HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

17 January 2007

TYSABRI 300 mg, concentrated solution for infusion
15 ml vial (20 mg/ml), box of 1 - CIP: 569 967.7

Applicant: Biogen Idec France

Natalizumab

List I
Drug available only on restricted medical prescription (see Posology and method of administration section in SPC)

Date of Marketing Authorisation (centralised procedure): June 28, 2006, November 28, 2006 (amendments)

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

natalizumab

1.2. Originality

Recombinant humanised IgG4 monoclonal antibody, which binds to anti-α4β1 and α4β7-integrins expressed on the surface of all leukocytes (with the exception of neutrophils), indicated as the primary treatment for highly active forms of relapsing-remitting multiple sclerosis (MS).

1.3. Indication

TYSABRI is indicated as single disease modifying therapy in highly active forms of relapsing-remitting MS for the following patient groups:

- Patients with high disease activity despite treatment with a beta-interferon (see Pharmacodynamic properties section of the SPC)

  or

- Patients with rapidly evolving, severe relapsing-remitting multiple sclerosis (see Pharmacodynamic properties section of the SPC).

1.4. Pharmacodynamic properties

TYSABRI is indicated as a single disease modifying therapy in relapsing-remitting MS to prevent relapses and delay progression of disability. Due to safety concerns (see sections 4.4 and 4.8 of the SPC) treatment is restricted to the following patient groups:

- Patients who have failed to respond to a full and adequate course of a 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.

  or

- Patients with rapidly evolving severe relapsing-remitting MS, defined by 2 or more incapacitating relapses in one year, with 1 or more Gadolinium-enhancing lesions on the brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

1.5. Dosage

TYSABRI therapy must be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with rapid access to MRI.

Patients treated with TYSABRI must be given a special alert card.

Resources for the management of hypersensitivity reactions and access to MRI should be available.

After dilution, the infusion is to be administered over approximately 1 hour and patients must be observed during the infusion and for 1 hour after its completion to monitor for signs and symptoms of hypersensitivity reactions.

TYSABRI must not be administered as a bolus injection.

Patients can switch directly from beta interferon or glatiramer acetate to natalizumab providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia. If there are signs of treatment-related abnormalities these must return to normal before treatment with natalizumab is started.

Some patients may have been exposed to immunosuppressive medications (e.g. mitoxantrone, cyclophosphamide, azathioprine); these drugs have the potential to cause prolonged immunosuppression, even after treatment is discontinued. Therefore, the physician must confirm that such patients are not immuno-compromised before starting treatment with TYSABRI.

Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months.

Data on the safety and efficacy of natalizumab beyond 2 years are not available. Continued therapy beyond this time should be considered only following a reassessment of the potential for benefit and risk.

Adults

TYSABRI 300 mg is administered by intravenous infusion once every 4 weeks.

Elderly patients

TYSABRI is not recommended for use in patients aged over 65 due to a lack of data in this population.

Children and adolescents

TYSABRI is contraindicated in children and adolescents.

Renal and hepatic impairment

Studies have not been conducted to examine the effects of renal or hepatic impairment.

However, the mechanism for elimination and results from population pharmacokinetic studies suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.

Readministration

The efficacy of readministration has not been established.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (WHO 2006)

L Antineoplastic and immunomodulating agents
04 Immunosuppressive agents
A Immunosuppressive agents
A Selective immunosuppressive agents
23 Natalizumab

2.2. Medicines in the same therapeutic category

TYSABRI is the only humanised monoclonal antibody indicated for the primary treatment of highly active relapsing-remitting forms of MS.

2.3. Medicines with a similar therapeutic aim

Mitoxantrone - ELSEP

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

- two relapses, both with sequelae, during the last 12 months and a new Gadolinium-enhancing lesion on an MRI performed within the previous 3 months

  or

- a 2-point increase in the EDSS score during the previous 12 months and a new Gadolinium-enhancing lesion on an MRI performed within the previous 3 months

3. ANALYSIS OF THE AVAILABLE DATA

3.1. Efficacy

The file submitted presents the results of two pivotal placebo-controlled comparative studies carried out in patients with relapsing-remitting MS.

