Gemeinsamer Bundesausschuss

Fingolimod (New Therapeutic Indication: Paediatric Patients with Highly Active Relapsing-remitting Multiple Sclerosis)

Resolution of: 20 June 2019 Valid until: unlimited
Entry into force on: 20 June 2019
BAnz AT 30 09 2019 B2

Approved therapeutic indication:

Gilenya is indicated as a disease modifying monotherapy in highly active relapsing-remitting multiple sclerosis for the following groups of adult patients and **paediatric patients aged 10 years and older**:

– Patients with highly active relapsing-remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease modifying therapy (see Sections 4.4 and 5.1 for exceptions and information on washout periods).

or

– Patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy.

This resolution relates exclusively to the newly approved therapeutic indication of 22 November 2018 (i.e. children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis).

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a1) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom escalation of therapy is indicated.

Appropriate comparator therapy:

- Therapy according to the doctor's instructions

Extent and probability of the additional benefit of fingolimod compared to the appropriate comparator therapy:

An additional benefit is not proven.

a2) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapeutics is indicated.

Appropriate comparator therapy:

- Interferon beta-1a or interferon beta-1b or glatiramer acetate, taking into account the authorisation status

Extent and probability of the additional benefit of fingolimod compared to interferon beta-1a:

Hint for a non-quantifiable additional benefit.

b1) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received disease modifying therapy.

Appropriate comparator therapy:

- Interferon beta-1a or interferon beta-1b or glatiramer acetate, taking into account the authorisation status

Extent and probability of the additional benefit of fingolimod compared to interferon beta-1a:

Hint for a non-quantifiable additional benefit.

b2) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy.

Appropriate comparator therapy:

- Therapy according to the doctor's instructions

Extent and probability of the additional benefit of fingolimod compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a1) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom escalation of therapy is indicated:

No relevant data were submitted.

a2) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapeutics is indicated:

PARADIGMS study[2]**:** Fingolimod vs interferon beta-1a

Mortality

Endpoint	**Fingolimod**		**Interferon beta-1a**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimate [95% CI] p value
Overall mortality	9	0 (0)	11	0 (0)	n. c.

Morbidity

Endpoint	**Fingolimod**			**Interferon beta-1a**			**Intervention vs control**
Confirmed relapses (EDSS based)							
	N	Number of relapses/patient years	Annual relapse rate [95% CI]	N	Number of relapses/patient years	Annual relapse rate [95% CI]	Effect estimate [95% CI] p value[a]
Annual rate of confirmed relapses	9	4 / no data available	No data available	11	19 / no data available	No data available	Rate Ratio 0.33 [0.08; 1.35] 0.123[b]

[1] Data from the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG) (A18-87) and from the addendum (A19-42), unless otherwise indicated.

[2] Relevant sub-populations of the PARADIGMS study: Children and adolescents with highly active RRMS despite appropriate and complete treatment with at least one disease modifying therapy (not interferon beta-1a) and for whom a change within the basic therapy is indicated.

Endpoint	Fingolimod		Interferon beta-1a		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%[c])	N	Median survival time in months [95% CI] Patients with event n (%[c])	Effect estimate [95% CI] p value[d]
Time to the first confirmed relapse	9	no data available 2 (22)	11	No data available 7 (64)	HR = 0.18 [0.03; 0.95] 0.043[b]
Confirmed change in disability (EDSS based)					
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimate [95% CI] p value[e]
Confirmed progression	9	2 (22)	11	1 (9)	RR = 1.90 [0.32; 11.41] 0.483
Confirmed improvement	9	2 (22)	11	2 (18)	RR = 1.23 [0.24; 6.22] 0.802

Health-related quality of life

Endpoint	Fingolimod			Interferon beta-1a			Intervention vs control
	N[f]	Values at start of study MV (SD)	Change at end of study MV (SE)[g]	N[f]	Values at start of study MV (SD)	Change at end of study MV (SE)[g]	MD [95% CI] p value[g]
PedsQL, overall score[h] (patient reported)	9	No data available	No data available	10	No data available	No data available	14.62 [2.50; 26.73] 0.018[b]

