Amendment of the conditional inclusion of the medicine Fingolimod (Gilenya®) for the treatment of relapsing remitting multiple sclerosis (RRMS), in the Medicines Reimbursement System (GVS)

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 25 March 2019

Zorginstituut Nederland carried out an assessment of medicinal product fingolimod (Gilenya®), whereby they came to the following conclusion.

In a letter dated 21 January 2019 (CIBG-19-07506), the Minister of VWS asked *Zorginstituut Nederland* to carry out a substantive assessment for including the pharmaceutical product fingolimod (Gilenya®) capsule 0.25 mg on List 1A (of the Medicines Reimbursement System, GVS). There is an extension in the existing indication of Gilenya capsule 0.5 mg for pediatric patients 10 years or older with highly active relapsing remitting multiple sclerosis (RRMS). And therefore this means a request tochange the specific conditions for reimbursement of fingolimod (Gilenya®). Fingolimod 0.5 mg is currently included on List 1A of the GVS only for adults with the indication RRMS. The new strength, 0.25 mg, is only intended for use in pediatric patients with RRMS.
This is an indication extension for children 10 years or older with highly active relapsing-remitting multiple sclerosis (RRMS). Fingolimod 0.5 mg is currently included for the RRMS indication for adults only on Appendix 1A and Appendix 2 of the Medicines Reimbursement System. The new 0.25 mg strength only applies to pediatric patients with RRMS.
As the request relates to a change in an existing indication for fingolimod, we will reply to this change in the specific conditions for reimbursement in the form of a letter-report, supplemented with a budget impact analysis.

Current situation
Fingolimod capsules 0.5 mg have been placed on List 1A of the Medicine Reimbursement System (GVS). Reimbursement is only possible based on the following condition:

Condition:
Only for an insured person aged eighteen years or older with highly active relapsing-remitting multiple sclerosis (RRMS) who has not responded to treatment with at least one disease-modifying pharmaceutical product that is registered for the treatment of MS.

Registered indication for fingolimod 0.5 mg in cases of RRMS:
Up till November 2018, fingolimod was indicated as a single disease-modifying therapy for highly active relapsing remitting multiple sclerosis in the following groups of adults patients:
- Patients with very active disease despite a full and adequate course of treatment with at least one disease-modifying drug;
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 the T2 lesion load as compared to a previous recent MRI.

In November 2018, the European Medicines Agency (EMA) approved an extension in the existing indication. The current indication for fingolimod was extended to include pediatric patients aged 10 years and older with the same indication as adults. The marketing authorisation holder is also asking for reimbursement for the 0.25 mg capsule.

Fingolimod dose
The recommended dose for adults is 0.5 mg 1x/day. The dose for pediatric patients is based on body weight, i.e. 0.25 mg for children ≤ 40 kg and 0.5 mg for children > 40 kg.

Background
Fingolimod has been included together with cladribine (Mavenclad®) on List 1A under the wording of an appendix 2 condition. The current condition for both fingolimod and cladribine only applies for adults and is more limited than the registered indications. For fingolimod, the registered sub-indication, severe RRMS that is deteriorating or rapidly evolving, is not included in the condition.

Conclusion on therapeutic value
The Minister was sent an enclosure describing the study(/studies).
Based on the data in that enclosure, we conclude that, analogous to conclusions from previous assessments of adults and based on 1 clinical study of children aged 10-18 years, fingolimod has an added therapeutic value for children aged 10 to 18 years with RRMS that is refractory for first-line treatment in the short term.

Outcome of the budget impact analysis
The budget impact analyse examined only the additional costs involved in extending the specific condition to include children aged 10 to 18 years.
Taking into account about 30 RRMS patients who are eligible for fingolimod each year, extending the indication will involve additional costs of €43,020 in the third year after its inclusion and €39,660 in the third year if the administration costs of substitution treatment with natalizumab are included.

In the current situation, when the disease flares up during first-line treatment, a switch is made to a different first-line treatment, or a second-line treatment is considered (natalizumab). Expectations are that in the new situation, the switch to fingolimod will be made more quickly in second-line treatment after the disease flares up during treatment with a first-line drug. However, with these calculations, uncertainty exists about the number of patients who will switch to fingolimod after the disease flares up during treatment with a first-line drug.

