for details).[3] Overall, in subjects exposed to cladribine, the incidence of herpes zoster infections was higher in patients with Grade 3 or Grade 4 lymphopenia.[7] Severe and opportunistic infections, such as progressive multifocal leukoencephalopathy (PML), are considered an important potential risk of cladribine, due to the risk of lymphopenia. Therefore risk mitigation measures include contraindications for immunocompromised patients – including patients currently receiving immunosuppresisive or myelosuppressive therapy - and patients with human immunodeficiency virus infection.[3] Above stated safety issues are considered to be manageable when cladribine is used in accordance with the conditions defined in the SmPC.[3]

According to the "CHMP Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis" special attention should be paid to tumour facilitating/inducing potential of immunomodulators such as cladribine.[4] Theoretically, the immunosuppressive properties, in particular the suppression of CD8+ and CD4+ T cells, may contribute to increased malignancy rates. Indeed, safety data suggested there is an increased malignancy risk for cladribine treated patients vs. placebo treated patients. However, the applicant has presented, amongst others, data regarding the CD4+ and CD8+ counts and associated malignancies and a causal relationship could not be established. Furthermore, in a review it was noted that the malignancy rate of cladribine-treated subjects in the CLARITY trial (0,34%) was not significantly different from all other active disease modifying treatment groups (amongst others fingolimod, alemtuzumab and natalizumab).[26] Nevertheless, uncertainties remained and the CHMP considered that any explanation regarding the observed imbalance in the incidence of malignancies remained largely speculative.[10] Cladribine should therefore not be used in patients with active malignancies and standard cancer screening guidelines should be followed in patients treated with oral cladribine.[3] Furthermore, a large, prospective, comparative Post Authorization Safety Study (PASS) will be performed to further monitor and characterize the potential malignancy risk with cladribine.[10]

Safety of 3.5 mg/kg cladribine vs. 0.5 mg fingolimod

The risk of withdrawal due to adverse events and the risk of serious adverse events is comparable between cladribine and fingolimod. The quality of the evidence, however, is very low. This is amongst others due to the significant difference in the proportion of withdrawals due to adverse events and the proportion of serious adverse events in the placebo groups in the cladribine and fingolimod studies and the wide confidence intervals. In case of the risk of withdrawal due to adverse events there was inconsistency in proportions in the two studies that were included in het Cochrane meta-analysis of fingolimod.

Safety profiles of cladribine and fingolimod partly overlap. Both drugs are accompanied by (potential) serious adverse events that need monitoring and special groups that need special attention. Cladribine's monitoring burden, however, is lower than fingolimod's monitoring burden. Consideration of the individual risk is an important aspect of treatment decision-making.

6.4 Conclusion

The main safety issues of oral cladribine are related to the risks of prolonged severe lymphopenia and infections including reactivation of latent infections (herpes zoster) and opportunistic infections. These adverse events with potential serious risks are considered to be acceptable when used in accordance with the conditions defined in the SmPC. Furthermore, there are remaining uncertainties pertaining to the increased rate of malignancies seen with cladribine. Further data are gathered in the post-marketing setting.

Safety profiles of cladribine and fingolimod partly overlap. Both drugs are accompanied by (potential) serious adverse events that need monitoring, although cladribine's monitoring burden is lower. There are no clinically relevant differences in incidences in serious adverse events or withdrawals due to adverse events between cladribine and fingolimod treated patients. Individual patient characteristics determine which interventional strategy is most appropriate.

7 CONCLUSION

Cladribine tablets administered as monotherapy at the approved dose of 3.5 mg/kg increases the probability of being relapse-free at 96 weeks compared to placebo in RRMS patients. The annualised relapse rate favoured cladribine 3.5 mg/kg compared to placebo. These benefits were confirmed with disease measures defined by MRI scans. However, there was no clinically relevant difference of cladribine at 3.5 mg/kg on preventing disability worsening. The treatment effect obtained in CLARITY was maintained in CLARITY Extension. There is no relevant added benefit of additional treatment courses beyond year two.

Across all subgroups, HDA patients had more pronounced effects than non-HDA patients for both annualized relapse rate and time to disability progression (3 months and 6 months), but not for MRI endpoints, where there was no difference. Altogether, subgroup analyses suggested a larger effect size in patients with high disease activity.

