HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 July 2011

GILENYA 0.5 mg, hard capsules, perforated unit dose blister packs
B/7 (CIP code: 417 785-3)

GILENYA 0.5 mg, hard capsules, blister packs
B/28 (CIP code: 417 787-6)

Applicant: NOVARTIS PHARMA S.A.S.

fingolimod
ATC code: L04AA27 (selective immunosuppressants)

List I
Initial prescription to be made in hospital, renewable quarterly
Only to be prescribed by neurologists
Medicine requiring special monitoring during treatment.
Initial administration must be carried out in a hospital environment.

Date of Marketing Authorisation (centralised procedure): 17 March 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (box of 28) and approved for hospital use (box of 7 and box of 28).

Medical, Economic and Public Health Assessment Division

1. PROPERTIES OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fingolimod

1.2. Background

Fingolimod is a sphingosine 1-phosphate receptor modulator, and is the first oral disease-modifying treatment for highly active forms of multiple sclerosis.

1.3. Indication

"GILENYA is indicated as single disease-modifying therapy in highly active forms of relapsing-remitting multiple sclerosis for the following adult patient groups:

- patients with high disease activity despite treatment with a beta-interferon.
These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy and have at least 9 T2-hyperintense lesions on the cranial MRI or at least 1 gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

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 previous recent MRI. "

1.4. Dosage

"The treatment should be initiated and supervised by a physician experienced in multiple sclerosis.

Dosage

The recommended dosage of GILENYA is one 0.5 mg capsule taken orally once daily. GILENYA can be taken with or without food.
If a dose is missed treatment should be continued with the next dose as planned.

Patients can switch directly from beta interferon or glatiramer acetate to GILENYA provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia.

Special populations

Elderly population

GILENYA should be used with caution in patients aged 65 years and over due to insufficient data on tolerance and efficacy.

Renal failure

GILENYA was not studied in patients with renal impairment in the multiple sclerosis pivotal studies. Based on clinical pharmacology studies, no dose adjustments are needed in patients with mild to severe renal impairment.

Hepatic impairment

GILENYA must not be used in patients with severe hepatic impairment (Child-Pugh class C). Although no dose adjustments are needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment in these patients.

Diabetic patients

GILENYA has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. GILENYA should be used with caution in these patients due to a potential increase in the risk of macular oedema. Regular ophthalmological examinations should be conducted in these patients to detect macular oedema.

Paediatric population

The tolerance and efficacy of GILENYA in children aged 0 to 18 years have not yet been established. Currently available data are described in section 5.2 of the SPC but no recommendation on a posology can be made. "

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

L	Antineoplastic and immunomodulating agents
L04	Immunosuppressants
L04A	Immunosuppressants
L04AA	Selective immunosuppressants
L04AA27	Fingolimod

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

Mitoxantrone - ELSEP 2mg/mL concentrate for solution for infusion
For hospital use only - Approved for hospital use (May 2004)

ELSEP is indicated for aggressive forms of relapsing-remitting or secondary progressive multiple sclerosis. The level of aggressiveness is defined by:

- two relapses, both having sequelae, during the last 12 months and a new gadolinium-enhancing lesion on an MRI taken less than three months before.

  or

- a two-point increase in the EDSS score during the previous 12 months and a new gadolinium-enhancing lesion on an MRI taken less than three months before

Natalizumab - TYSABRI 300 mg, concentrate for solution for infusion
For hospital use only - Approval for hospital use (March 2007)

The indication for TYSABRI has the same wording as that for GILENYA.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy studies

Two phase III studies have been carried out: the FREEDOMS study versus placebo and the TRANSFORMS study versus interferon β1-a (AVONEX).

3.1.1 FREEDOMS study[1] - fingolimod versus placebo

FREEDOMS was a randomised, double-blind superiority study comparing the efficacy and tolerance of fingolimod 0.5 mg and 1.25 mg with placebo in patients with relapsing-remitting MS according to the McDonald criteria,[2] who had had at least one relapse during the year prior to inclusion or at least two in the two years prior to inclusion. Baseline EDSS score[3] was between 0 and 5.5 (mild to moderate disability).

The dosage of fingolimod was 0.5 mg or 1.25 mg once daily, given orally.

