HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

05 March 2014

AUBAGIO 14 mg, film-coated tablet

B/28 tablets (CIP: 3400927499890)

Applicant: GENZYME SAS

INN	Teriflunomide
ATC code	L04AA31 (Selective immunosuppressants)
Reason for the review	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123 2)
Indication concerned	**"AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS)."**

AB	**Substantial**
IAB	**In the absence of a conclusive comparative study versus active treatment, AUBAGIO does not provide an improvement in actual benefit (IAB V, non-existent) in the treatment of relapsing-remitting multiple sclerosis (RRMS). However, the Transparency Committee recognises the benefit of providing an oral proprietary medicinal product as an alternative to interferon beta and glatiramer acetate.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	26/08/2013
Prescribing and dispensing conditions/special status	List I Medicine requiring special monitoring during treatment. Prescription restricted to specialists in and departments of NEUROLOGY

ATC Classification	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AA	Selective immunosuppressants
	L04AA31	teriflunomide

02 BACKGROUND

This is an application for inclusion for reimbursement of AUBAGIO (teriflunomide), an immunosuppressant administered orally, indicated in the long-term treatment for adults patients with the relapsing-remitting form of multiple sclerosis.
Teriflunomide is the predominant active metabolite of leflunomide, marketed since 1999 under the proprietary medicinal product name ARAVA in the treatment of rheumatoid arthritis and psoriatic arthritis.

03 THERAPEUTIC INDICATION

"AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS)."

04 DOSAGE

The recommended dose is one 14 mg tablet once daily with or without food.

Pharmacokinetic note:
Teriflunomide is excreted through the digestive tract. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. Elimination of teriflunomide may be accelerated by the administration of cholestyramine or activated carbon.

Please refer to the SPC for more detailed information.

05 THERAPEUTIC NEED

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. It is a progressive and incapacitating neurological disease and the leading cause of non-traumatic disability in young adults in France.[1]
Its general progression and prognosis are heterogeneous and not considered very predictable.[2]
Within the progressive forms of MS, we can distinguish:

- Relapsing-remitting forms (RRMS), which occur the most and which are characterised by the presence of relapses without there being any disability progression between the relapses;
- So-called secondary progressive multiple sclerosis (SPMS), secondary to the relapsing-remitting forms and characterised by a sustained build-up of disability, completely independent of any relapses;
- Primary progressive multiple sclerosis (PPMS) characterised by symptoms which gradually get worse following their onset with no remission, completely independent of any relapses.

The long-term treatment for RRMS is based on first-line interferon beta (interferon beta-1a and 1b) and glatiramer acetate.
The aim of these treatments is to reduce the frequency of relapses and the progression of the disability in the short-term. There is currently no evidence that these products alter the progression of the disability in the long-term.[3]
Natalizumab (TYSABRI) and fingolimod (GILENYA) have a Marketing Authorisation indication restricted to very active forms of RRMS.[4]

1 C. Confavreux et S. Vukusic. "L'évolution naturelle de la sclérose en plaques" Rev. Prat 2006;. 56: 1313-20,
2 Moreau T. Vie quotidienne et sclérose en plaques. Rev Neurol (Paris) 2001; 157(8-9): 1157-62
3 HAS. Re-assessment of interferon beta and glatiramer acetate in multiple sclerosis. June 2010. www.has-sante.fr
4 Very active forms of RRMS correspond to the following disease groups:
- patients with a very active form of disease despite treatment with full interferon beta, which is usually well conducted, lasting at least one year. The patients must have presented with at least one relapse during the previous year whilst under treatment and must present with at least nine T2 hyperintense lesions with cerebral MRI or at least one Gd-enhancing lesion. A "non-responder" may also be defined as a patient for whom the level of relapses has not changed or has increased compared with the previous year or who continues to have severe relapses,
- patients with a severe form and rapid progression, defined by two or more incapacitating relapses within one year combined with one or more Gd-enhancing lesion(s) shown on the cerebral MRI or a significant increase in the T2 lesion load compared with a recent previous MRI scan.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The AUBAGIO comparators are immunomodulating medicinal products, interferon beta and glatiramer acetate, indicated as a first-line therapy in the treatment of RRMS. They are administered subcutaneously or intramuscularly at varied rhythms (1 to 7 times a week).
Natalizumab (TYSABRI) and fingolimod (GILENYA) have an indication restricted to very active forms of RRMS.4

Table 1. List of proprietary medicinal products indicated for the treatment of MS.