Annualized relapse rate, participants free from relapse, participants free from disability and participants free from MRI Gd+ lesions did not differ significantly between cladribine and fingolimod treated patients. Therefore, we conclude there is no difference in efficacy between cladribine and fingolimod in (highly active) RRMS patients.

The main safety issues of cladribine are related to the risks of prolonged severe lymphopenia and infections including reactivation of latent infections (herpes zoster) and opportunistic infections. These adverse events are considered to be acceptable when used in accordance with the conditions defined in the SmPC. Furthermore, there are remaining uncertainties pertaining to the increased rate of malignancies seen with cladribine. Further data are gathered in the post-marketing setting.

Safety profiles of cladribine and fingolimod partly overlap. Both drugs are accompanied by (potential) serious adverse events that need monitoring, although cladribine's monitoring burden is lower. There are no clinically relevant differences in incidences in serious adverse events or withdrawals due to adverse events between cladribine and fingolimod treated patients. Individual patient characteristics determine which interventional strategy is most appropriate.

The National Health Care Institute of the Netherlands (ZIN) concludes cladribine and fingolimod have a comparable therapeutic value. This conclusion also applies to alemtuzumab and natalizumab, given the earlier conclusions drawn in the assessment report of alemtuzumab.[1,2]

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APPENDIX: METHODS AND DESCRIPTION OF THE EVIDENCE USED

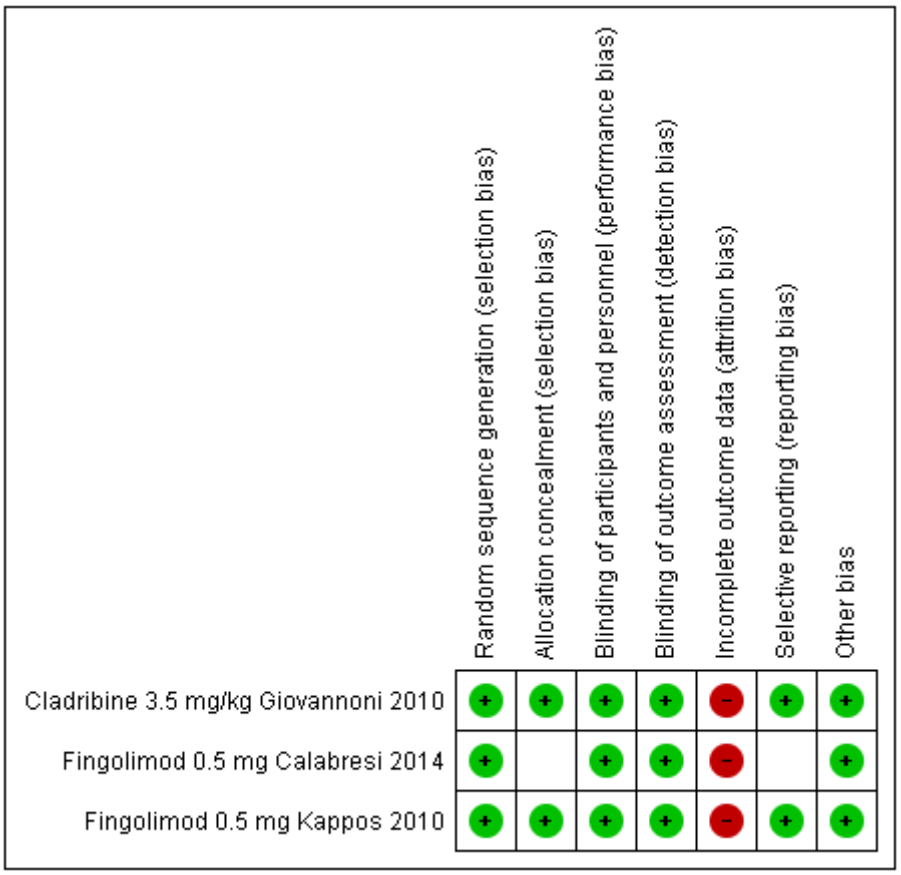
Guidelines for diagnosis and management

Table A1: Overview of guidelines

Dutch Guideline of MS are outdated. Therefore we consulted the Dutch website of the Farmacotherapeutisch Kompas.