***Zorginstituut Nederland*'s advice**
Fingolimod 0.5 mg has already been included on List 1A, under conditional inclusion, for adults with RRMS. Based on the above considerations, we advise the Minister to alter the condition for fingolimod, by adding pediatric patients, as indicated below; fingolimod 0.25 mg can be added to this. Altering this specific condition will be accompanied by additional costs.
As cladribine is not registered for pediatric patients, no research is taking place involving children and because we do not expect such research to start in the near future,[1] we advise the Minister **not** to alter the condition for reimbursement of cladribine, with which fingolimod is clustered.

Extension in the specific condition for fingolimod 0.25 mg and 0.5 mg for children with RRMS.

Fingolimod condition
Only for an insured person aged ten years or older with highly active relapsing-remitting multiple sclerosis (RRMS) who did not respond to treatment with at least one disease-modifying drug that is registered for the treatment of MS.
APPENDIX

Assessment of extending the RRMS indication to include children
The *Zorginstituut* has not previously assessed fingolimod in pediatric patients aged 10 to < 18 years with RRMS.

RRMS in children[2]
Pedriatic MS is a rare disorder. About 3-5% of MS patients were diagnosed with MS when they were children (up to 16 years old).
RRMS in children is characterised by frequent relapses. Disease progression is slower than in adults. In the early years of the disease, cognitive deterioration occurs in one-third of the children, which stabilises after 5 years. Frequent symptoms such as tiredness (up to 75%) and depression (up to 50%) affect how they function on a daily basis.

Guidelines for treating children with RRMS
No national guidelines on MS in pediatric patients have been published in the Netherlands. For the usual treatment in the Netherlands, the guidelines of the Erasmus MC (revised in 2018)[2] refer to a European statement[3].

Treatment options
The guidelines of the Erasmus MC (revised in 2018), other guidelines and consensus documents[4,5] advise starting with immuno-modulating drugs as soon as the diagnosis of childhood-MS is definite. Interferon beta and glatiramer are cited as first-line treatment, with the comment that efficacy and adverse events in the long term (> 5 year) are still uncertain. If insufficient effect is achieved with first-line drugs (after at least 6 months' use and monitoring for therapy compliance), the guidelines of the Erasmus MC advise first to switch between different first-line drugs and then to consider second-line therapy. Second-line options cited are natalizumab, cyclophosphamide, mitoxantrone or possibly, fingolimod. Triggers cited for switching medication are:
- if severe adverse events occur;
- during treatment lasting at least 1 year the number of disabling relapses has not fallen or has even increased;
- more than 2 relapses in 1 year.

Only interferon beta and glatiramer are registered for children with RRMS. Second-line medication other than fingolimod is used off label. A study of teriflunomide and dimethyl fumarate in children with RRMS is currently still in progress.

Study data
The EMA recently described the effectiveness of fingolimod 0.25 and 0.5 mg 1x/day in pedriatric patients aged 10 to < 18 years with relapsing remitting

multiple sclerosis[6,7]. Extending the indication seems to have been based on 1 published RCT with 215 children aged 10 to 18 years in which oral fingolimod (n = 107) 1x/day was directly compared, during up to 2 years, with i.m. 30 µg interferon beta-1a, 1x/week (Study D2311; PARADIGMS[8]). Fingolimod was dosed based on body weight and concentration measurements.
The median baseline characteristics of the children were: age 16 years, duration of disease 1.5 years and EDSS-score 1.5; during the preceding 2 years 2 relapses and 2 gadolinium-enhancing lesions on the brain MRI. Most patients were in Tanner-stage 2 or higher (94.4%) and weighed more than 40 kg (95.3%). The Tanner stages describe phases of physical development in children, adolescents and adults on visible primary and secondary sexual characteristics. At Tanner stage 2 girls start to develop breasts and the volume of boys' testes starts to increase (though their voices do not yet break). Most children in the study (72%) were 14 to 18 years; only 10% were 12 years or younger. 63% had not received prior medication for MS; 37% had already received prior treatment, 32% with interferon beta and 9% with another DMT (disease-modifying therapy).
In total 180 patients (84%) completed the study medication (n = 99; [92.5%] on fingolimod and 81 [75%] on interferon beta-1a).