Proprietary Medicinal product (INN) COMPANY	Admin.	Indications*	Date of TC opinion	AB[$]	IAB[$]	Reimbursement
AVONEX (IFN beta-1a) BIOGEN IDEC	IM 1/week	• RRMS • Patients with a single demyelinating event at high risk of MS.	02/06/2010	Substantial	IAB III in treatment	Yes
REBIF (IFN beta-1a) MERCK SERONO	SC 3/week	• RRMS	02/06/2010	Substantial	IAB III in treatment	Yes
		• Patients with a single demyelinating event at high risk of MS.	20/06/2012	Substantial	IAB III in treatment	Yes
BETAFERON (IFN beta-1b) BAYER SANTE	SC 1 day/2	• RRMS • Patients with a single demyelinating event at high risk of MS.	02/06/2010	Substantial	IAB III in treatment	Yes
EXTAVIA (IFN beta-1b) NOVARTIS PHARMA	SC 1 day/2	• Secondary progressive MS	21/07/2010	Substantial	IAB V compared with BETAFERON	Yes
COPAXONE (glatiramer acetate) TEVA PHARMA	SC 1/day	• RRMS	02/06/2010	Substantial	IAB III in treatment	Yes
		• Patients with a single demyelinating event at high risk of MS.	06/04/2011	Substantial	IAB V in treatment	Yes
For information						
TYSABRI (natalizumab) BIOGEN IDEC	IV infusion 1/month	• Patients with a very active form of RRMS despite interferon beta treatment. • Rapidly evolving severe RRMS	29/02/2012	Substantial in the aggressive forms of RRMS	IAB III in the treatment of patients with an aggressive form of RRMS[§]	Yes
GILENYA (fingolimod) NOVARTIS	Oral		20/07/2011	Substantial	IAB IV in treatment	Yes

* please refer to the SPC of the proprietary medicinal products for the detailed wording of the indications.
$ please refer to the opinion of the Transparency Committee for the full wording of the AB and IAB.
§ defined by the occurrence of two or more incapacitating relapses within one year combined with one or more Gd enhancing lesion(s) shown on the cerebral MRI or a significant increase in the T2 lesion load compared with a recent previous MRI scan.

◗ Conclusion

The AUBAGIO comparators are interferon beta and glatiramer acetate, indicated as a first-line therapy in the treatment of RRMS.

07 ANALYSIS OF AVAILABLE DATA

The record presented by the company is based on four studies:
- Two phase III, controlled, double-blind studies, TEMSO and TOWER, which evaluated the efficacy of teriflunomide versus placebo on the reduction in the frequency of relapses in patients with relapsing MS; at the end of the TEMSO study, the patients had the opportunity to take part in a 5-year open-label extension phase whose objective was to evaluate the long-term safety of teriflunomide;
- A phase III, open-label TENERE study which compared teriflunomide and interferon beta-1a (REBIF) on the time to treatment failure in patients with relapsing MS;
- A phase II, controlled, double-blind study which evaluated the efficacy of teriflunomide versus placebo on the MRI parameters in patients with relapsing MS for 42 weeks. The results of this phase II study are consistent with those of the two phase III studies versus placebo and will therefore not be detailed here.

07.1 Efficacy

7.1.1 TEMSO[5] study

7.1.1.1 Study design

The TEMSO study is a multicentre, randomised, double-blind versus placebo study aiming to evaluate the efficacy and safety of teriflunomide at doses of 7 and 14 mg in patients with relapsing MS.

The main aim was to demonstrate the efficacy of teriflunomide on the reduction in the frequency of relapses.

The inclusion criteria for the patients were as follows:
- To be between 18 and 55 years old;
- To have relapsing MS with or without progression[6] defined according to McDonald criteria with an EDSS score[7] ≤ 5.5;
- To have presented with at least one relapse in the year prior to inclusion or at least 2 relapses in the 2 years prior to inclusion;
- To have not been treated with corticosteroids in the 4 weeks prior to randomisation.

Patients were randomised to three groups (1:1:1 ratio):
- Placebo;
- Teriflunomide 7 mg;
- Teriflunomide 14 mg.

The treatment lasted 108 weeks.

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[5] P. O'Connor et al. "Randomized trial of oral teriflunomide for relapsing multiple sclerosis" N Eng J Med 2011; 365: 1293-1303.