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation
Farmacotherapeutisch Kompas	2017	The Netherlands	Alemtuzumab: first and second-line treatment. Natalizumab: second-line treatment. Fingolimod: second-line treatment.
Dutch Guideline of MS		The Netherlands	
ZIN	2016	The Netherlands	Assessment report alemtuzumab (Lemtrada®) Therapeutic value of alemtuzumab as second-line treatment is similar to therapeutic value of natalizumab and fingolimod (conclusion based on a network meta-analysis executed for ZIN).

Risk of bias tables



Note that the two studies that were used in the Cochrane review are presented for risk of bias separately. Further note that in contrast to the Cochrane review, we did not downgrade for other bias due to the fact a study was sponsored by the applicant and co-authors of the published paper were affiliated to the pharmaceutical company. This is usual in Clinical trials. Overall, the risk of bias is low.

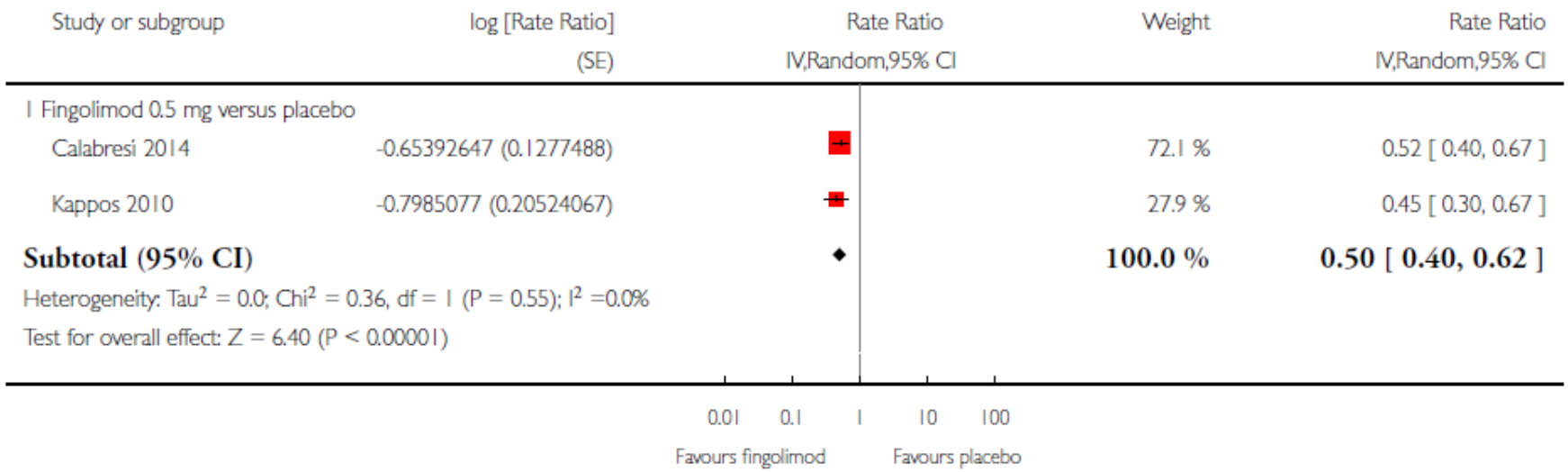
Forest plots presented in fingolimod's Cochrane review

Analysis 4.3. Comparison 4 Annualised relapse rate, Outcome 3 At 24 months.

Review: Fingolimod for relapsing-remitting multiple sclerosis

Comparison: 4 Annualised relapse rate

Outcome: 3 At 24 months



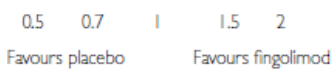
Analysis 1.3. Comparison 1 Participants free from relapse, Outcome 3 At 24 months.

