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THE ITALIAN NATALIZUMAB REGISTRY

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On behalf of
The Italian Neurological Panel

EMA, London July 2011

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Background

Natalizumab is approved by **EMEA** as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

patients with high disease activity despite *adequate* course of a beta-interferon.

patients with rapidly evolving severe relapsing remitting multiple sclerosis.

Because of the established risk of PML and potential risk of cancer and lymphoma the approval has been delivered with a risk Management Plan promoted by EMEA.

The **Italian Medicine Agency** (AIFA) promoted a discussion within the Neurological Panel about the actions to increase the Benefit/Risk Ratio (BRR) and to monitor the safety

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To increase the expected benefit

The **Italian** Medicines Agency (AIFA) established more restrictive criteria to dispense and reimburse natalizumab, aiming to select patients with higher probability of developing disability

EMEA criteria

Patients with high disease who have failed to respond to a full and adequate course of treatment with 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 GD-enhancing lesion

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

Additional AIFA criteria

1) Treatment with immunomodulatory treatment in the previous 12 months
2) At least 2 relapses **or** 1 relapse with incomplete recovery in the previous year and current EDSS≥ 2

1) Incomplete recovery after relapses
2) Current EDSS ≥2

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To monitor safety and increase BRR

Implementation of WEB based Italian Registry:

- Access only to MS centers (206) authorized on the basis of predetermined professional competence and organizational features
- Central authorization to Tysabri treatment only for patients satisfying AIFA criteria
- Prompt communication of ADRs

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Data Flow

Patient Registration → **Eligibility (A – B)** → **Clinical Data** →
- **Treatment**
- **Follow-Up** (patient's status & expected drug reactions)
- **Adverse Drug Reactions**
- **End of treatment**

- ✓Active since jan 2007
- ✓Registry Web based
- ✓F/U every 3 months

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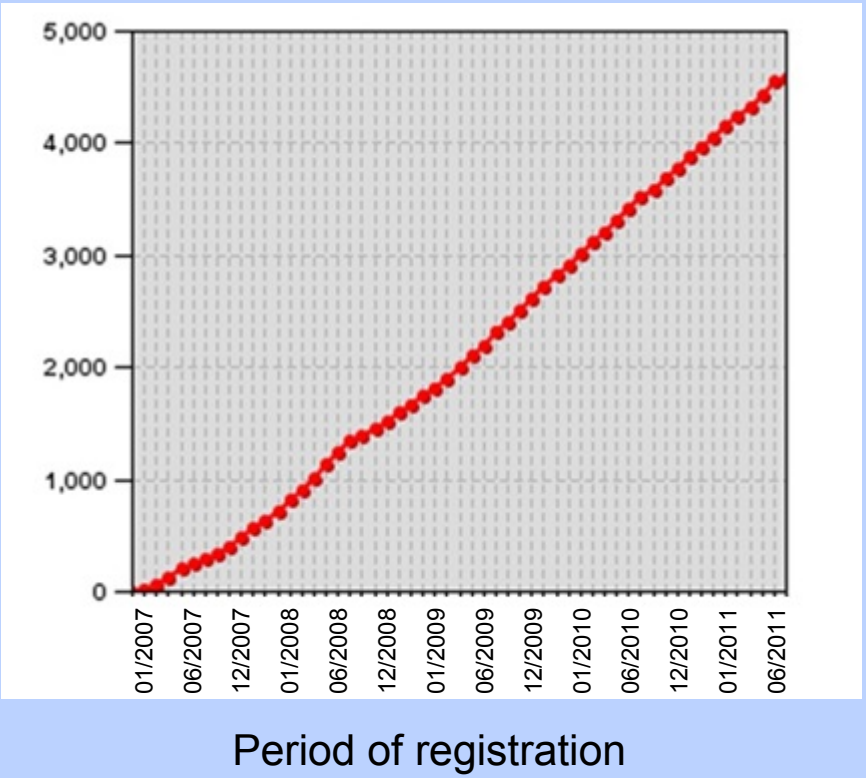
Patients enrolled

4523 pts (70% female) were enrolled in the registry: 85.4% as non-responders to β-interferon (group A), and 14.5% with aggressive RRMS (group B).