[6] I.e. RRMS, SPMS or PPMS

[7] The EDSS (Expended Disability Status Scale) scale assesses the severity of the disability. The neurological examination is divided into eight functional areas (FA). A severity score increasing from 0 to 6 or 7 is attributed to each FA (four major ones: pyramidal function, cerebellar function, sensory function and brainstem function; four minor ones; vesicosphincteral function, visual function, cerebral (or mental) function and others). The overall EDSS score ranges from 0 (normal neurological examination) to 10 (death). The overall score of the scale is measured on a 20-point scale (0 to 10 by half-points). Up to level 3.5, the score obtained in each FA and the number of FS achieved automatically determines the EDSS score. From 4 to 7, the definition of each level is also indicated by inability to walk (ability to walk without stopping, need for assistance). A score of 5.5 is "a stroll without assistance or rest at a distance of about 100 metres: disability sufficient to exclude any full activity during the day".

The primary evaluation endpoint was the annualised relapse rate, defined as the number of relapses confirmed by patient-year.
A relapse was defined as the onset of a new clinical sign or symptom - or worsening of a pre-existing clinical sign or symptom - lasting at least 24 hours, with no fever. Each relapse should be confirmed by a second neurologist and meet the following objective criteria:

- an increase of 1 point in at least two functional areas or 2 points in one functional area7 (except digestive, urinary and cognitive functions) compared with the previous evaluation considered stable on a clinical level;
- or an increase of 0.5 point in the EDSS score (if the EDSS score = 0, an increase of 1.0 was needed) compared with the previous evaluation.

The principal secondary endpoints were:

- progression of the disability defined by sustained progression and confirmed at 3 months by 1 point in the EDSS score for an EDSS score at baseline ≤ 5.5 or 0.5 point for an EDSS score > 5.5;
- the percentage of patients without relapses;
- the MRI parameters (total number of lesions, number and volume of Gd-enhancing lesions, volume of T1 hypointense lesions, volume of T2 lesions and cerebral atrophy);
- quality of life (EQ-5D, SF-36 scales) and fatigue (Fatigue Impact Scale).

At the end of the TEMSO study, the patients had the opportunity to take part in a 5-year extension phase whose main objective was to evaluate the long-term safety of teriflunomide. The results of this extension study are presented in the safety section.

7.1.1.2 Results

A total of 1086 patients were included in the intention-to-treat (ITT) analysis. Overall, 26.7% ended the study prematurely: 104/363 in the placebo group, 91/366 in the teriflunomide 7 mg group and 95/359 in the teriflunomide 14 mg group.

Patient characteristics

The average age of the patients was 37.9 ± 8.8 years and the median time since initial MS diagnosis was 3.5 years (minimum: 0.1; maximum: 31.6).
A large majority of patients (91.5%) presented with RRMS; 51 patients (4.7%) had SPMS and 42 patients (3.9%) had PPMS.
The median EDSS score at baseline was 2.5; 249 patients (22.9 %) had an EDSS score > 3.5 at baseline.
Overall, 73 % of patients had not received long-term treatment (interferon or glatiramer acetate) for their MS in the 2 years prior to their inclusion.

Primary efficacy endpoint:

The frequency of relapses was significantly reduced in the teriflunomide groups compared with the placebo group: the reduction in the frequency of relapses was 31.2 % in the teriflunomide 7 mg group ($p < 0.01$ versus placebo) and 31.5 % in the teriflunomide 14 mg group ($p < 0.001$ versus placebo, see Table 2).

Table 2. Annualised relapse rate in the TEMSO study.

	Placebo n = 363	Teriflunomide 7 mg n = 365	Teriflunomide 14 mg n = 358
Number of patients with ≥ 1 relapse, n (%)	184 (50.7)	154 (42.2)	141 (39.4)
Total number of relapses	335	233	227
Total number of patient-years	627.7	633.7	615.0
Adjusted annualised relapse rate*			
%	0.539	0.370	0.369
[95% CI]	[0.466 to 0.623]	[0.318 to 0.432]	[0.308 to 0.441]
RR		0.688	0.685
[95% CI]		[0.563 to 0.839]	[0.554 to 0.847]
p value		0.0002	0.0005

* derivative of the Poisson distribution. The adjustment variables were the treatment, the EDSS score at baseline and the region.

Secondary endpoints

- Disability progression

The risk of disability progression confirmed at 3 months was reduced in the teriflunomide 14 mg group compared with the placebo with group (Hazard ratio [HR]: 0.702; 95 % CI [0.506 to 0.973]). The reduction in the risk of disability progression was not demonstrated in the teriflunomide 7 mg group.

No difference between teriflunomide 7 and 14 mg and the placebo was observed in terms of the risk of disability progression confirmed at 6 months (p = 0.1459; p = 0.1259).