Review: Fingolimod for relapsing-remitting multiple sclerosis

Comparison: 1 Participants free from relapse

Outcome: 3 At 24 months

Study or subgroup	Fingolimd n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fingolimod 0.5 mg versus placebo					
Calabresi 2014 (1)	256/358	187/355		50.6 %	1.36 [1.21, 1.53]
Kappos 2010 (2)	299/425	191/418		49.4 %	1.54 [1.36, 1.74]
Subtotal (95% CI)	**783**	**773**		**100.0 %**	**1.44 [1.28, 1.63]**
Total events: 555 (Fingolimd), 378 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.13$, df = 1 (P = 0.14); $I^2 = 53\%$					
Test for overall effect: Z = 5.83 (P < 0.00001)					



(1) Estimated by Kaplan-Meier as reported in the primary study (Page 549)

(2) Estimated by Kaplan-Meier as reported in the primary study (Page 393)

(3) Estimated by Kaplan-Meier as reported in the primary study (Page 549)

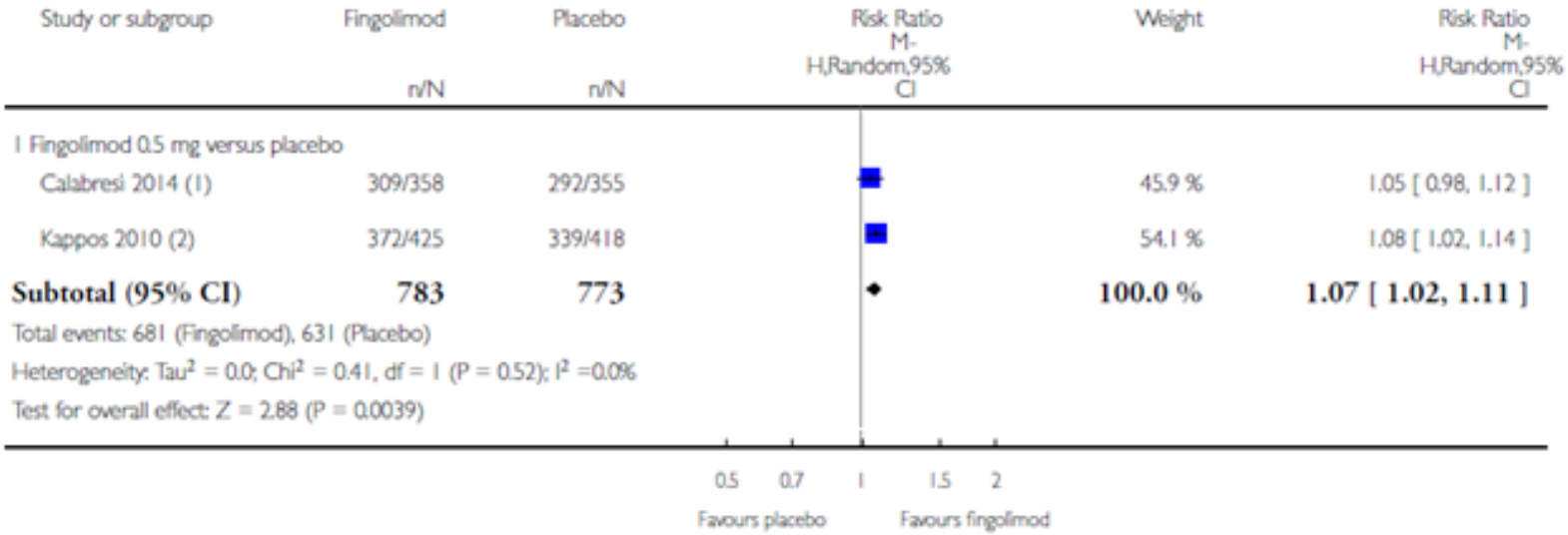
(4) Estimated by Kaplan-Meier as reported in the primary study (Page 393)

Analysis 2.2. Comparison 2 Participants free from disability worsening, Outcome 2 At 24 months.

Review: Fingolimod for relapsing-remitting multiple sclerosis

Comparison: 2 Participants free from disability worsening

Outcome: 2 At 24 months



(1) Estimated by Kaplan-Meier as reported in the primary study (Page 549)

(2) Estimated by Kaplan-Meier as reported in the primary study (Page 393)

(3) Estimated by Kaplan-Meier as reported in the primary study (Page 549)