Elegibility Criteria	N. enrolled patients	%
A	3864	85.4
B	658	14.5
Tot	4523	100.0

Data updated to July 13 2011



Clinical features at baseline

Group A	# Patients	Disease duration (yr)	Mean age at entry (yr)
F	70% (2711)	10.1	36.5
M	30% (1153)	9.8	37
Total	3864	10	36.7

Group B	# Patients	Disease duration (yr)	Mean age at entry (yr)
F	65% (431)	5.1	33
M	35% (227)	4.4	32.3
Total	658	4.8	32.7

Patients under treatment

N. Cycles	Patients
<12 months	**35.8%** (1591)
12-17 months	**15.5%** (688)
18-23 months	**15.5%** (688)
≥24 months	**34.7%** (1542)
Total	**4441**

Previous Therapies

- Immunosuppressants (Aza, Cyclof, Methotrex, Mitox): 1173 (26.41%) out of 4441

Italian Registry vs AFFIRM study: comparison of populations
Clinical features at baseline

	Group A	Group B	AFFIRM
Total number	3864	658	627
Age (yr)	36.7	32.7	36
Disease duration (yr)	10	4.8	5
EDSS mean (range)	3.5 (1-8)	3.5 (1-7)	2.3 (0-5)

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Italian Registry vs AFFIRM study: comparison of populations
Relapses

N. relapses in last 12 months	AFFIRM	Italian Registry	
		Group A	Group B
0	<1% (6)	0.3% (11)	0.3% (2)
1	59% (368)	27.7% (1063)	1.1% (7)
2	31% (197)	48.9% (1878)	57.6% (378)
≥3	9% (56)	23.2% (889)	41.1% (269)
Relapses with residual deficit			
Yes	ND	86% (3302)	98.9% (649)
No	ND	14% (539)	1.1% (7)

Italian Registry vs AFFIRM study: comparison of populations Neuroradiological features

New lesions on GD-MRI within 12 m	AFFIRM	Italian Registry	
		Group A	Group B
Yes	**49%** (307)	**59.2%** (2272)	**76.5%** (502)
No	**51%** (319)	**40.8%** (1569)	**23.5%** (154)
At least 9 T2 lesions			
Yes	ND	**98.6%** (3789)	**98.3%** (645)
No	ND	**1.4%** (52)	**1.7%** (11)
Increasing T2 lesions within 12 m			
Yes	ND	**77.7%** (2985)	**93%** (610)
No	ND	**22.3%** (856)	**7%** (46)

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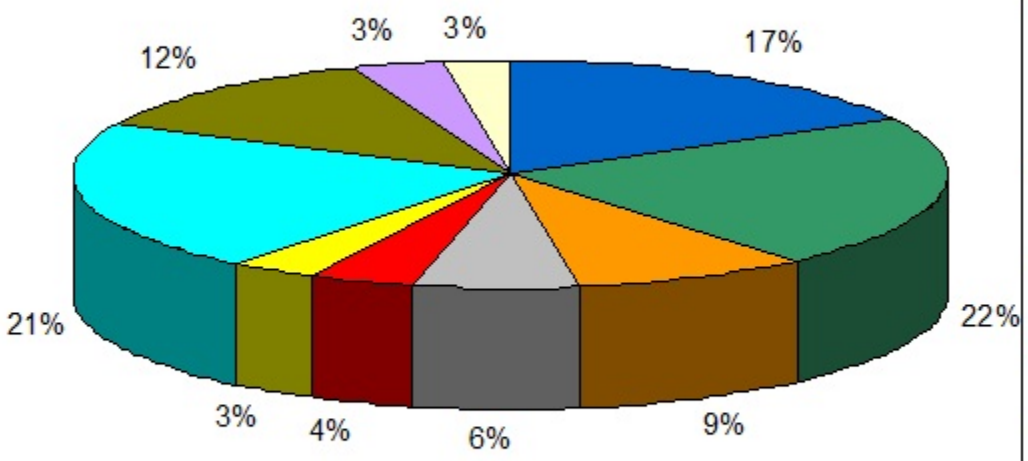
Mild Adverse Drug Reactions

357 (7.9%) out of 4523 patients reported at least 1 Mild ADR



- Allergic symptoms
- Infections
- Gastrointestinal disease
- Blood disease
- Cardiovascular disease
- Neurological disease (not MS correlated)
- MS relapses
- Systemic disease
- Osteoarticular and skeletal muscle disease
- Reproductive system disease

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Serious Adverse Drug Reactions

Meningitis	1
Relapse of multiple sclerosis	4
Partial seizures	1
Inflammation CNS †	1
Urinary incontinence	1
Urinary tract infection	2
Partial Gastrectomy	1
Anaphilactoid reaction	1
Urticaria	2
Cardiovascular failure	1
Intentional self-arm	1
Myocarditis	1
Appendicitis	1
Sistemic CMV infection	1
Psoriasis	1
Hemorrhagic Cystitis	1
High fever	1

An adverse drug reaction is defined serious if results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage.