3.1.1 AFFIRM study - placebo-controlled with natalizumab as monotherapy

Polman CH et col. A randomized placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;345:899-910.

The AFFIRM randomised, double-blind superiority study compared the efficacy and safety of natalizumab 300 mg with those of a placebo in patients with relapsing-remitting MS according to the McDonald[1] criteria, with lesions on the MRI compatible with MS and with at least one relapse during the year prior to inclusion.

The EDSS[2] score (0 to 10) at the time of inclusion was between 0 and 5 (minimal to moderate disability).

Patients with secondary progressive or primary progressive MS were not included.

The dosage was 300 mg, administered by intravenous infusion once every 4 weeks.

After one year, the primary endpoint was the annual[3] relapse[4] rate. After two years, the primary endpoint was the cumulative probability of progression of disability, defined by a 1-

1 McDonald WI, Compston A, Edan G, et al. Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001;50:121-7.

2 Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52.

3 Quotient of the total number of relapses divided by the total number of days participation, multiplied by 365 days.

4 Occurrence or recurrence of neurological symptoms, with no fever or infection, lasting at least 24 hours, accompanied by neurological signs during the neurological examination.

point or more increase in the EDSS score for initial scores of at least 1 or by a 1.5-point increase in the EDSS score for an initial score of 0, with the increase being maintained for 12 weeks.

The patients could continue to participate in the study when a progression occurred. In this case, they were permitted to receive another primary treatment for MS in combination with the study treatment.

The secondary endpoints which were evaluated included the number of new lesions or newly enlarging T2-hyperintense lesions on the MRI, the number of Gadolinium (Gd+) enhancing lesions on the MRI and the percentage of patients without any relapse at 1 year.

942 patients with an average age of 36 years were randomised (ratio 2:1): natalizumab (n=627), placebo (n=315).

84% of patients had had at least two relapses and had at least two lesions on the MRI (McDonald criterion 1) and 12% of patients had had at least two relapses and one lesion on the MRI (McDonald criterion 2).

The median disease duration was 5 years (0 to 34 years). 58% of patients had had one MS relapse in the year prior to inclusion, 32% had had two relapses and 41% of patients had had at least two relapses.

Over 80% of patients had an EDSS score between 1 and 3.5, while 63% had a score between 1 and 2.5.
95% of patients had at least 9 T2 lesions and 49% of patients had at least 1 Gadolinium-enhancing lesion.
34% had previously received treatment for MS: corticosteroids (18%), glatiramer acetate (3%), interferon beta-1a (4%), interferon beta-1b (2%).

Efficacy data

122 patients stopped the treatment prematurely before the end of the double-blind period: 12**%** (76/627) of patients treated with natalizumab, 14% (46/315) of patients taking the placebo. Adverse effects were the most common reason for discontinuing treatment: 6**%** of patients treated with natalizumab versus 4% patients treated with placebo.

856 patients were monitored for 2 years. 24/575 patients had discontinued treatment in the natalizumab group and 15/281 patients in the placebo group. 88% of patients received at least 26 infusions.

Corticosteroids, which were permitted to treat relapses, were administered systemically to 48% of patients treated with placebo and 27% of patients treated with natalizumab. 77 patients resorted to immunomodulating or immunosuppressive treatments (12% of patients treated with placebo versus 6% of patients treated with natalizumab) during the study.

Results of Intention to treat (ITT) analysis (n=627 natalizumab, n=315 placebo)