The primary efficacy endpoint was annualised rate[4] of relapse[5] at two years.
Among all the secondary endpoints, the following were evaluated: percentage of patients with no increase in disability,[6] number of new or enlarging T2 hyperintense lesions on MRI, number of gadolinium-enhancing (Gd+) lesions on MRI and percentage of relapse-free patients.

A total of 1272 patients with a mean age of 37 years were randomised (ratio 1:1:1): fingolimod 0.5 mg (n=425): fingolimod 1.25 mg (n=429), placebo (n=418).
Median time between first symptoms and inclusion in the study was 7 years.
Mean number of MS relapses in each patient was 1.5 within 1 year prior to inclusion in the study and 2.1 within two years prior to inclusion. Mean initial EDSS score was 2.4.

Initial MRI showed no gadolinium-enhancing lesions in 62% of patients. Mean initial number of Gd+ lesions was 1.6.

Forty-one percent of these patients had previously received a disease-modifying treatment: interferon β (29%), glatiramer acetate (11%), natalizumab (0.6%). None of the patients were receiving disease-modifying treatment at randomisation.

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1 Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, Agoropoulou C, Leyk M, Zhang-Auberson L, Burtin P; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. Engl J Med. 2010; 362(5):387-401. Epub 2010 Jan 20.

2 Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005;58(6):840-6.

3 Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52. (score between 0 and 10).

4 Quotient of the total number of relapses per total number of days of participation, multiplied by 365 days.

5 New, worsened or recurrent neurological symptoms, in the absence of fever and infection, that persist for at least 24 hours, occurring at least 30 days after the start of a previous relapse, accompanied by an increase of at least 0.5 points on the EDSS score, at least 1 point on two functional FSS scores, or 2 points on one of these functional scores (apart from bowel-and-bladder and cerebral scores)

6 1-point increase in EDSS, 0.5 points if the initial EDSS score was 5.5, confirmed at three or six months in the absence of relapses.

Efficacy data

The number of patients who withdrew from treatment before the end of the double-blind period was 326 (25.6%): They represented 30.5% of patients on fingolimod 1.25 mg, 18.8% of patients on fingolimod 0.5 mg and 27.5% of patients on placebo.

In total, 1,034 patients (81%) were followed up over two years; 6.9% of these patients had stopped treatment.
Injectable methylprednisolone, which is a treatment authorised for use during relapses, was given to 22% of patients receiving fingolimod 1.25 mg, 26% of patients on fingolimod 0.5mg and 48.5% of patients on placebo.

Intention-to-treat analysis results (patients having received at least one dose of treatment):

Endpoints	Fingolimod 1.25 n=429	Fingolimod 0.5 n=425	Placebo n=418	p 1.25 mg vs Pl	p 0.5 mg vs Pl
Annualised relapse rate†	0.16 (0.13-0.19)	0.18 (0.15-0.22)	0.40 (0.34-0.47)	<0.001	<0.001
Ratio	0.40	0.46			
No increase in disability* (12 weeks) % Pts	83.4	82.3	75.9		
Hazard ratio**	0.68 (0.50-0.93)	0.70 (0.52-0.96)		0.02	0.02
No increase in disability* (24 weeks) % Pts	88.5	87.5	81.0		
Hazard ratio**	0.6 (0.41-0.86)	0.63 (0.44-0.90)		0.006	0.01
% patients with no relapses*	74.7	70.4	45.6		
Hazard ratio**	0.38 (0.30-0.48)	0.48 (0.39-0.61)		<0.001	<0.001
No new or enlarging T2-weighted lesions¶	175/337 (52)	187/370 (50.5)	72/339 (21)	<0.001	<0.001
Mean number of lesions ∫	2.5	2.5	9.8	<0.001	<0.001
No new Gd+ lesions ¶¶	308/343 (90)	331/369 (90)	216/332 (65)	<0.001	<0.001
Mean number of lesions ∫∫	0.2	0.2	1.1	<0.001	<0.001

Negative binomial regression, adjusted by treatment, country, number of relapses in the two years prior to inclusion and initial EDSS score.

* Kaplan-Meier estimate of the percentage of patients with worsened disability. Log-rank test

** Cox proportional hazards model, adjusted for treatment, country, initial EDSS and age

¶ Logistical regression adjusted for treatment and country

∫ Negative binomial regression adjusted for treatment and country

¶¶ Excluding data collected in the 30 days following steroid treatment for a relapse.