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Serious Adverse Drug Reactions

Breast cancer	3
Cardiac arrest †	1
Melanoma with superficial diffusion	1
Psychosis	2
Depression	1
Persecution delusions	1
Manic-depressive diseaese	2
Epilepsy state	1
Convulsion	1
Stomach cancer IV stadium	1
Spontaneous abortion	2
Deafness	1
Intracranial aneurysm	1
Toxic encephalopathy	2
Liver failure	1
Jaundice	1
Mixed delusions	1
Ovarian cyst	1
Arthritic pain	1

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Serious Adverse Drug Reactions

Atrial fibrillation	1
Adenocarcinoma	1
Testis cancer	1
Renal cell carcinoma II stadium	1
Follicular thyroid cancer	1
Cervical cancer stadium III	1
Colon cancer	1
PML	8
Red cells aplasia	1
Raynaud's phenomenon	1
Herpes Zoster neurological infection	1
Hepatopathy Edema	1
Meningioma ben	1
Emorragia cereb	1
Bacterial Pneumonia	1
Bleeding	1
Suicide attempt	1
Total	73

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Adverse Drug Reactions Summary

- 430 (9.5%) pts reported at least one Adverse Drug Reaction (mild and serious)

- 73 pts (1.6%) reported a Serious Adverse Drug Reaction

- **2 deaths:**
  - 1 cardiac arrest
  - 1 inflammation CNS

- 170 pts (3.8%) ended drug treatment due to Adverse Drug Reaction

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PML CASES

Pt	NZ Cycles	Previous therapy	Tx Duration months	Clinical presentation	Treatment	Outcome	RMN features	Blood PCR JCV (+)	CSF PCR JCV (+)
1	29	Other Mitox	0,92 2,03	Cognitive deficits	Plasm	Unchanged or worsened	Cortical, subcortical extensive hyperi T2 lesions, bilateral in fronto-parietal regions	Yes	No
2	34	Avonex Rebif 22 Mitox	3,67 33,08 33,74	Cognitive and motor disturbances	Plasm	Unchanged or worsened	WM T2 hyper in right frontal, temporal, occipital and superior cerebellar regions; lack of GD +	Yes	Yes
3	31	Avonex	24,1	Visual field deficits			Extensive subcortical parieto-occipital T2 lesion with involvment of U fibers	No	Yes
4	19	Betaferon Mitox	2,98 30,98	Speech deficits, facial emispasm, extrapiramidal symptoms	Hosp. Steroids Copax	Unchanged or worsened	T2 hyperi lesions in right lenticular nucleus and right subcortical frontal region; lack of GD +	Yes	Yes

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PML CASES

Pt	NZ Cycles	Previous therapy	Tx Duration months	Clinical presentation	Treatment	Outcome	RMN features	Blood PCR JCV (+)	CSF PCR JCV (+)
5	17	Aza	0,92	Cognitive, speech and motor disturbances	Plasma	Improved	Subcortical parieto-occipital lesion T1 hypointense	Yes	Yes
		Mitox	5,02						
		Betaferon	48,98						
6	44	Glatiramer	41,48	Epilepsy; Behavioral disturbances	Steroids	Improved			Yes
		Rebif 44	34,26						
		Mitox	5,97						
7	22	Glatiramer	12,59	Hemiplegia	Plasma Mirtazapina Meflochina	Unchanged or worsened			Yes
		Rebif 44	1,25						
		Mitox	14,89						
		Cyclophos	15,87						
8	34	Avonex	37,9		Plasma Mirtazapina Meflochina	Unchanged or worsened			Yes
		Rebif 22	15,8						
		Rebif 44	59,02						

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Reasons for end of treatment