	1 year			2 years		
Endpoints	Natalizumab	Placebo	P	Natalizumab	Placebo	p
Annual relapse rate[†]	0.26 (0.21-0.32)	0.81 (0.67-0.97)	< 0.001	0.24 (0.19-0.29)	0.73 (0.62-0.87)	< 0.001
Progression of disability* (12 weeks) / Hazard ratio **				17%	29%	
				0.58 (0.43-0.77)		< 0.001
Progression of disability* (24 weeks) / Hazard ratio **				11%	23%	
				0.46 (0.33-0.64)		< 0.001
Relapses - No. patients (%)						
0	495 (79)	180 (57)		454 (72)	146 (46)	
1	111 (18)	76 (24)		123 (20)	65 (21)	
2	17 (3)	42 (13)		36 (6)	63 (20)	
≥ 3	4 (<1)	8 (3)		14 (2)	41 (13)	
At least 1 relapse	21%	43%		28%	54%	
% relapse free patients	76%	53%	< 0.001	67%	41%	< 0.001
T2 lesions on MRI [†]						
0	382 (61)	72 (23)		360 (57)	46 (15)	
1	112 (18)	41 (13)		106 (17)	32 (10)	
2	40 (6)	23 (7)		48 (8)	24 (8)	
≥ 3	93 (15)	179 (57)		113 (18)	213 (68)	
Mean	1.2	6.1	< 0.001	1.9	11	< 0.001
Gd+ lesions on MRI [††]						
0	605 (96)	213 (68)		608 (97)	227 (72)	
1	17 (3)	42 (13)		12 (2)	39 (12)	
2	3 (<1)	15 (5)		1 (<1)	9 (3)	
≥ 3	2 (<1)	45 (14)		6 (<1)	40 (13)	
Mean	0.1	1.3	< 0.001	0.1	1.2	< 0.001

[†] Analysis adjusted to the number of relapses in the year prior to inclusion, the initial EDSS score (≤3.5 vs >3.5), Gd+ lesions (present or absent), age (<40 vs ≥40). Relapses which occurred after initiating alternative treatment have been ignored.

* Kaplan-Meier estimate of the percentage of patients with a progression of their disability. Patients who received another primary treatment without any progression of their disability were ignored.

** Analysis adjusted to the initial EDSS score (≤3.5 vs >3.5) and age (<40 vs ≥40)

[†] The mean value for the study population was assigned to the missing values. The baseline values and values after 1 year were available for 893 patients.

** Analysis adjusted to the initial number of T2 lesions (<9 vs ≥9)

A post-hoc analysis was carried out on a subgroup of patients who had at least 2 relapses in the year prior to inclusion, with the presence of one or more Gadolinium-enhancing lesions at the time of inclusion (n=209, natalizumab n=148, placebo n=61).

Results of the subgroup analysis after 2 years

Endpoint	Natalizumab	Placebo	p
Annual relapse rate†	0.28	1.46	< 0.001
Progression of disability*	HR = 0.47 (0.24-0.93)		0.029
% relapse free patients	68%	23%	< 0.001
Mean T2 lesions on MRI	4.2	19.1	< 0.001
Mean Gd+ lesions on MRI ¶¶	0.5	3.2	< 0.001

Safety data

More than 95% of patients reported at least one adverse event. The most frequently reported adverse events were headache (35% treated with natalizumab *vs* 31% treated with placebo), nasopharyngitis (32% *vs* 33%), MS relapse (30% *vs* 57%) and fatigue (27% *vs* 21%).

A severe event was observed in 19% of patients treated with natalizumab and 24% of patients treated with placebo. The most common of these events was relapse (6% *vs* 13%).

Infusion reactions were reported in 24% of patients in the natalizumab group (severe 2%) *vs* 18% in the placebo group (severe <1%).

284 patients (45%) in the natalizumab group and 121 patients (39%) in the placebo group reported an adverse event considered by the investigator as related to the treatment. The most common treatment-related events were headache (11% *vs* 8% treated with placebo), fatigue (5% *vs* 2%) and nausea (5% *vs* 4%).

Immunogenicity

Anti-natalizumab antibodies were detected in 57 patients treated with natalizumab and persisted in 37 patients.

3.1.2 SENTINEL study - Natalizumab/interferon β1-a combination *vs* placebo/interferon β1-a combination

The SENTINEL randomised, double-blind superiority study compared the efficacy and safety of natalizumab 300 mg with those of a placebo in patients with relapsing-remitting MS according to the McDonald[1] criteria, with lesions on the MRI compatible with MS and with at least one relapse while on interferon β1-a during the year prior to inclusion. The EDSS[2] score (0 to 10) at the time of inclusion was between 0 and 5 (minimal to moderate disability). The patients had been treated with interferon β1-a for at least 12 months prior to randomisation. Patients with secondary progressive or primary progressive MS were excluded.