Logistical regression adjusted for treatment, country and number of initial lesions

∫∫ ANCOVA adjusted for treatment, country and number of initial Gd+ lesions

One of the post hoc sub-group analyses included:

- patients who had previously received disease-modifying treatment or who had not had at least two relapses in the year prior to inclusion, with one or more gadolinium-enhancing lesions *(it was not specified whether these relapses were disabling, as stated in the wording of the indication)*
- patients who had been on treatment (≥ six months) and who had had at least one relapse in the year prior to inclusion, with the presence of one or more gadolinium-enhancing lesions.

This analysis showed that the ratio of annualised relapse rate versus placebo (n=71) was 0.33 (0.21-0.51) for fingolimod 1.25 mg (n=72) and 0.36 (0.24-0.54) for fingolimod 0.5 mg (n=84) at two years. The risk of increase in disability progression on fingolimod was not different from that seen for placebo for these patients.

Tolerance data

Ninety-four percent of patients presented with at least one adverse event. The most common adverse events were: nasopharyngitis (26% on fingolimod 1.25 mg, 27% on fingolimod 0.5 mg vs 27.5% on placebo) and headache (27%, 25% vs 23%).

The percentages of patients who discontinued treatment because of an adverse event were 7% in the fingolimod 1.25 mg arm, 3.5% in the fingolimod 0.5 mg arm and 6% in the placebo arm.

The adverse events that were observed more frequently in those on fingolimod (1.25 mg and 0.5 mg) than on placebo were: leukopenia (6.3%, 2.8% vs 0.2%), lymphocytopenia (5%, 3.5% vs 0.5%) and lower respiratory tract infections (11%, 10% vs 6% on placebo).
Twenty-three cases of bradycardia/sinus bradycardia (14 and 9) vs three on placebo and eight cases of atrioventricular block (six and two), one of which was second-degree, vs three on placebo, were observed for fingolimod 1.25 mg and fingolimod 0.5 mg.
Seven patients developed macular oedema while taking fingolimod 1.25 mg, and three of these events were severe. Five of these cases occurred in the first three months.
Hypertension was observed more commonly for fingolimod 1.25 mg (6%) and for fingolimod 0.5 mg (6%) than for placebo (4%).

Serious adverse events were observed in 11.9% of patients taking fingolimod 1.25 mg, 10.1% on fingolimod 0.5 mg and 13.4% on placebo. Two cases of lymphocytopenia and three of macular oedema were reported in the fingolimod arms. Seven cases of bradycardia (three and four vs one on placebo) were observed in patients taking fingolimod. Five cases of basal cell carcinoma (one and four vs three), one melanoma (vs one) and one breast cancer (vs three) were reported. Three deaths occurred during the study, one of which was of a patient receiving fingolimod (suicide).

Increased ALT (> 3 x ULN) were observed for fingolimod 1.25 mg and 0.5 mg (12.5%, 8.5% vs 1.7% for placebo). At one month, the circulating lymphocyte count was reduced by 73% (fingolimod 0.5 mg) and 76% (fingolimod 1.25 mg). Counts of less than 0.2 x 10^9/L were observed in 30% and 18% of patients receiving fingolimod 1.25 mg and 0.5 mg (vs 0% for those on placebo).

3.1.2 TRANSFORMS study[1] - fingolimod versus interferon β1-a

TRANSFORMS was a randomised double-blind study that compared the efficacy and tolerability of fingolimod (1.25 mg and 0.5 mg) with those of interferon β1-a 30 µg in patients with relapsing-remitting MS according to the McDonald criteria,[2] who had had at least one relapse within one year prior to inclusion or at least two within two years prior to inclusion. Baseline EDSS score[3] was between 0 and 5.5 (mild to moderate disability). It was acceptable for patients to have recently received treatment with interferon β or glatiramer acetate.

The dosage of fingolimod was 1.25 mg or 0.5 mg once daily, given orally. The dosage of interferon β-1a was one IM injection of 30 µg per week.

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1 Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, Pelletier J, Capra R, Gallo P, Izquierdo G, Tiel-Wilck K, de Vera A, Jin J, Stites T, Wu S, Aradhye S, Kappos L; TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010; 362(5):402-15. Epub 2010 Jan 20.

2 Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005;58(6):840-6.

3 Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52. (score between 0 and 10)

The primary efficacy endpoint was annualised relapse rate[1] [2] at 12 months.
The secondary endpoints which were evaluated included number of new or enlarging T2-hyperintense lesions on MRI, number of gadolinium-enhancing (Gd+) lesions on MRI and percentage of relapse-free patients at one year.