Intended effects in PARADIGMS:
Of the patients who received fingolimod, 14% (15 out of 107) suffered a relapse, in comparison with 54% (58 out of 107) of the patients who received interferon beta-1a. Extrapolating towards the primary endpoint, i.e the annualized relapse rate, this was significantly lower in the fingolimod arm, i.e. 0.122 vs. 0.675 for interferon beta 1a. Moreover, fingolimod also scored significantly more favourably in comparison with interferon beta 1a on secondary endpoints: the annualized rate of new or newly enlarged T2 lesions, the number of Gd-enhancing T1 lesions per scan up to 24 months and the degree of brain atrophy.

Unintended effects: the safety profile of pediatric patients (10 to 18 years) who received 0.25 mg or 0.5 mg fingolimod per day was in general comparable with that of adult patients[6]. In the RCT on pediatric patients, there were more frequent reports of convulsions, anxiety, depressive states in patients treated with fingolimod compared with pediatric patients treated with interferon beta-1a. Convulsions occurred in 5.6% of the patients treated with fingolimod and in 0.9% of those treated with interferon beta-1a. A slight increase in bilirubin was also mentioned in children treated with fingolimod. Further, the SmPC advises prudence with pediatric patients due to the very limited knowledge that is available from clinical studies.

Discussion
In one clinical study, in a direct comparison with interferon beta, fingolimod in pediatric patients aged 10 to 18 years with RRMS led to a reduction in the annualised relapse rate. This effect was supported by the results of the secondary outcome parameters.
Most of the pediatric patients included in the study were teenagers (the average age was 16 years[9]).

The risk of serious adverse events with fingolimod seems to be higher than with interferon beta or glatiramer. For adults, due to the heterogeneous safety profile (adverse effects on cardiac, ocular, the immune, hepatic and pulmonary systems, and also risks of infections, thromboembolic events skin cancer and other

malignancies), the EMA has not registered fingolimod for the broad population in which it was studied in the RCTs, but has limited its indication to 2 sub-groups with highly active disease.
The EMA stated that, due to serious adverse events, the place for fingolimod is as second-line treatment for pediatric patients with RRMS, and has registered fingolimod for pediatric patients – just as for adults – for only 2 subpopulations.

Conclusion on fingolimod for the treatment of children with RRMS
In summary, we conclude that, analogous to conclusions from previous assessments of adults and based on one clinical study of pediatric patients aged 10-18 years, fingolimod has an added therapeutic value for pediatric patients n aged 10 to 18 years with RRMS that is refractory for first-line treatment in the short term.

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The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.

[1] European Medicines Agency. A product specific waiver for cladribine (EMEA-000383-PIP01-08) 2009. https://www.ema.europa.eu/en/medicines/human/paediatric-investigation-plans/cladribine, consulted 11 February 2019.
[2] Ketelslager IA, Pelt-Gravesteijn ED van, Catsman-Berrevoets CE et al. Guidelines on MS in children. Revised version 2018). https://www6.erasmusmc.nl/neurologie/voorartsen/richtlijnenvoorartsen/richtlijnen-klinische-neurofysio/. consulted 5 February 2019.
[3] Ghezzi A, Banwell B, Boyko A, Amato MP, Anlar B, Blinkenberg M, et al. The management of multiple sclerosis in children: a European view. Multiple sclerosis (Houndmills, Basingstoke, England). 2010 16:1258-67.
[4] McGinley M, Rossman IT. Bringing the HEET: The Argument for High-Efficacy Early Treatment for Pediatric-Onset Multiple Sclerosis. Neurotherapeutics. 2017;14:985-998.
[5] Simone M, Chitnis T. Use of Disease-Modifying Therapies in Pediatric MS. Curr Treat

Options Neurol. 2016;18:36.

[6] SmPC Gilenya. Last updated 18/12/2018.

[7] Gilenya EPAR-Medicine overview. Last updated 18/12/2018. EMA/685570/2018. EMEA/H/C/002202

[8] Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. N Engl J Med 2018; 379: 1017-27.

[9] Antel J [editorial]. Therapy in Multiple Sclerosis — Coming of Age. N Engl J Med. 2018 13;379:1085-1086.