Side effects

Endpoint	Fingolimod		Interferon beta-1a		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimate [95% CI] p value[e]
AEs (additionally shown)	9	9 (100)	11	11 (100)	–
SAEs	9	2 (22)	11	1 (9)	RR = 1.90 [0.32; 11.41] 0.483
Withdrawal because of	9	0 (0)	11	1 (9)	RR = 0.44 [0.02; 9.11]

Endpoint	Fingolimod		Interferon beta-1a		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimate [95% CI] p value[e]
AEs					0.557[i, j]
Specific AE					
Infections and parasitic diseases (SOC)	9	7 (78)	11	7 (64)	RR = 1.24 [0.70; 2.21] 0.459
Influenza-like disease (PT)	9	0 (0)	11	3 (43)	RR = 0.19 [0.01; 3.03] 0.129 [i, j]
Psychiatric disorders (AE, SOC)	9	1 (11)	11	1 (9)	RR = 1.22 [0.09; 16.93] 0.967[i]
Cardiac disorders (AE, SOC)	9	1 (11)	11	0 (0)	RR = 3.60 [0.16; 79.01] 0.340[i]

a) Results from subgroup analysis regarding the previous therapy (glatiramer acetate, IFN-β 1a, IFN-β 1b) in the sub-population on question "D" from the dossier of the pharmaceutical company; negative binomial model with treatment, previous therapy, treatment × previous therapy, region, and pubertal status (Tanner stages) as well as the number of relapses in the last 2 years; observation period in years as offset.
b) Calculation by the IQWiG, meta-analysis with fixed effect, inverse variance method.
c) Calculation of the IQWiG
d) Results from subgroup analysis regarding the previous therapy (glatiramer acetate, IFN-β 1a, IFN-β 1b) in the sub-population on question "D" from the dossier of the pharmaceutical company; Cox proportional hazards model with treatment, previous therapy, and treatment × previous therapy.
e) Calculation by the IQWiG, meta-analysis with fixed effect, Mantel-Haenszel method.
f) Number of patients included in the evaluation to calculate the effect estimation. Values at the start of study (for other times, if necessary) may be based on different patient numbers.
g) Results from subgroup analysis regarding the previous therapy (glatiramer acetate, IFN-β 1a, IFN-β 1b) in the sub-population on question a2; ANCOVA, adjusted for baseline value and with treatment, previous therapy, treatment × previous therapy, region, pubertal status (Tanner stages), and number of relapses in the last 2 years before randomisation.
h) A positive change from start of study to end of study indicates an improvement; a positive effect estimator means an advantage for fingolimod.
i) Calculation by the IQWiG, exact unconditional test (CSZ method according to Andrés et al., 1994).
j) Effect on children and adolescents with highly active RRMS previously treated with glatiramer acetate. No events occurred for children and adolescents pretreated with IFN-β 1b.

Abbreviations used:
ANCOVA = Analysis of Covariance; EDSS = Expanded Disability Status Scale; HR = Hazard Ratio; IFN-β = Interferon-beta; CI = confidence interval; LOCF = Last Observation Carried Forward; MD = Mean Difference; MW = Mean Value; N = Number of Patients Evaluated; n = Number of Patients with (at least one) Event; n.c. = not calculable; PedsQL = Paediatric Quality of Life Inventory; PT = Preferred Term; RCT = Randomised Controlled Trial; RR = Relative Risk; RRMS = Relapsing-Remitting Multiple Sclerosis; SD = Standard Deviation; SE = Standard Error; SOC = System Organ Class; SAE = Serious AE; AE = Adverse Event; vs = versus

b1) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received disease modifying therapy:

PARADIGMS study[3]**:** Fingolimod vs interferon beta-1a

Mortality

Endpoint	**Fingolimod**		**Interferon beta-1a**		**Intervention vs control**
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimate [95% CI] p value
Overall mortality	17	0 (0)	12	0 (0)	n. c.