A total of 1292 patients with a mean age of 36 years were randomised (ratio 1:1:1): fingolimod 1.25 mg (n=426): fingolimod 0.5 mg (n=431), interferon β-1a (n=435).

Median time between first symptoms and inclusion in the study was six years. During the two years prior to inclusion in the study, 28% of these patients had had one MS relapse, and 60% had had two or three relapses. Mean number of MS relapses in each patient was 1.5 within the year prior to inclusion in the study and 2.2 within the two years prior to inclusion.
Mean baseline EDSS score was 2.2.

Baseline MRI showed no gadolinium-enhancing lesions in 65% of patients. Mean initial number of Gd+ lesions was 1.2.

Fifty-seven percent of patients had previously been treated with interferon β (49%) or glatiramer acetate (15%). Seventy-five percent of these patients had received interferon β (INF) or glatiramer acetate (GA) during the three months prior to the start of treatment.

Efficacy data

The number of patients who withdrew from treatment before the end of the double-blind period was 157 (12.2%): 14.6% of patients receiving fingolimod 1.25 mg, 10.2% of those receiving fingolimod 0.5 mg, 11.7% of those receiving interferon ß-1a. Adverse effects were the most common reason for discontinuing treatment.

In total, 1,153 patients (89%) were followed up over one year; 2.3% of these patients had stopped treatment.
Injectable methylprednisolone, which is a treatment authorised for use during relapses, was given to 19% of patients on fingolimod 1.25 mg, 16% of patients on fingolimod 0.5mg and 31% of patients on interferon β.

1 Quotient of the total number of relapses per total number of days of participation, multiplied by 365 days.

2 New, worsened or recurrent neurological symptoms, in the absence of fever and infection, that persist for at least 24 hours, occurring at least 30 days after the start of a previous relapse, accompanied by an increase of at least 0.5 points on the EDSS score, at least 1 point on two functional FSS scores, or 2 points on one of these functional scores (apart from bowel-and-bladder and cerebral scores)

Intention-to-treat analysis results (patients who received at least one dose of treatment):

Endpoints	Fingolimod 1.25 n=420	Fingolimod 0.5 n=429	Interferon β1-a n=431	p 1.25 mg *vs* INF	p 0.5 mg *vs* INF
Annualised relapse rate†	0.20 (0.16-0.26)	0.16 (0.12-0.21)	0.33 (0.26-0.42)	<0.001	<0.001
Ratio	0.61	0.48			
No increase in disability* (12 weeks) % Pts	93.3	94.1	92.1	ns	ns
No. of patients experiencing relapse (%)					
0	338 (80.5)	354 (82.5)	302 (70.1)	<0.001	<0.001
1	61 (14.5)	63 (14.7)	90 (20.9)		
2	19 (4.5)	11 (2.6)	30 (7.0)		
≥ 3	2 (0.5)	1 (0.2)	9 (2.1)		
No new or enlarging T2 lesions on MRI‡	168/350 (48)	204/372 (54.8)	165/361 (45.7)	ns	0.01
Mean number of lesions	1.5	1.7	2.6	<0.001	0.004
No new Gd+ lesions on MRI‡‡	321/352 (91.2)	337/374 (90.1)	286/354 (80.8)	<0.001	<0.001
Mean number of lesions	0.14	0.23	0.51	<0.001	<0.001

† Negative binomial regression, adjusted by country, number of relapses in the two years prior to inclusion and initial EDSS score.

* Kaplan-Meier estimate of the percentage of patients with a progression of their disability. Log-rank test

‡ Logistical regression adjusted for treatment and country

‡‡ Excluding data collected in the 30 days following steroid treatment for a relapse.

ANCOVA adjusted for treatment, country and number of initial Gd+ lesions

One of the post hoc sub-group analyses included:

- patients who had previously received disease-modifying treatment or who had not had at least two relapses in the year prior to inclusion, with one or more gadolinium-enhancing lesion(s) *(it was not specified whether these relapses were disabling, as stated in the wording of the indication)*
- patients who had been on treatment *(≥ six months)* and who had had at least one relapse in the year prior to inclusion, with the presence of one or more gadolinium-enhancing lesion(s).

This analysis showed that the ratio of annualised relapse rate versus interferon β (n=80) was 0.62 (0.35-1.09) for fingolimod 1.25 mg (n=74) and 0.48 (0.27-0.87) for fingolimod 0.5 mg (n=74) at one year.