- Percentage of patients without relapses

The estimated percentage of patients without relapse after 108 weeks (Kaplan-Meier estimator) was 45.6 % (95 % CI [0.402 to 0.510]) in the placebo group, 53.7 % (95 % CI [0.483 to 0.591]) in the teriflunomide 7 mg group (p < 0.01 versus placebo) and 56.5 % (95 % CI [0.510 to 0.620]) in the teriflunomide 14 mg group (p < 0.01 versus placebo).

- MRI parameters

The results on the MRI parameters (lesion load, number of lesions enhanced by gadolinium, T1 hypointense lesions and T2 lesions) highlighted the efficacy of teriflunomide over the placebo.

- Criteria evaluated by the patients

No difference between teriflunomide and the placebo was observed in terms of fatigue and quality of life evaluated by the patients.

Sub-group analyses (considered in the protocol)[8]

Several sub-group analyses according to patient characteristics at baseline (EDSS score, number of relapses before inclusion, type of MS and treatment in the two years preceding inclusion) were performed.

The efficacy of teriflunomide on the annualised relapse rate and on the disability progression confirmed at 3 months was homogeneous in the different sub-groups.

[8] A. Miller et al. "Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis" Mult. Scler., vol. 18, pp. 1625-1632, 2012.

7.1.2 TOWER study

7.1.2.1 Study design

The TOWER study is a multicentre randomised double-blind versus placebo study aiming to evaluate the efficacy and safety of teriflunomide in patients with relapsing MS.
The study design of the TOWER study is exactly like that of the TEMSO study. The inclusion criteria for the patients were identical.
The patients were randomised to three groups (1:1:1 ratio): placebo, teriflunomide 7 mg or teriflunomide 14 mg, administered in one daily oral dose.
The duration of treatment was 48 weeks at least (the patients received the treatment until the end of the treatment period of the last patient included).
The primary evaluation endpoint was the annualised relapse rate, defined as the number of relapses confirmed by patient-year.

7.1.2.2 Results

A total of 1165 patients were included in the ITT analysis. Overall, 32.9 % ended the study prematurely: 125/389 in the placebo group, 134/408 in the teriflunomide 7 mg group and 126/372 in the teriflunomide 14 mg group.

Patient characteristics

The average age of the patients was 37.9 ± 9.3 years and the median time since initial MS diagnosis was 3.17 years (minimum: 0; maximum: 33.8).
A very large majority of patients (97.5 %) presented with relapsing-remitting MS.
The median EDSS score at baseline was 2.5; 284 patients (24.3 %) had an EDSS score > 3.5 at baseline.
Overall, 67 % of patients had not received long-term treatment (interferon or glatiramer acetate) for their MS in the 2 years prior to their inclusion.

Primary efficacy endpoint:

The frequency of relapses was significantly reduced in the teriflunomide groups compared with the placebo group: the reduction in the frequency of relapses was 22.3 % in the teriflunomide 7 mg group ($p < 0.05$ versus placebo) and 36.3 % in the teriflunomide 14 mg group ($p < 0.001$ versus placebo, see Table 3).

Table 3. Annualised relapse rate in the TOWER study.

	Placebo n = 363	Teriflunomide 7 mg n = 365	Teriflunomide 14 mg n = 358
Number of patients with ≥ 1 relapse, n (%)	186 (47.9)	144 (35.4)	122 (33.0)
Total number of relapses	296	235	177
Total number of patient-years	608.4	614.0	573.6
Adjusted annualised relapse rate*			
%	0.501	0.389	0.319
[95 % CI]	[0.432 to 0.581]	[0.332 to 0.457]	[0.267 to 0.381]
RR		0.777	0.637
[95 % CI]		[0.630 to 0.958]	[0.512 to 0.793]
p value		0.0189	0.0001

* derivative of the Poisson distribution. The adjustment variables were the treatment, the EDSS score at baseline and the region.

Secondary endpoints

- Disability progression

The risk of disability progression confirmed at 3 months was reduced in the teriflunomide 14 mg group compared with the placebo group (Hazard ratio [HR]: 0.685; 95 % CI [0.467 to 1.004]; p = 0.0442). No difference was observed in terms of the risk of disability progression between the teriflunomide 7 mg group and the placebo group.

No difference between teriflunomide 7 and 14 mg and the placebo was observed in terms of the risk of disability progression confirmed at 6 months (p = 0.8218; p = 0.4456).