Morbidity

Endpoint	**Fingolimod**			**Interferon beta-1a**			**Intervention vs control**
Relapses (EDSS based)							
	N	Number of relapses/patient years	Annual relapse rate [95% CI]	N	Number of relapses/patient years	Annual relapse rate [95% CI]	Effect estimate [95% CI] p value
Annual rate of confirmed relapses	17	6 / no data available	0.11 [0.03; 0.49]	12	14 / no data available	0.84 [0.28; 2.53]	Rate Ratio = 0.13 [0.02; 0.93] 0.043
	N	Median time to event in weeks [95% CI] Patients with event n (%)		N	Median time to event in weeks [95% CI] Patients with event n (%)		Effect estimate [95% CI] p value
Time to the first confirmed relapse	17	n.a. 3 (17.6[a])		12	n.a. 5 (41.7[a])		HR = 0.29 [0.06; 1.46] 0.132
Confirmed change in disability (EDSS based)							
	N	Patients with event n (%)		N	Patients with event n (%)		Effect estimate [95% CI] p value[b]
Confirmed progression	17	1 (5.9[a])		12	0 (0)		RR = 2.70 [0.10; 49.07] 0.566

[3] Relevant sub-populations of the PARADIGMS study: Therapy-naive children and adolescents with rapidly evolving severe RRMS.

Endpoint	Fingolimod		Interferon beta-1a		Intervention vs control
Confirmed improvement	17	9 (52.9[a])	12	1 (8.3[a])	RR = 6.35 [0.92; 43.74] 0.014

Health-related quality of life

Endpoint	Fingolimod[c]			Interferon beta-1a[c]			Intervention vs control
	N	Values at start of study MV (SD)	Change at end of study MV (SE)	N	Values at start of study MV (SD)	Change at end of study MV (SE)	MD [95% CI] p value[d]
PedsQL, overall score[e] (patient reported)	17	73.91 (17.05)	7.97 (2.56)	12	78.62 (12.31)	6.28 (3.07)	1.70 [−6.63; 10.02] 0.679

Side effects

Endpoint	Fingolimod		Interferon beta-1a		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimate [95% CI] p value[b]
AEs (additionally shown)	17	14 (82.4)	12	12 (100)	–
SAEs	17	3 (17.7)	12	0 (0)	RR = 5.06 [0.28; 89.71] 0.141
Withdrawal because of AEs	17	0 (0)	12	0 (0)	–
Specific AE					
Infections and parasitic diseases (AE, SOC)	17	7 (41.2)	12	5 (41.7)	RR = 0.99 [0.41; 2.38] > 0.999
Influenza-like disease (AE, PT)	17	1 (5.9)	12	4 (33.3)	RR = 0.18 [0.02; 1.39] 0.060
Psychiatric disorders (AE, SOC)	17	2 (11.8)	12	1 (8.3)	RR = 1.41 [0.14; 13.86] 0.822
Cardiac disorders (AE, SOC)	17	1 (5.9)	12	1 (8.3)	RR = 0.71 [0.05; 10.21] 0.913

Endpoint	Fingolimod		Interferon beta-1a		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimate [95% CI] p value[b]

a) Calculation of the IQWiG
b) Calculation of the IQWiG, p value using unconditional exact test (CSZ method according to Andrés et al., 1994; possibly discrepancy between p value (exact) and confidence interval (asymptotic) because of different calculation methods).
c) Number of patients who were taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of study (at other times, if necessary) can be based on other patient figures.
d) ANCOVA, adjusted for baseline value and with treatment, previous therapy, treatment × previous therapy, region, pubertal status (Tanner stages), and number of relapses in the last 2 years before randomisation.
e) A positive change from start of study to end of study indicates an improvement; a positive effect estimator means an advantage for fingolimod.