Tolerance data

Nearly 90% of patients presented with at least one adverse event. The most common adverse events were: nasopharyngitis (22% on fingolimod 1.25 mg, 20.5% on fingolimod 0.5 mg vs 20% on interferon β), headache (23%, 23% vs 20%) and fatigue (14%, 10% vs 10%).

The percentages of patients who discontinued treatment because of an adverse event were 7.5% in the fingolimod 1.25 mg arm, 4% in the fingolimod 0.5 mg arm and 3% in the interferon arm.

The adverse events that were observed more frequently for interferon β than for fingolimod were: fever (18% vs 4% for fingolimod 1.25 mg, 4% for fingolimod 0.5 mg), flu-like symptoms (37% vs 4% and 3.5%), myalgia (10% vs 3% and 3%) and depression (7% vs 4% and 5%).
Seven patients developed macular oedema (five while taking fingolimod 1.25 mg), of which two were reported as severe events. Six of these cases occurred in the first three months.

Hypertension was observed more commonly for fingolimod 1.25 mg (5%) and for fingolimod 0.5 mg (4%) than for interferon β (2%).

A serious adverse event was observed in 10.7% of patients taking fingolimod 1.25 mg, 7% taking fingolimod 0.5 mg and 5.8% receiving interferon β.
Of the serious events that were only reported for fingolimod, seven were atrioventricular block, four of which were second-degree (three on fingolimod 1.25 mg) and twelve cases of bradycardia/sinus bradycardia were observed (ten on fingolimod 1.25 mg).
Two deaths occurred during the study. These deaths were caused by infection and occurred in the fingolimod 1.25 mg arm (primary infection with varicella zoster virus, herpes viral encephalitis).
Four cases of herpes virus infection (one case on fingolimod 0.5 mg vs one case on interferon β) were observed in both fingolimod arms, as well as five cases of basal cell carcinoma (three for fingolimod 0.5 mg vs one), three melanomas (three for fingolimod 0.5 mg vs zero) and four breast cancers (two for fingolimod 0.5 mg vs zero).

Increased ALT (> 3 x ULN) were observed for fingolimod 1.25 mg and 0.5 mg (6.9%, 8.4% vs 2.3% for interferon β). At one month, the circulating lymphocyte count was reduced by 73% (fingolimod 0.5 mg) and 77% (fingolimod 1.25 mg). Counts of less than 0.2 x 10^9/L were observed in 34% and 15% of patients receiving fingolimod 1.25 mg and 0.5 mg (vs 0.7% for those on interferon β). Five cases of lymphocytopenia were reported in patients taking fingolimod (four on fingolimod 1.25 mg vs zero on interferon β).

3.2. Tolerance data from phase II and III studies

The product's tolerance profile was based on data from three phase II and III clinical studies (FREEDOMS/TRANSFORMS) including study extension periods. Taking extension phases into account, 2615 patients received at least one dose of fingolimod (0.5 mg, 1.25 mg and/or 5 mg), giving an estimated exposure of 4582.6 patient-years. A total of 1891 patients were exposed to fingolimod during the controlled periods of these studies (placebo n=511, β-1a INF n=431); 70.5% of these patients were exposed to fingolimod for at least one year and 47% for at least two years. Five percent of patients received at least one 5 mg dose per day.

A reduction of over 75% in circulating lymphocyte count was observed at one month of treatment. The percentage of patients who had a lymphocyte count of less than 0.2 x 10^9/L was higher in patients who had previously been treated with immunosuppressants. Among the reported serious adverse events there were five cases of lymphocytopenia.

Infections and infestations were the most common adverse events. The incidence of these events increases with the duration of treatment. Three cases of disseminated herpes infection, two of which were fatal (disseminated primary infection with varicella zoster, herpes encephalitis) were reported in patients treated with fingolimod 1.25 mg.
Of the serious events, 25 cases of bradycardia (six cases on fingolimod 0.5 mg), 13 cases of atrioventricular block (two on fingolimod 0.5 mg), eight of which were second-degree (one on fingolimod 0.5 mg) and 12 cases of macular oedema (two on fingolimod 0.5 mg), eight of which were confirmed (six of these in the first four months) were reported.
Hypertension (4-6% of patients) and elevated liver transaminase levels (ALT > 3 x ULN in 8.5% of patients) were more common in the fingolimod arms than in the control arms.