The dosage was 300 mg, administered by intravenous infusion once every 4 weeks. Interferon β1-a 30µg was administered by IM injection every week in combination with the study treatment.

After one year, the primary endpoint was the annual[3] relapse[4] rate. After two years, the primary endpoint was the cumulative probability of disability progression, defined by a 1-point or more increase in the EDSS score for initial scores of at least 1 or by a 1.5-point increase in the EDSS score for an initial score of 0, with the increase being maintained for 12 weeks.

The patients could continue to participate in the study when a progression occurred and had the opportunity to continue the treatment. Permission was given to receive another primary treatment for MS in combination with the treatment using natalizumab (IFN-ß or glatiramer acetate) or with interferon β1-a (azathioprine or mitoxantrone).

The secondary endpoints which were evaluated included the number of new lesions or newly enlarging T2-hyperintense lesions on the MRI, the number of Gadolinium (Gd+) enhancing lesions on the MRI and the percentage of patients without any relapse after 1 year.

1,171 patients with an average age of 39 years were randomised (ratio 1:1): natalizumab/interferon β1-a (n=589), placebo/interferon β1-a (n=582).

91% of patients had had at least two relapses and had at least two lesions on the MRI (McDonald criterion 1) and 8% of patients had had at least two relapses and one lesion on the MRI (McDonald criterion 2).

The median disease duration was 4 years (0 to 30 years). 64% of patients had had one MS relapse in the year prior to inclusion, 28% had had two relapses and 36% of patients had had at least two relapses.

Over 80% of patients had an EDSS score between 1 and 3.5, while 60% had a score between 1 and 2.5.

89% of patients had at least 9 T2 lesions and 34% of patients had at least 1 Gd+ lesion.
All patients had been treated with interferon β1-a for at least 12 months. Some patients had previously received corticosteroids (5%), glatiramer acetate (5%) or interferon beta-1b (9%).

1 McDonald WI, Compston A, Edan G, et al. Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001;50:121-7.

2 Kurtzke JF. Rating neurological impairment in multiple sclerosis : an expanded disability status scale (EDSS). Neurology 1983;33:1444-52.

3 Quotient of the total number of relapses divided by the total number of days participation, multiplied by 365 days.

4 Occurrence or recurrence of neurological symptoms, with no fever or infection, lasting at least 24 hours, accompanied by neurological signs during the neurological examination.

Efficacy data

229 patients stopped the treatment prematurely before the end of the double-blind period: 17**%** of patients on natalizumab versus 22% of patients treated with placebo. Adverse effects were the most common reason for discontinuing treatment: 8% of patients on natalizumab/interferon ß-1a *vs* 7% on placebo/interferon ß-1a.

1,003 patients were monitored for 2 years. 27/516 patients discontinued treatment in the natalizumab group and 34/487 patients in the placebo group. 83% of patients received at least 26 infusions. 89% of patients received at least 73 interferon ß-1a injections.

Corticosteroids, which were permitted as treatment during relapses, were administered systemically to 65% of patients treated with placebo/interferon β1-a and 43% of patients with natalizumab/interferon β1-a.

Results of the ITT analysis (n=589 natalizumab, n=582 placebo)