- Percentage of patients without relapses

The estimated percentage of patients without relapse (Kaplan Meier estimator) after 108 weeks was 37.7 % (95 % CI [0.302 to 0.452]) in the placebo group, 55.4 % (95 % CI [0.488 to 0.620]) in the teriflunomide 7 mg group (p < 0.01 versus placebo) and 51.5 % (CI 95 % [0.502 to 0.595]) in the teriflunomide 14 mg group (p < 0.01 versus placebo).

- Criteria evaluated by the patients

No difference between teriflunomide and the placebo was observed in terms of fatigue and quality of life evaluated by the patients.

7.1.3 TENERE[9] study

7.1.3.1 Study design

The TENERE study is a multicentre randomised open-label study which compared the efficacy and safety of teriflunomide and interferon beta-1a (REBIF) in patients with relapsing MS.

The main aim was to demonstrate the superiority of teriflunomide at doses of 7 and 14 mg comparatively with interferon beta-1a in terms of the time to treatment failure.

The inclusion criteria of patients was identical to those of the TEMSO and TOWER studies.

Patients were randomised to three groups (1:1:1 ratio):
- Teriflunomide 7 mg, one tablet/day;
- Teriflunomide 14 mg, one tablet/day;
- REBIF 22 or 44 mcg, three subcutaneous injections/week (progressive increase in doses for the first four weeks).

The duration of treatment was 48 weeks at least (the patients received the treatment until the end of the 48-week treatment period of the last patient included).

The study was performed open-label. The two doses of teriflunomide were administered blindly.
Two neurologists took part in the study in each centre: a "treating" neurologist in charge of making sure the patients were eligible, the administration and evaluation of the safety of treatments and an "evaluating" neurologist in charge of clinical examinations and evaluation of the disability.

The primary endpoint was the time to treatment failure.
Treatment failure was defined as the occurrence of a new relapse or the definitive discontinuation of the treatment, whatever the cause.

The principal secondary endpoints were the annualised relapse rate and the evaluation of fatigue and patient satisfaction (the TSQM scale[10]).

[9] Vermersch P et al. for the TENERE Trial Group. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler J. 2013; online first version.

[10] The TSQM (Treatment Satisfaction Questionnaire for Medication) questionnaire is a self-questionnaire which assesses patient satisfaction according to four dimensions: satisfaction in terms of efficacy (three questions), adverse events (five questions), convenience (three questions) and general satisfaction (three questions). The score for each dimension is between 0 and 100 and the higher the score the greater the satisfaction.

7.1.3.2 Results

A total of 324 patients were included in the ITT analysis. In total, 22.2 % ended the study prematurely: 20/109 in the teriflunomide 7 mg group, 22/111 in the teriflunomide 14 mg group, 30/104 in the REBIF group.

Patient characteristics

The average age of the patients was 36.3 ± 10 years and the median time since initial MS diagnosis was 1 year (0.88; minimum: 0.1; maximum: 36.5).
A very large majority of patients (99.1 %) presented with relapsing-remitting MS.
The median EDSS score at baseline was 2.0; 40 patients (12.3 %) had an EDSS score > 3.5 at baseline.
Overall, 81 % of patients had not received long-term treatment (interferon or glatiramer acetate) for their MS in the 2 years prior to their inclusion.

Primary efficacy endpoint:

Teriflunomide did not show any superiority over REBIF in terms of the time to treatment failure (see Table 4).

Table 4. Treatment failure in the TENERE study.

	Teriflunomide 7 mg (*n*=109)	Teriflunomide 14 mg (*n*=111)	Interferon beta-1a SC (*n*=104)
Number of patients experiencing treatment failure	53 (48.6%)	42 (37.8%)	44 (42.3%)
Relapse	**46 (42.2%)**	**26 (23.4%)**	**16 (15.4%)**
Definitive treatment discontinuation	7 (6.4%)	15 (13.5%)	25 (24.0%)
Other reason for failure	0	1 (0.9%)	3 (2.9%)
Likelihood of failure estimated according to Kaplan-Meier [95% CI]			
24 weeks	0.257 [0.175-0.339]	0.243 [0.163-0.323]	0.298 [0.210-0.386]
48 weeks	0.358 [0.268-0.448]	0.333 [0.246-0.421]	0.365 [0.273-0.458]
96 weeks	0.588 [0.461-0.714]	0.411 [0.309-0.514]	0.444 [0.343-0.544]
HR (95 % CI)	1.122 [0.752-1.674]	0.861 [0.564-1.314]	-
p value	0.5190	0.5953	-

Secondary endpoints

- Annualised relapse rate

The adjusted annualised relapse rate was 0.410 for teriflunomide 7 mg, 0.259 for teriflunomide 14 mg and 0.216 for REBIF.
Most patients did not have any relapse during the study: teriflunomide 7 mg (57.8 %), teriflunomide 14 mg (76.6 %) and REBIF (84.6 %).