Six cases of severe neurological disorders were observed in patients on high doses of fingolimod (1.25 mg or 5 mg) including two cases of posterior reversible encephalopathy syndrome (PRES), one fatal case of acute disseminated encephalomyelitis (ADEM), one neurological event that may have been linked to ADEM and one case of severe neurodegenerative disease.

Eighteen cases of basal cell carcinoma (nine on fingolimod 0.5 mg) and six malignant melanomas (two on fingolimod 0.5 mg) were reported. Three cases of lymphoma were observed; the incidence is estimated at 3 per 10,000 patient-years [95% CI 0.6; -8.8].
There has been limited duration of exposure to the product. A relationship between the incidence of reported malignant neoplastic disease and administration of the product cannot be ruled out.

3.3. Conclusion

a. Efficacy

One study (FREEDOMS) compared fingolimod with placebo over a period of two years in patients with relapsing-remitting MS who had had at least one relapse during the year prior to inclusion, or at least two during the two years prior to inclusion.
The annualised relapse rates after two years were 0.16 for fingolimod 1.25 mg, 0.18 for fingolimod 0.5 mg and 0.40 for placebo. The percentages of patients who were relapse-free in these three arms were 75%, 70% and 46% respectively.
Estimatedpercentage of patients with no disability progression at two years was 83% for fingolimod 1.25 mg, 82% for fingolimod 0.5 mg and 76% for placebo.
Mean number of new or enlarging T2 lesions and mean number of Gd+ lesions were reduced in the fingolimod arm compared with the placebo arm.

One study (TRANSFORMS) compared fingolimod with interferon β-1a over a period of one year in patients with relapsing-remitting MS who had had at least one relapse during the year prior to inclusion, or at least two during the two years prior to inclusion. The majority of patients had received interferon β or glatiramer acetate during the three months prior to inclusion.
Annualised relapse rates at one year were 0.20 for fingolimod 1.25 mg, 0.16 for fingolimod 0.5 mg and 0.33 for interferon β1-a. Percentages of relapse-free patients in the three arms were 80.5%, 82.5% and 70% respectively.
Estimated percentage of patients who experienced no disability progression after one year is 93% for fingolimod 1.25 mg, 94% for fingolimod 0.5 mg and 92% for interferon β-1a. The risk of disability progression was similar for all arms.
Mean number of new or enlarging T2 lesions and mean number of Gd+ lesions were reduced in the fingolimod arm compared with the interferon β-1a arm.

These results showed that there was no difference in efficacy between the two dosages of fingolimod; only fingolimod 0.5 mg got Marketing Authorisation.
The efficacy of fingolimod 0.5 mg is greater than that of placebo in terms of annualised relapse rate at two years, and has a more modest effect on disability progression.
The superiority of fingolimod 0.5 mg in comparison with interferon β on annualised relapse rate at one year is modest; the percentages of patients with no disability progression were similar.
Results of the post hoc sub-group analyses for both studies are exploratory in nature and must be interpreted with caution.

The population of patients included in these studies, who did not have very severe forms of the disease, did not correspond to those given in the indication for GILENYA, which is restricted to highly active forms of relapsing-remitting MS, taking into consideration the reservations about the product's tolerability profile.

b. Tolerance

A reduction in circulating lymphocytes of at least 70% was observed in patients taking fingolimod. Lymphocytopenia was more common in patients who had previously received immunosuppressive treatment.
The risk of bradyarrhythmia, including atrioventricular block, requires close medical monitoring during first dose administration period.
The risk of severe infection (which increases with duration of treatment), or macular oedema and of liver enzymes elevation require particular monitoring during treatment. Severe neurological disorders have been observed at high doses (1.25 mg and 5 mg).

The cancer risk associated with fingolimod can only be evaluated once longer-term tolerance data become available. Given its teratogenic potential, pregnancy must be avoided during treatment.