	1 year			2 years		
Endpoint	Natalizumab	Placebo	p	Natalizumab	Placebo	p
Annual relapse rate[†]	0.38 (0.33-0.45)	0.82 (0.72-0.92)	< 0.001	0.34 (0.29-0.39)	0.75 (0.67-0.84)	< 0.001
Disability Progression * (12 weeks) / Hazard ratio **				23%	29% 0.76 (0.61-0.96)	0.024
Disability Progression * (24 weeks) / Hazard ratio **				15%	18% 0.82 (0.61-1.09)	ns
Relapses – Number. patients (%)						
0	412 (70)	284 (49)		359 (61)	217 (37)	
1	135 (23)	180 (31)		158 (27)	164 (28)	
2	36 (6)	74 (13)		41 (7)	105 (18)	
≥ 3	6 (1)	44 (6)		31 (5)	96 (16)	
At least 1 relapse	30%	51%		39%	63%	
% patients with no relapses	67%	46%	< 0.001	54%	32%	< 0.001
T2 lesions on MRI [†]						
0	422 (72)	248 (43)		394 (67)	176 (30)	
1	108 (18)	114 (20)		76 (13)	55 (9)	
2	32 (5)	66 (11)		39 (7)	59 (10)	
≥ 3	27 (5)	154 (26)		80 (14)	292 (50)	
Mean	0.5	2.4	< 0.001	0 .9	5.4	< 0.001
Gd+ lesions on MRI [††]						
0	563 (96)	436(75)		568(96)	435(75)	
1	19(3)	73(13)		13(2)	67(12)	
2	3 (<1)	28(5)		4(<1)	33(6)	
≥ 3	4(<1)	45(8)		4(<1)	47(8)	
Mean	0,1	0,8		0,1	0,9	< 0.001

[†] Analysis adjusted to the number of relapses in the year prior to inclusion, the initial EDSS score (≤3.5 vs >3.5), Gd+ lesions (present or absent), age (<40 vs ≥40). Relapses which occurred after initiating alternative treatment have been ignored.

* Kaplan-Meier estimate of the percentage of patients with a disability progression. Patients who received another primary treatment without any disability progression were ignored.

** Analysis adjusted to the initial EDSS (≤3.5 vs >3.5)

[†] The mean value for the study population was assigned to the missing values. The baseline values and values after 1 year were available for 990 patients.

[†] Analysis adjusted to the initial number of T2 lesions (<9 vs ≥9)

Safety data

More than 99% of patients presented with at least one adverse event. The most common adverse events were headache (46% *vs* 44% on placebo), MS relapse (43% *vs* 67%), nasopharyngitis (39% *vs* 35%) and fatigue (32% *vs* 33%).

A severe event was observed in 18% of patients treated with natalizumab and 21% of patients treated with placebo. The most common of these events was relapse (5% *vs* 9% with placebo).

Among the severe events reported in connection with natalizumab, one case of progressive multifocal leucoencephalopathy (PML) was observed in a patient who had received concomitant treatment using interferon beta-1a for over 2 years.

Infusion reactions were reported in 24% of patients in the natalizumab group (severe 2%) *vs* 20% in the placebo group (severe <1%). Hypersensitivity reactions were observed in 3% of patients.

261 patients (44%) in the natalizumab group and 239 patients (41%) in the placebo group reported an adverse event considered by the investigator to be related to the treatment. The most common treatment-related events were headache (14% *vs* 11% treated with placebo), nausea (5% *vs* 4%), fatigue (5% *vs* 6%) and dizziness (2% *vs* 5%).

Immunogenicity: Anti-natalizumab antibodies were detected in 70 patients on natalizumab and persisted in 38 patients.

3.2. Adverse effects

a. Data resulting from the development studies

Patients were exposed to natalizumab for around 4,500 patient-years during the product's development for MS and Crohn's disease.

In the placebo-controlled studies 1,617 patients with MS were treated with natalizumab (n=1135 placebo). 79% were treated with a 300 mg dose every 4 weeks, while 69% of them were monitored for at least 1 year and 66% for 2 years or more.

During the development for MS and Crohn's disease, an event related to the infusion was observed in 24% of patients treated with natalizumab (18% of patients receiving the placebo).

Among the potentially treatment-related events reported during the 2 pivotal studies carried out in MS, the events related to the infusion such as dizziness, nausea, urticaria and shivering were more common with natalizumab than with placebo.

Hypersensitivity reactions occurred in about 4% of patients treated with natalizumab as monotherapy for MS and in 2% of patients treated with the natalizumab/interferon ß-1a combination. Anaphylactic / anaphylactoid reactions occurred in less than 1% of patients treated with natalizumab. These hypersensitivity reactions usually occurred during or in the hour after the infusion.