Group A

Reasons	N.	%
End of therapeutical cycle	157	21.4
Ineffective	109	14.9
ADR (serious and minor)	146	19.9
Positivity to antibodies	93	12.7
Moving	3	0.4
Missed (or poor) compliance	54	7.4
Pregnancy	30	4.1
Loss to follow-up	12	1.6
Death	2	0.3
Other	126	17.2
Total	732	100

Group B

Reasons	N.	%
End of therapeutical cycle	36	30
Positivity to antibodies	14	11.7
Ineffective	9	7.5
Loss to follow-up	2	1.7
ADR	24	20
Moving	1	0.8
Pregnancy	3	2.5
Missed (or poor) compliace	8	6.7
Other	23	19.2
Total	120	100

N. administrations	N. patients	%
0	1	0.1
1	32	3.8
2	65	7.6
3	32	3.8
4	25	2.9
5	32	3.8
6	31	3.6
7	32	3.8
8	30	3.5
9	23	2.7
10	25	2.9
11	28	3.3
12	34	4.0
13	23	2.7
14	25	2.9
15	23	2.7
16	14	1.6
17	25	2.9
18	16	1.9
19	8	0.9
20	12	1.4

Patients with end of treatment and administrations number

852 (18.8%) with end of treatment specified out of 4523

Mean number of administrations: 16 (range 0-48)

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Patients with end of treatment and administrations number

N. administrations	N. patients	%
21	9	1.1
22	22	2.6
23	12	1.4
24	61	7.2
25	26	3.1
26	17	2.0
27	18	2.1
28	16	1.9
29	14	1.6
30	8	0.9
31	15	1.8
32	16	1.9
33	10	1.2
34	8	0.9
35	6	0.7
36	17	2.0
37	5	0.6
38	5	0.6
39	6	0.7
40	4	0.5

N. administrations	N. patients	%
41	4	0.5
42	4	0.5
43	2	0.2
44	5	0.6
45	2	0.2
46	3	0.4
48	1	0.1
Total	852	100.0

852 (18.8%) with end of treatment specified out of 4523

Mean number of administrations: 16 (range 0-48)

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Relapses

667 patients had at least 1 relapse
Based on 2737 (76.6%) patients treated for at least 6 months

Relapses during therapy	Relapses during 12 months before therapy								
	1	2	3	4	5	6	7	8	9
	N. pts	N. pts	N. pts	N. pts	N. pts	N. pts	N. pts	N. pts	N. pts
1	99	209	98	31	11	6	1	0	1
2	13	62	30	14	4	5	2	0	0
3	7	27	18	5	1	0	0	0	0
4	1	8	5	1	3	0	0	0	0
5	0	0	1	0	1	0	0	0	0
Total	120	306	152	51	20	11	3	0	1

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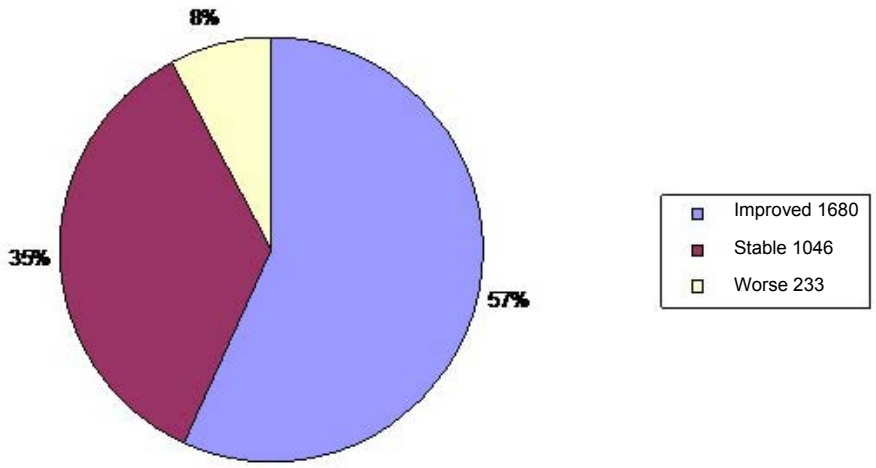
EDSS at the last follow-up

2959 (65.4%) with at least 1 FUP out of 4523

Condition	Patients	%
Improved	1680	56.8
Stable	1046	35.3
Worse	233	7.9
Total	2959	100.0



Improved: confirmed increase of EDSS

$1 \leq 5.5$

$0.5 > 5.5$

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