The European Risk Management Plan contains provisions for prospective observational studies over five years to monitor long-term tolerance of fingolimod, and in particular the incidence of opportunistic infection, skin cancer and other malignant neoplastic disease, cardiovascular adverse events (hypertension, thromboembolic events), elevation in liver transaminase levels and macular oedema. Specific studies are planned to look at bradyarrhythmia (including conduction disorders) and macular oedema. Cumulative reviews of such events, as well as leukopenia, lymphocytopenia, bronchoconstriction, posterior reversible encephalopathy syndrome, acute disseminated encephalomyelitis, prolonged QT interval and virus reactivation will be included in periodic tolerance reports of this product. Set-up of a registry of pregnancies occurring in patients under treatment is planned.
The risk minimisation plan includes provisions for making available a prescribing guide for healthcare professionals, a patient alert card and a joint GP/hospital log book.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Multiple sclerosis is an incapacitating, progressive, chronic neurological disorder. It causes multiple deficiencies, which vary depending on disease progression and individual characteristics: motor and sensory disorders, sensory deficits, bladder and sphincter problems, sexual problems, and cognitive and mood disorders. These deficiencies may reduce patients' independence considerably and worsen their quality of life. There is a large variation in the severity of the disease, with benign forms which are hardly incapacitating to severe forms which result in major disabilities within a few years.

GILENYA is intended as a preventive treatment of relapses and disability progression in highly active forms of relapsing-remitting multiple sclerosis.

The efficacy/adverse effects ratio of this proprietary medicinal product over the medium term (two years) is moderate. The efficacy/adverse effects ratio in the longer term remains to be determined.

Natalizumab and mitoxantrone are also indicated in the highly active forms of relapsing-remitting multiple sclerosis.

Public Health Benefit:

Multiple sclerosis (MS) currently affects between 70,000 and 90,000 patients in France, with a probable annual incidence of 4-6 per 100,000 inhabitants.[1] Disease onset occurs at a mean age of 30 years (20-40 years), in most cases in women, and is the primary non-traumatic cause of severe acquired disability in young people. The severity of the disease arises from the disability it causes, its effect on quality of life and its social and economic impact. MS is considered to represent a moderate public health burden, including the patient sub-population covered by the indication for GILENYA.

Reducing the functional limitations caused by multiple sclerosis and improving the quality of life of patients with the disease is a public health need that is part of the set of established public health priorities (objective 65 of the French public health policy law dated 9 August 2004, the Plan to improve quality of life of patients with chronic diseases 2007-2001).

In the absence of data comparing this product with natalizumab, and in view of the results of the only phase III study versus an active comparator (interferon β-1a), which was of limited duration (one year), the impact of fingolimod in terms of reduction in morbidity (reduction of relapses) is low.
However, no improvement in quality of life was demonstrated in these studies, and impact on disability progression was only evaluated over the short term, particularly in the study versus interferon β, and infectious, cardiac, liver and eye adverse effects were observed in the pivotal studies.
There is no guarantee that the results of trials can be transposed into clinical practice, for the following reasons:
- the characteristics of patients included in these studies; they had a form of the disease that was less severe than that reflected in the French epidemiological data;
- uncertainties about long-term tolerance (in particularcancer risk) of this proprietary medicinal product.

Because of the availability of this product in an oral dosage form, and because monthly hospital admissions are not necessary, it can be expected to have a positive impact on the organisation of care. However, the requirement for regular patient monitoring could limit this impact.

GILENYA does not therefore appear, given the current data, to provide an additional response to an identified public health need.

The actual benefit (AB) of these proprietary medicinal products is substantial.

4.2. Improvement in actual benefit (IAB)

Taking into consideration the tolerance concerns, GILENYA, an oral medication, is indicated in highly active forms of relapsing-remitting multiple sclerosis. As a drug alternative, GILENYA provides a minor improvement in actual benefit (level IV) in the management of these patients.

4.3. Therapeutic use

Multiple sclerosis is an incapacitating, progressive, chronic neurological disorder. Its general progression and prognosis vary and are regarded as being difficult to predict.

In approximately 85% of cases the disease begins in the form of a relapse followed by remission (relapsing-remitting forms) and begins with a progressive form in the remaining 15% of cases (primary progressive forms). In the case of relapsing-remitting forms, the second relapse occurs during the first two years in 50% of patients. The median time for secondary

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progressive MS to occur after the relapsing-remitting form is estimated as between 15 and 19 years according to the series. The primary progressive form develops progressively after its clinical onset, with our without additional relapses, but without any relapsing-remitting phase.
The “aggressive” form describes MS which leads to a rapid increase in disability. It may be characterised by a high frequency of relapses (at least two relapses with sequelae) or a two-point increase in the EDSS score in the previous 12 months.