Anti-natalizumab antibodies were detected in 10% of patients tested (over 2,500). 6% of patients developed persistent antibodies (a positive test, with a second positive test at least 6 weeks after). The presence of persistent antibodies was associated with an increase in the frequency of hypersensitivity reactions and relapses.

There were two cases of PML, with one resulting in death, during the pivotal studies on patients with MS who had also received concomitant treatment with interferon beta-1a for over 2 years. A third case of PML, also fatal, was diagnosed later in a patient with Crohn's disease who had received prolonged immunosuppressive treatments.

The prevalence of other infections, including opportunistic infections was about 1.54 per patient-year for natalizumab and 1.5 for the placebo.

There was no difference in the incidences of malignant tumours between patients treated with natalizumab and those treated with placebo. Only longer-term safety data will make it possible to exclude any increase in the incidence of malignant tumours associated with natalizumab.

b. US post-marketing data

Natalizumab was launched on the US market on 23 November 2004, marketing was suspended in February 2005 as a result of two cases of PML, including one death. These two cases occurred in patients with MS who had received concomitant treatment using interferon beta-1a for over 2 years. A third case of PML, identified after the event in March 2005, occurred in a patient with Crohn's disease, who was assumed to have died as a result of a malignant astrocytoma, having received prolonged treatments with immunosuppressants.

Between its launch on the market and marketing suspension, around 7,000 patients were exposed to natalizumab in the US, where a majority of these patients only received 1 to 2 doses of the product.

After the file was re-evaluated by the FDA in April 2006, a new Marketing Authorisation was issued for natalizumab on 6 June 2006 for the following indication "Treatment of relapsing-remitting MS, as monotherapy". TYSABRI is usually recommended for patients who present an inadequate response or who do not tolerate other MS treatments.

3.3. Conclusion

a. Efficacy

The AFFIRM study compared the efficacy of natalizumab with that of the placebo for a period of 2 years in patients with relapsing-remitting MS, who had had at least one relapse during the year prior to inclusion.

The annual relapse rates after one year were 0.26 for natalizumab and 0.81 for the placebo. The analysis showed a 68% reduction in the rate compared with the placebo. After 2 years, the rates were 0.24 versus 0.73, giving a 68% reduction compared with the placebo.

After one year, 76% of patients on natalizumab and 53% of patients treated with placebo were relapse-free.

The estimate (Kaplan-Meier) of the percentage of patients who have had a disability progression after 2 years is 17% for natalizumab and 29% for the placebo. The risk of disability progression was therefore reduced by 42%.

The mean number of new or newly enlarged T2 lesions and the mean number of Gd+ lesions were reduced in the natalizumab group compared with the placebo group.

A post-hoc analysis carried out on a subgroup of patients with at least 2 relapses in the year prior to inclusion, with the presence of one or more Gadolinium-enhancing lesions, highlighted an 81% reduction in the annual relapse rate for natalizumab after two years (0.28 *vs* 1.46 for the placebo). The risk of disability progression was reduced by 53%.

The SENTINEL study compared the efficacy of natalizumab combined with interferon β1-a to that of the placebo combined with interferon β1-a for a period of 2 years in patients with relapsing-remitting MS, who had had at least one relapse on interferon β1-a during the year prior to inclusion.

The annual relapse rates after one year were 0.38 for natalizumab/interferon β1-a and 0.82 for the placebo/interferon β1-a. The analysis highlighted a 53% reduction in the annual relapse

rate versus placebo/interferon β1-a. After 2 years, the rates were 0.34 versus 0.75, giving a 55% risk reduction compared with the placebo.

After one year, 67% of patients treated with natalizumab/interferon β1-a and 46% of patients treated with placebo/interferon β1-a were relapse-free.

The estimate (Kaplan-Meier) of the percentage of patients who have had a disability progression after 2 years is 23% for natalizumab/interferon β1-a and 29% for the placebo/interferon β1-a. The risk of disability progression was therefore reduced by 24%.