- Evaluation criteria reported by the patients

Patient satisfaction regarding their treatment was evaluated after 48 weeks by the TSQM questionnaire.[10] Patient satisfaction was higher in the patients treated with teriflunomide compared with those receiving REBIF for three dimensions: overall satisfaction (teriflunomide 14 mg: 68.8 versus REBIF: 61.0; p = 0.02), adverse effects (teriflunomide 14 mg: 93.1 versus REBIF: 71.4; p < 0.0001) and ease of use (teriflunomide 14 mg: 89.9 versus REBIF: 61.9; p < 0.0001. No difference was observed in terms of the dimension of efficacy (teriflunomide 14 mg: 63.1 versus REBIF: 59.3; p = 0.28). Interpretation of these results must remain cautious in view of the open character of the TENERE study.
No difference was observed in terms of fatigue between the teriflunomide groups and the REBIF group.

07.2 Adverse effects

Teriflunomide is the main metabolite of leflunomide. The safety of use profile of leflunomide in patients with rheumatoid arthritis or psoriatic arthritis may be considered if teriflunomide is prescribed to patients with MS.

7.2.1 Common adverse effects

According to the SPC, the most common adverse effects reported in the clinical studies in patients treated with teriflunomide were: flu, upper respiratory tract infections, urinary tract infections, paresthesia, diarrhoea, increases in ALAT, nausea and alopecia. In general, diarrhoea, nausea and alopecia were mild to moderate in intensity, temporary and rarely needed the treatment to be interrupted.

7.2.2 Specific risks

Unless otherwise noted, the data are from a pooled analysis of phase II studies and the TEMSO and TOWER studies.

Hepatic effects

Small increases in ALAT less than or equal to 3 times the upper limit of normal (ULN) were more commonly observed in the groups treated with teriflunomide than in the placebo group (see Table 5). The frequency in increases more than 3 times the ULN was comparable between the two treatment groups. These increases in transaminase generally occurred over the first 6 months of treatment and were reversible after discontinuation of treatment with a return to normal within a period of several months to several years.

Table 5. Increase in ALAT in the studies versus placebo (phase II study, TEMSO study and TOWER study).

Increases in ALAT	Placebo (n = 806)	Teriflunomide 7 mg (n = 838)	Teriflunomide 14 mg (n = 786)
Patients tested	804	835	736
ALAT > 3 X ULN, n (%)	48 (6.0)	56 (6.7)	54 (6.9)
ALAT > 5 X ULN, n (%)	25 (3.1)	20 (2.4)	20 (2.6)
ALAT > 10 X ULN, n (%)	11 (1.4)	5 (0.6)	6 (0.8)
ALAT > 20 X ULN, n (%)	4 (0.5)	1 (0.1)	2 (0.3)

Dosing of liver enzymes before starting the teriflunomide treatment is recommended every two weeks throughout the first 6 months of treatment then every 8 weeks.

Alopecia

Alopecia reported as thinning hair, a reduction in hair mass or hair loss was observed in 14.6 % of patients treated with teriflunomide 14 mg as opposed to 4.5 % of patients under placebo. Most of the cases generally occurred over the first 6 months with a resolution observed in 100 patients in 115 (87 %) treated with teriflunomide 14 mg. The treatment was interrupted on account of alopecia in 1.5 % of patients in the teriflunomide 14 mg group versus 0.1 % in the placebo group.

Infections

No increase in the number of serious infections was observed with teriflunomide 14 mg (2.5 %) compared to the placebo (2.5 %).

Haematological effects

A haematological adverse effect was reported in 10.3 % of patients in the teriflunomide 7 mg group, 8.7 % of patients in the teriflunomide 14 mg group versus 2.6 % of patients in the placebo group.[11] It was usually a decrease in the number of leukocytes, mainly neutrophils and lymphocytes, less than 15 % compared with what it was at baseline. On average, this decrease occurred during the first 6 weeks of treatment and stabilised over the course of the treatment.
Two cases of neutropenia grade 4 (under teriflunomide 7 mg) and two cases of lymphopenia grade 4 (one under teriflunomide 7 mg and one under teriflunomide 14 mg) were reported.
These four cases were all resolved spontaneously with continued teriflunomide treatment in three of them.