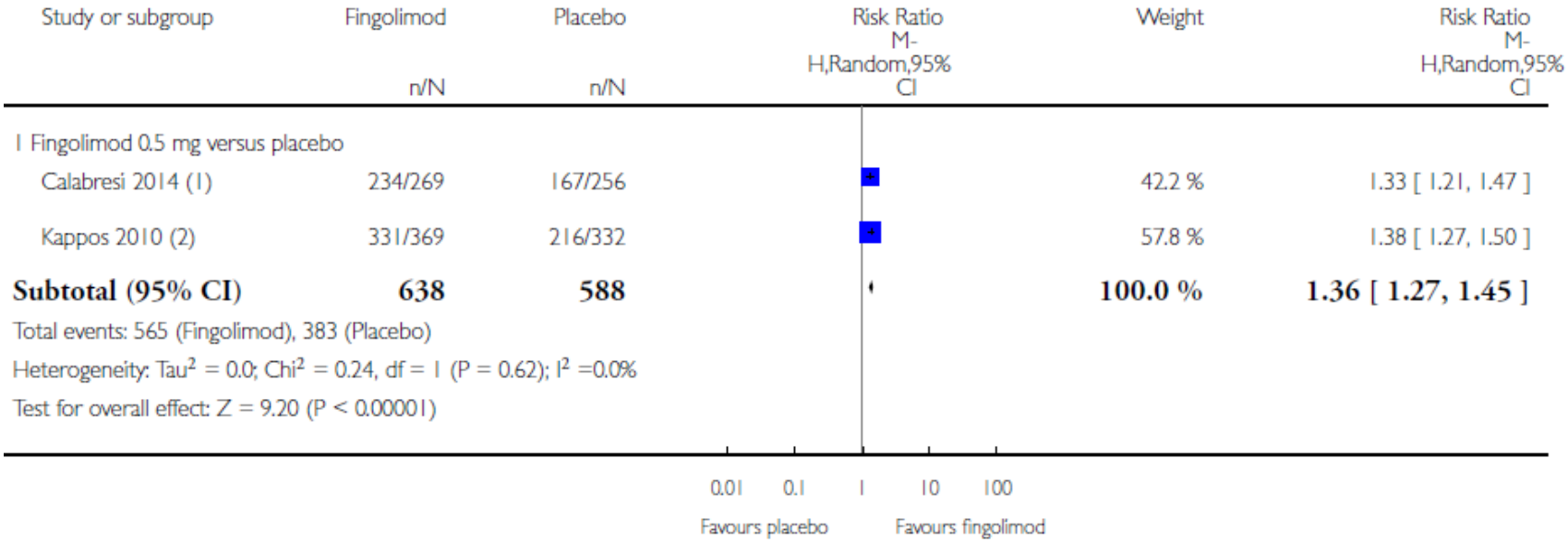
(4) Estimated by Kaplan-Meier as reported in the primary study (Page 393)

Analysis 5.3. Comparison 5 Participants free from gadolinium-enhancing lesions, Outcome 3 At 24 months.

Review: Fingolimod for relapsing-remitting multiple sclerosis

Comparison: 5 Participants free from gadolinium-enhancing lesions

Outcome: 3 At 24 months



(1) The analysis involved 776 out of 1083 (72%) of partecipants.

(2) the analysis involved 1049 out of 1272 (82% of partecipants)