Three immunosuppressive treatments are currently indicated for highly active forms of MS, although their effect on the natural history of the disease cannot yet be measured: these are are mitoxantrone, natalizumab and fingolimod.

Mitoxantrone is reserved for aggressive forms of relapsing-remitting or secondary progressive multiple sclerosis. An aggressive form is defined by two relapses with sequelae during the previous 12 months and a new gadolinium-enhancing lesion on an MRI taken less than three months before, or by a two-point increase in the EDSS score during the previous 12 months and a new gadolinium-enhancing lesion on an MRI taken less than three months before.
The haematological risk in the short term (neutropenia) and long term (leukaemia) requires regular monitoring of the patient. Treatment also requires regular monitoring of the patient’s left ventricular ejection fraction. Mitoxantrone is administered via infusions, with a total cumulative dose for one patient not exceeding 120 mg (six doses).

Natalizumab and fingolimod are indicated as single disease-modifying therapies in highly active forms of relapsing-remitting multiple sclerosis (MS) for patients with:
- a highly active form of the disease, despite full and properly administered beta interferon treatment given over at least one year. A "non-responder" patient is defined as a patient who has had at least one relapse during the previous year, despite being treated with interferon β, and who has at least 9 hyperintense T2 lesions on brain MRI or at least one gadolinium-enhancing lesion, or a patient whose relapse rate is unchanged or increased in comparison with the previous year, or who continues to have severe relapses.

or

- a severe and rapidly evolving form of disease, 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 previous recent MRI.

Hypersensitivity reactions have been linked to the use of TYSABRI; these usually occur during infusion or in the hour following infusion. These reactions may take the form of severe systemic reactions.
Patients must be monitored at regular intervals in order to detect any opportunistic infection, particularly PML (via annual MRI), the first symptoms of which can be difficult to distinguish from a MS relapse.

Onset of bradyarrhythmia (including conduction disorders) following an initial administration of GILENYA requires close medical monitoring during the first six hours following first administration. Patients must be monitored at regular intervals throughout treatment, in order to detect any infection, macular oedema and liver function problems. The limited length of exposure so far, and the fact that there have been reported cases of skin cancers and other malignant neoplastic disease, mean that a cancer risk cannot be ruled out for this product. Given its teratogenic potential, pregnancy must be avoided during treatment.

Current data do not provide enough information to clarify the role of GILENYA in treatment strategies for highly active forms of relapsing-remitting MS, particularly in comparison with TYSABRI. The choice of treatment in these highly active forms of MS will be made on a case-by-case basis.

4.4. Target population

The population of patients with a highly active form of RR-MS, as estimated in 2007,[1] was between 9,000 and 11,000 patients; this group is the maximum target population for GILENYA.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance (pack of 28) and on the list of medicines approved for hospital use and various public services (packs of 7 and 28) for the indication and at the dosage in the Marketing Authorisation.

The Committee regrets that there are insufficient data concerning the efficacy of GILENYA for the population defined in the indication.
Given the current reservations raised by the tolerance data for fingolimod, especially long term, and the existence of a Risk Management plan, a reassessment of the application (and in particular all available tolerance data for the product) is scheduled for one year.

Furthermore, the Transparency Committee wishes to be provided with data on the follow-up of patients with MS who are being treated with GILENYA in France. The purpose of this is to document in a real-life treatment situation:

- the characteristics of the patients being treated;
- use of this proprietary medicinal product as part of therapeutic strategy;
- any discontinuation of treatment and reasons for this and for any switching of treatment;
- the impact of this treatment on the disability progressio (e.g. EDSS score, transition to progressive form, etc.), frequency of relapses and quality of life for patients receiving this treatment in comparison with other treatments.

If the planned studies and those currently being carried out, especially as part of the European Risk Management Plan, are not able to answer the questions raised by the Transparency Committee, a specific study will need to be carried out. The study's duration will be approved by an independent scientific committee.
These data may be collected via a pharmacoepidemiology study that was launched as part of the "French Multiple Sclerosis Observatory" project.
The initial data must be made available to the Committee within two years following registration.

4.5.1 Packaging

The Committee points out that in accordance with its decision of 20 July 2005 it recommends that pack sizes for one-month treatments be harmonised with the size of the packaging for 30 days of treatment.

4.5.2 Reimbursement rate: 65%

4.5.3 Exceptional medicinal product ("Médicament d'exception")

1 Opinion CT-3657 - 17 January 2007