After 2 years, the mean number of new or newly enlarged T2 lesions and the mean number of Gd+ lesions were reduced in the natalizumab/interferon β1-a group compared with the placebo/interferon β1-a group.

b. Safety

The safety profile is based on the clinical study data for 2,752 patients with MS (1,617 patients exposed to natalizumab) and 1,688 patients with Crohn's disease (1,182 patients exposed to natalizumab) and on the data for about 7,000 patients who received 1 to 3 infusions since the product was marketed in the US.

The most common adverse effects were: reactions related to the infusion during or in the hour after the infusion was given, nausea, vomiting, fatigue, fever, nasopharyngitis, urinary infections, arthralgia, pains in the limbs and headache.

Risks of hypersensitivity reactions and opportunistic infections were identified.

A European Risk Management Plan is currently being evaluated by the EMEA. The pharmacovigilance plan includes a programme for monitoring patients being treated with natalizumab in the US, aimed at evaluating the incidence of PML and cancers. A prospective observational study is planned in Europe and the US whose main objective is to determine the incidence of hypersensitivity reactions, opportunistic infections, cancers and adverse cardiovascular effects in patients being treated with TYSABRI. The risk minimisation plan includes a programme designed to provide training in product risks for healthcare professionals and patients.

A national pharmacovigilance monitoring operation is planned. The company has proposed the inclusion of 500 French patients in the observational study. The establishment of a French cohort study of the [exposed non exposed] type is being discussed..

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Multiple sclerosis is an incapacitating, progressive, chronic neurological disorder. It involves the selective, chronic inflammation and demyelinisation of the central nervous system. This disease causes multiple deficiencies, which vary according to its progression and the individual: motor and sensory disorders, sensory, vesicosphincteral and sexual dysfunctions, cognitive function and mood disorders. These deficiencies may considerably reduce patients' autonomy 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.

TYSABRI is intended as a preventive treatment against relapses and of disability progression with aggressive forms of relapsing-remitting multiple sclerosis.

The efficacy/adverse effects ratio of this medicinal product over the medium term (2 years) is modest. The efficacy/adverse effects ratio in the longer term remains to be determined.

Mitoxantrone is indicated also in aggressive forms of relapsing-remitting MS.

Public health benefit

MS represents a moderate public health burden, included the patient sub-population covered by the indication of TYSABRI. Improving the management of MS is a public health need. It is in particular one of the priorities identified by the GTNDO[1].

A review of the available data and existing treatments shows that this medicinal product is expected to have a moderate impact in terms of morbidity. TYSABRI should therefore be able to provide a supplementary response to the identified public health requirement.

However, due to uncertainty about the long-term safety of this phamaceutical product, transposability of the study results to real life is not guaranteed.

Consequently, the expected public health benefit of this product is slight.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual clinical benefit (IAB)

Given the current reservations raised by the safety data for natalizumab, TYSABRI provides a moderate improvement in actual benefit (Level III) for managing patients with an aggressive form of relapsing-remitting MS, defined by the occurrence of two or more incapacitating relapses during a year, and with one or more Gadolinium-enhancing lesions on the brain MRI or with a significant increase in the T2 lesion load compared with a recent MRI.

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.

However, three main progressive types can be distinguished: relapsing-remitting, secondary progressive and primary progressive.

The start of the disease takes the form of relapse and remission in about 85% of cases (relapsing-remitting forms) and is progressive in nature 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 secondary progressive MS occurs after the relapsing-remitting form is estimated as between 15 and 19 years according to the series. The primary progressive form is highlighted from its clinical onset by a progressive development, with or 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 2 relapses with sequelae) or a 2-point increase in the EDSS score in the previous 12 months.

1 National Technical Group for Defining Public Health Objectives (DGS)

Two immunosuppressants are currently indicated for these forms, currently without any possibility to measure their actual impact on the natural progression of the disease: mitoxantrone and natalizumab.