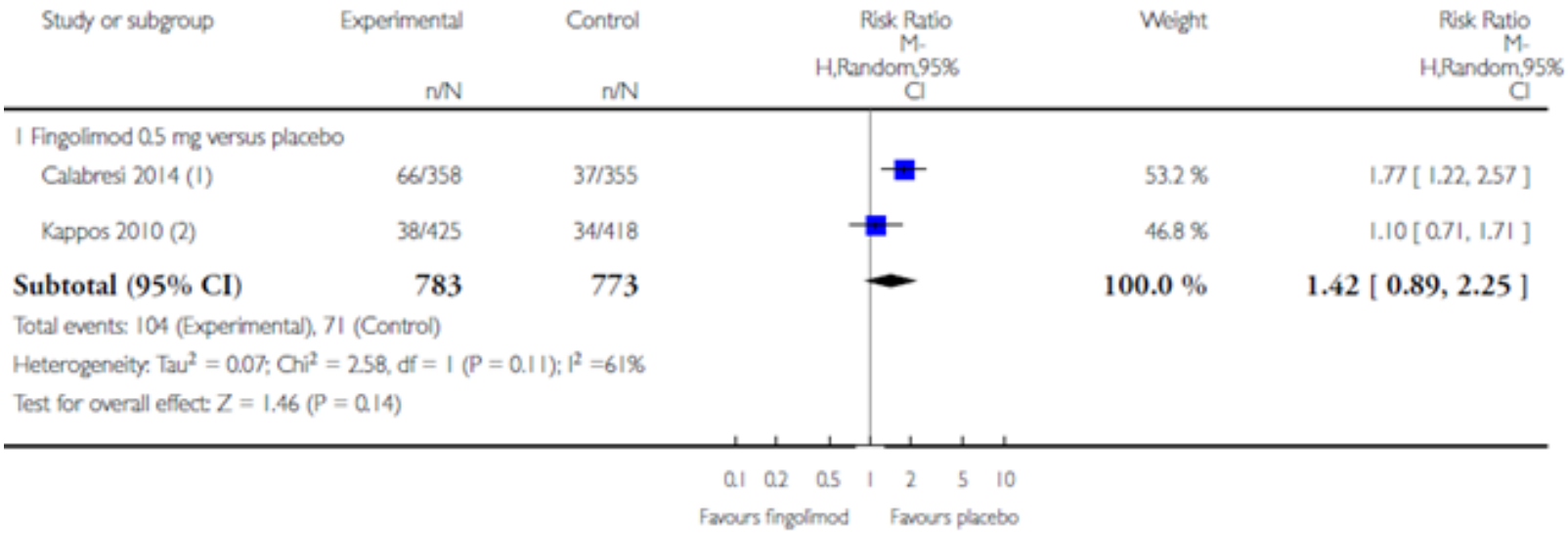
(3) The analysis involved 776 out of 1083 (72%) of partecipants.

Analysis 3.3. Comparison 3 Number of withdrawals due to adverse events, Outcome 3 Withdrawals due to adverse events over 24 months.

Review: Fingolimod for relapsing-remitting multiple sclerosis

Comparison: 3 Number of withdrawals due to adverse events

Outcome: 3 Withdrawals due to adverse events over 24 months



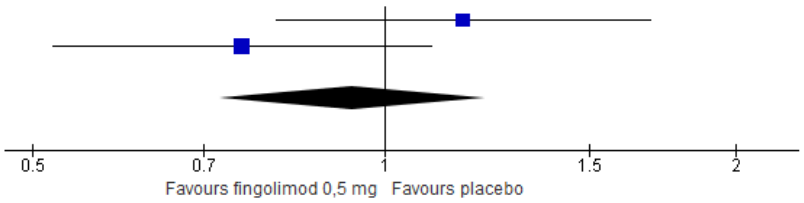
(1) table 3 page 552

(2) see Figure 1 page 391

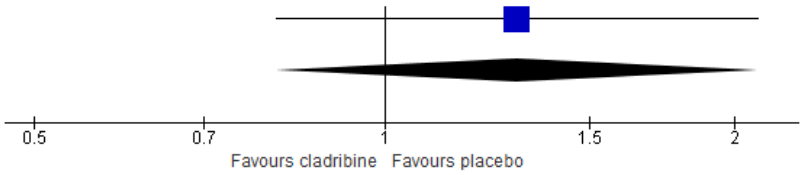
(3) see Figure 1 page 391

Forest plots serious adverse events of cladribine and fingolimod (follow-up 24 months)

Study or Subgroup	Fingolimod 0,5 Events	Fingolimod 0,5 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Calabresi 2014	53	358	45	355	44.5%	1.17 [0.81, 1.69]
Kappos 2010	43	425	56	418	55.5%	0.76 [0.52, 1.10]
Total (95% CI)		783		773	100.0%	0.94 [0.72, 1.22]
Total events	96		101			
Heterogeneity: Chi² = 2.65, df = 1 (P = 0.10); I² = 62%						
Test for overall effect: Z = 0.48 (P = 0.63)						



Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Giovannoni 2017	36	430	28	435	100.0%	1.30 [0.81, 2.09]
Total (95% CI)		430		435	100.0%	1.30 [0.81, 2.09]
Total events	36		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						



Number of patients with serious adverse events are enrolled from La Mantia's Cochrane review of fingolimod: total serious adverse events (≥2 patients in any group). Follow-up is 24 months.