The effect on the red blood cell count (< 3 %) and platelets (< 10 %) was less pronounced.

Peripheral neuropathies

Peripheral neuropathies (including polyneuropathies and carpal tunnel syndrome) confirmed by electromyogram were observed in 0.6 % of patients who received the placebo as opposed to 2.2 % of patients treated with teriflunomide 14 mg.[12]
In four patients treated with teriflunomide 14 mg, peripheral neuropathy caused the treatment to be stopped. The neuropathy was resolved in two patients after the treatment was stopped.

Pregnancies

The studies performed on animals showed toxicity to reproduction. Teriflunomide proved to be embryotoxic and teratogenic in rats and rabbits.
Out of 43 pregnancies occurring in patients exposed to teriflunomide, the outcome was known in 40 of them: 12 new-borns, 8 spontaneous miscarriages and 20 abortions.

Teriflunomide is contraindicated in pregnancy. Women of child-bearing age must use effective contraception during and after teriflunomide treatment until they have obtained plasma concentrations less than 0.02 mg/l. The elimination of teriflunomide may be accelerated by the administration of cholestyramine or activated carbon. When the plasma concentration of teriflunomide is less than 0.02 mg/l, a second dose must be given after a minimum period of 14 days. There is expected to be no risk for the foetus if the plasma concentration of teriflunomide is less than 0.02 mg/l when these two doses are administered.

7.2.3 Long-term adverse effects

The TEMSO study and the phase II study were followed by an open-label extension phase of 5 and 7 years respectively.
Overall, 742 patients/1086 took part in the extension phase of the TEMSO study and 147 patients/179 took part in the extension phase of the phase II study.
The most common adverse events observed during the teriflunomide treatment were: rhinopharyngitis, headaches and increases in ALAT.
No unexpected adverse event that could be attributed to prolonged exposure to teriflunomide was reported.

[11] These data versus placebo are from the pooled analysis of the phase II study and the TEMSO study.
[12] The data versus placebo on peripheral neuropathies confirmed by electromyogram were only available for the phase II study and the TEMSO study.

07.3 Summary & discussion

◗ Two randomised, double-blind studies (TEMSO 1086 patients and TOWER 1165 patients) compared teriflunomide (7 and 14 mg/d) with placebo in patients with relapsing MS, mainly relapsing-remitting (RRMS), and where the EDSS score at baseline was < 3.5 in 75 % of patients.
Teriflunomide 14 mg reduced the annualised relapse rate comparatively with the placebo:
- 0.37 versus 0.54 (RR: 0.72; 95 % CI [0.58 to 0.89] in the TEMSO study.
- 0.32 versus 0.50 (RR: 0.63; 95 % CI [0.50 to 0.79], in the TOWER study.

In the two TEMSO and TOWER studies, teriflunomide 14 mg reduced the risk of disability progression confirmed at 3 months but not at 6 months.
The data for the very active forms of RRMS are very limited (TEMSO study sub-group analyses).

◗ A randomised, open-label (with blinded evaluator) study (TENERE) compared teriflunomide (7 and 14 mg/d) with interferon beta-1a REBIF in 324 patients with relapsing MS. Teriflunomide 14 mg was not superior to interferon beta-1a REBIF in terms of the risk of treatment failure.
The Committee regrets the absence of additional comparative data on the efficacy of teriflunomide versus active treatment on the frequency of relapses and the disability progression in patients with RRMS.

◗ According to the SPC, the most common adverse effects reported in patients treated with teriflunomide in the clinical studies were: flu, upper respiratory tract infections, urinary tract infections, paresthesia, diarrhoea, increase in ALAT, nausea and alopecia. No unexpected adverse effect was observed in patients exposed more long-term to teriflunomide in the extension phases of the TEMSO study and the phase II study.

◗ Teriflunomide is contraindicated in pregnancy. Women of child-bearing age must use effective contraception during and after teriflunomide treatment until they have obtained plasma concentrations less than 0.02 mg/l, which may be accelerated by administering cholestyramine or activated carbon.

08 THERAPEUTIC USE

The long-term treatment for RRMS is based on first-line interferon beta-1a (AVONEX and REBIF), interferon beta-1b (BETAFERON and EXTAVIA) and glatiramer acetate (COPAXONE). These treatments are administered subcutaneously (BETAFERON, EXTAVIA, REBIF, COPAXONE) or intramuscularly (AVONEX).