Abbreviations used:
ANCOVA = Analysis of Covariance; EDSS = Expanded Disability Status Scale; HR = Hazard Ratio; IFN-β = Interferon-beta; CI = confidence interval; LOCF = Last Observation Carried Forward; MD = Mean Difference; MW = Mean Value; N = Number of Patients Evaluated; n = Number of Patients with (at least one) Event; n.c. = not calculable; n.a. = not achieved; PedsQL = Paediatric Quality of Life Inventory; PT = Preferred Term; RCT = Randomised Controlled Trial; RR = Relative Risk; RRMS = Relapsing-Remitting Multiple Sclerosis; SD = Standard Deviation; SE = Standard Error; SOC = System Organ Class; SAE = Serious AE; AE = Adverse Event; vs = versus

b2) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy:

No relevant data were submitted.

2. Number of patients or demarcation of patient groups eligible for treatment

a1) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom escalation of therapy is indicated:

Approx. 60–230 patients

a2) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapeutics is indicated:

Approx. 70–250 patients

b1) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received disease modifying therapy:

Approx. 40–230 patients

b2) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy:

Approx. 20–130 patients

3. Requirements for a quality-assured application

The requirements of the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Gilenya® (active ingredient: fingolimod) at the following publicly accessible link (last access: 02 May 2019):

https://www.ema.europa.eu/documents/product-information/gilenya-epar-product-information_de.pdf

For fingolimod, there are several Dear Healthcare Professional Communications ("Rote-Hand-Brief") referring to serious adverse reactions (including cardiac side effects, haemophagocytic syndrome with death, occurrence of PML, opportunistic infections) and the corresponding monitoring measures.

The European Medicines Agency will regularly evaluate new information on this medicinal product and, if necessary, update the summary of product characteristics. Consequently, the status of the summary of product characteristics must be reviewed for up-to-datedness, in particular against the background of the continuously increasing knowledge about the risk profile of fingolimod; changes must be taken into account accordingly.

The initiation and monitoring of treatment must be carried out by a neurologist with experience in the treatment of multiple sclerosis.

In accordance with the guidelines of the European Medicines Agency (EMA) regarding additional risk minimisation measures, the pharmaceutical company must provide a check-list for doctors (including information on the fingolimod Intensive Monitoring Programme, on the outcome of pregnancies under fingolimod therapy, and on the fingolimod Pregnancy Registry) as well as a reminder card for all patients, their parents, and caregivers.

There are only very few data for use in children aged 10–12 years, children under 40 kg, or children of Tanner stage < 2. Long-term safety data for children and adolescents are not available.

4. Treatment costs

Annual treatment costs:

a1) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom escalation of therapy is indicated:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fingolimod	€ 11,454.22 – € 22,142.50
Appropriate comparator therapy:	
Therapy according to the doctor's instructions	patient-individualized

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 June 2019)

a2) Children and adolescents ≥ 10 and < 18 years of age with highly active relapsing-remitting multiple sclerosis despite treatment with a full and adequate course with at least one disease modifying therapy for whom a change within the basic therapeutics is indicated:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fingolimod	€ 11,454.22 – € 22,142.50
Appropriate comparator therapy:	
Interferon beta-1a	€ 19,933.42
Interferon beta-1b	€ 16,029.11
Glatiramer acetate	€ 13,120.78

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 June 2019)

b1) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI who have not yet received disease modifying therapy:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fingolimod	€ 11,454.22 – € 22,142.50
Appropriate comparator therapy:	
Interferon beta-1a	€ 19,933.42
Interferon beta-1b	€ 16,029.11
Glatiramer acetate	€ 13,120.78

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 June 2019)

b2) Children and adolescents ≥ 10 and < 18 years of age with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI despite disease modifying therapy:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Fingolimod	€ 11,454.22 – € 22,142.50
Appropriate comparator therapy:	
Therapy according to the doctor's instructions	patient-individualized

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 June 2019)

Costs for additionally required SHI services: not applicable