Mitoxantrone is reserved for aggressive forms of relapsing-remitting or secondary progressive multiple sclerosis. An aggressive form is defined by two relapses, where both have sequelae, during the previous 12 months and a new Gadolinium-enhancing lesion on an MRI performed less than 3 months before, or by a 2-point increase in the EDSS score during the previous 12 months and a new Gadolinium-enhancing lesion on an MRI performed less than 3 months before.

The short term haematological risk (neutropenia) and long term (leukaemia) requires regular monitoring of the patient. Treatment also requires regular monitoring of the patient's cardiac function through measuring the left ventricular ejection fraction. It must be limited to 6 infusions per patient (total cumulative dose of 120 mg) and must not be readministered to the same patient.

Natalizumab is indicated as monotherapy for the primary treatment of aggressive forms of relapsing-remitting MS. Due to safety concerns (risk of hypersensitivity reactions, opportunistic infections, especially PML and the potential risks of cancers), the treatment is limited to the following groups of patients:

- Patients who have failed to respond to a full and adequate course of a 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 in cranial MRI or at least 1 Gadolinium-enhancing lesion.

  or

- Patients with rapidly evolving severe relapsing-remitting MS, defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing lesions on the brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Hypersensitivity reactions which usually occur during infusion or within one hour of the completion of the infusion have been related to the use of natalizumab. These reactions may be severe systemic reactions.

Patients must be monitored at regular intervals in order to detect the appearance or deterioration of the symptoms or neurological signs which may cause PML. Prescribers must be warned that other opportunistic infections may occur with natalizumab.

Extending treatment beyond two years should be considered only after a reassessment of the benefit / risk ratio of the product.

4.4. Target population[1]

The calculated prevalence of MS in several regions in France is greater than 100/100 000 inhabitants, or 60 000 to 65 000 patients. Among these patients, 60% have a form of recurring-remitting MS (35 000-40 000 patients).

According to the data (centralised by the EDMUS Coordination Center in Lyon) of MS patients who were consulted or hospitalised in one of the 13 French centres that participate in the project (more than 18 000 files), 46% of the patients having a form of recurring-remitting MS had been treated with an interferon or other first line treatment. Among these patients, 55% had had at least one relapse during the year preceding inclusion. Among the non-treated patients, (54% of patients), 17% had had at least 2 relapses during the year.

1Livre blanc de la Sclérose en plaques - Steering Committee for General Multiple Sclerosis Conditions - April 2006

The SENTINEL study included patients with relapsing-remitting MS according to the McDonald[1] criteria, with lesions on the MRI compatible with MS and having at least one relapse during treatment with interferon β1-a during the year prior to inclusion. Among these patients, 89% presented at least 9 severe T2 lesions at the time of inclusion (34% had at least one Gadolinium-enhancing lesion).

The AFFIRM study included patients with relapsing-remitting MS according to the McDonald criteria, with lesions on the MRI compatible with MS and with at least one relapse during the year prior to inclusion. Among the patients included who had had at least 2 relapses in the year prior to inclusion, 55% had a Gadolinium-enhancing lesion at the time of inclusion.

According to the data from these two studies, the estimated population likely to receive TYSABRI is between 9 000 and 11 000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and at the posology in the Marketing Authorisation.

The Committee regrets the absence of any comparative study with mitoxantrone for the treatment of aggressive recurring-remitting forms of MS and the insufficient amount of data on natalizumab's efficacy as a monotherapy in the population defined by the indication.

Given the current reservations raised by the safety data for natalizumab, especially long term and the existence of a risk management plan, a reassessment of the file, especially of all the data available concerning natalizumab's safety, is planned in a year's time.

Furthermore, the Transparency Committee wishes to be provided with data on the follow-up of the patients with MS being treated with TYSABRI in France. The purpose of this is to document in a real-life treatment situation:
- the characteristics of the patients being treated;
- the conditions of use of this medicinal product, especially concomitant treatments;
- the impact of this treatment on the disability progression (EDSS score, transition to progressive form, etc), frequency of relapses and the quality of life for these patients.

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.

4.5.1 Packaging

Appropriate for the prescription conditions.

1 McDonald WI, Compston A, Edan G, et al. Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001;50:121-7.