Pharmacotherapeutic report on fingolimod (Gilenya®) for 'relapsing-remitting multiple sclerosis'

Medicine. Fingolimod, 0,5 mg capsule.

Summary of the therapeutic value

Intended effects. In a *direct comparison* of fingolimod with interferon beta (Avonex) in ambulatory patients with relapsing-remitting multiple sclerosis (RMMS), the efficacy of fingolimod in reducing the annual relapse rate was statistically significant, though there was no statistically significant difference in the effect on disease progression. In an indirect comparison of *the populations studied*, the efficacy of fingolimod seems broadly similar to that of natalizumab, particularly in reducing the frequency of relapses and in MRI endpoints. The delaying effect fingolimod has on disease progression seems slightly smaller than that of natalizumab and mitoxantrone, but is it comparable with that of interferon 1a. The effect on disease progression is a limited short-term effect, the clinical relevance of which remains to be determined. There are insufficient data on effects in the long term.

Fingolimod was not specifically investigated for the registered indications. The required data on the registered subpopulations are missing that would facilitate carrying out an indirect comparison between fingolimod and the other MS drugs. There are several shortcomings involved in using post-hoc formulated subgroups for examining the approved indications.

Unintended effects. The risk of serious side effects seems greater with natalizumab and fingolimod than with interferon beta or glatiramer. Treatment with mitoxantrone is associated with potentially even more serious side effects. Due to the heterogeneous safety profile (adverse effects on cardiac, ocular, immune, hepatic and pulmonary systems, and risk of infection, thromboembolic events, skin cancer and other malignancies), the EMA did not approve fingolimod for use on the general population, i.e., the population on which it was examined in RCTs. Instead the EMA restricted the indication to two subgroups with high disease activity in RRMS, analogous to the registered indication of natalizumab. There are no specific data on unwanted effects for these subgroups. Neither are there any data on long-term side effects or rare side effects that may emerge only after the drug has been put to wider use. The difference in the nature and severity of the risk profile between natalizumab and fingolimod provides no tools for distinguishing between the two drugs.

Experience. Experience with fingolimod is limited and less than that obtained with interferon beta, glatiramer and natalizumab.

Applicability. The applicability of natalizumab and fingolimod is more limited than that of interferon beta and glatiramer. Treatment with fingolimod will demand a lot of monitoring due to concerns about the heterogeneous safety profile.

Ease of use. Fingolimod has the advantage that it is the only oral MS medication. Other MS medications are administered i.m. or i.v.; patients may not self-inject natalizumab. Fingolimod has the disadvantage that a lot of monitoring will be needed (blood count, transaminases, blood pressure, ophthalmologic).

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Final conclusion. The therapeutic value of fingolimod for treating patients with relapsing remitting multiple sclerosis with high disease activity who have failed to respond to a beta-interferon and glatiramer is comparable with that of natalizumab.
Due to insufficient data, fingolimod has a lower therapeutic value than interferon beta and glatiramer for the treatment of rapidly evolving, severe, relapsing-remitting multiple sclerosis (2 or more relapses in one year, and with 1 or more Gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared to a previous recent MRI).