AUBAGIO tablet administered orally in one dose per day is an alternative to interferon beta and glatiramer acetate in long-term RRMS treatment.

The data for the very active forms of RRMS are too limited to recommend AUBAGIO in this group of patients.

A dosage of liver enzymes must be carried out on starting the treatment then at regular intervals.

AUBAGIO is contraindicated in pregnancy and breastfeeding. Women of child-bearing age must use effective contraception during and after teriflunomide treatment until they have obtained plasma concentrations less than 0.02 mg/l, which may be accelerated by administering cholestyramine or activated carbon (see SPC).

AUBAGIO tablet administered orally in one dose per day is an alternative to interferon beta and glatiramer acetate in long-term RRMS treatment.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

09.1 Actual benefit

- Multiple sclerosis is an incapacitating, progressive, chronic neurological disorder. It involves the selective, chronic inflammation and demyelinisation of the central nervous system. The manifestations are many: motor and sensory disorders, sensory, vesicosphincteral and sexual impairment, and cognitive function and mood disorders. These disorders may considerably reduce patients' autonomy and impair their quality of life. The severity of the disease is very variable from mildly disabling forms which lead to severe disabilities within a few years. Relapsing-remitting forms (RRMS), which occur the most and which are characterised by the presence of relapses without there being any disability progression between the relapses;

- AUBAGIO is a long-term preventative treatment for RRMS relapses.

- The efficacy/adverse effects ratio for this medicinal product is high.

- Treatment alternatives are interferon beta and glatiramer acetate.

- *Public health benefit*

Today, multiple sclerosis (MS) affects between 70,000 and 90,000 patients in France, with a probable annual incidence of four to six for 100,000 inhabitants. Starting on average at the age of 30 (20-40 years) with a female preponderance, it is the leading non-traumatic cause of severe disability in young subjects. The severity of the disease is due to the disability it causes, its impact on quality of life and its socio-economic impact. The burden in terms of public health represented by relapsing remitting MS is considered moderate.

Reducing the functional limitations introduced by multiple sclerosis and improving the quality of life of patients with the disease are a public health need within the framework of established priorities (objective 65 of the act of 9 August 2004 on French public health policy, plan for improvement in quality of life of patients with chronic illnesses 2007-2011).

Given the results of the only phase III, open-label versus active comparator (interferon beta-1a) study, teriflunomide is not expected to have any additional impact in terms of the reduction in morbidity (reduction in relapses and disability progression), but the improvement of patient satisfaction in terms of the treatment measured using the Treatment Satisfaction Questionnaire for Medication scale was statistically significant on three of the four dimensions evaluated.
The adverse effects of particular import reported in the pivot studies were: alopecia, hepatic and haematological effects and peripheral neuropathies.

Through the provision of an oral form, thus avoiding repeated subcutaneous or intramuscular injections, the medicine could be assumed to have an impact on the organisation of care (use of nurses). However, this impact is difficult to assess given the self injections that take place.
The proprietary medicinal product AUBAGIO is therefore unlikely to provide any additional response to the identified public health need.
Consequently, it is not anticipated that there will be any public health benefit from AUBAGIO in this indication.

Taking account of these points, the Committee considers that the actual benefit of AUBAGIO is substantial.

09.2 Improvement in actual benefit (IAB)

Without a conclusive comparative study versus active treatment, AUBAGIO does not provide an improvement in actual benefit (IAB V, non-existent) in the treatment of the relapsing-remitting form of multiple sclerosis (RRMS). However, the Transparency Committee recognises the benefit of providing an oral proprietary medicinal product as an alternative to interferon beta and glatiramer acetate.

09.3 Target population

The prevalence of persons affected long-term by multiple sclerosis was 126/100,000 as of 31 December 2012 for the general system.[13] Applying this prevalence to the general population, the number of persons currently treated for multiple sclerosis in France is estimated to be about 83,000.
Among them, about 60 % had remitting MS,[14] i.e. almost 50,000 patients.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Proposed reimbursement rate: 65 %

◗ Packaging

It is not appropriate for the prescribing conditions according to the indication. The Committee points out that, in accordance with its deliberations of 20 July 2005, it recommends the standardisation of pack sizes to 30 days for treatments lasting 1 month.

◗ Specific requests inherent to reimbursement

Exception drug status

[13] Statistical data from National Health Insurance. www.ameli.fr.
[14] HAS. Transparency Committee Re-assessment of interferon beta and glatiramer acetate. Juillet 2010 [June 2010]. www.has-sante.fr.