CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202992Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	7/27/12
From	Billy Dunn, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	202992
Applicant	sanofi-aventis U.S. LLC
Date of Submission	8/12/11
PDUFA Goal Date	9/12/12
Proprietary Name / Established (USAN) names	Aubagio/Teriflunomide
Dosage forms / Strength	14 mg oral tablet
Proposed Indication(s)	Treatment of patients with relapsing forms of multiple sclerosis (b) (4)
Recommended:	Approval

1. Introduction

The sponsor (sanofi-aventis U.S. LLC) has submitted a new drug application (NDA) to support the marketing of teriflunomide (Aubagio), a new oral drug with a proposed indication for the treatment of patients with relapsing forms of multiple sclerosis (MS) (b) (4) .

Teriflunomide has not been previously approved and is categorized as a new molecular entity. A closely related drug, leflunomide, the active and primary metabolite of which is teriflunomide, is an approved drug for the treatment of rheumatoid arthritis. The proposed mechanism of action of teriflunomide in MS (and of leflunomide in rheumatoid arthritis) is inhibition of dihydroorotate dehydrogenase, an enzyme required for de novo pyrimidine synthesis in proliferating cells, leading to anti-inflammatory effects.

The review team for this NDA included the following primary reviewers:

Chemistry – Prafull Shiromani, PhD
Chemistry (Biopharmaceutics) – Tien-Mien Chen, PhD
Nonclinical – Rick Houghtling, PhD
Nonclinical (Carcinogenicity) – Matthew Jackson, PhD
Clinical Pharmacology – Veneeta Tandon, PhD
Clinical Pharmacology (Pharmacometrics) – Joo-Yeon Lee, PhD
Clinical Pharmacology (Pharmacogenomics) – Jeffrey Kraft, PhD
Clinical Pharmacology (IRT-TQT) – Moh Jee Ng, MD
Statistics – Sharon Yan, PhD

Clinical (Efficacy) – Jody Green, MD
Clinical (Safety) – Lourdes Villalba, MD, and Evelyn Mentari, MD
Division of Medication Error Prevention and Analysis – Jung Lee, RPh
Division of Risk Management – Yasmin Choudhry, MD
Division of Medical Policy Programs – Robin Duer, RN
Pediatric and Maternal Health Staff (Maternal) – Upasana Bhatnagar, MD
Pediatric and Maternal Health Staff (Pediatric) – Elizabeth Durmowicz, MD
Controlled Substance Staff – Katherine Bonson, PhD
Division of Professional Drug Promotion – Quynh-Van Tran, PharmD
Division of Consumer Drug Promotion – Meeta Patel, PharmD
Office of Scientific Investigations – Antoine El-Hage, PhD

I discuss below the key conclusions of each reviewer and provide my recommendations regarding this submission.

2. Background

Teriflunomide is not an approved drug product anywhere in the world. It has been under investigational development (IND 67476) in the United States for the treatment of multiple sclerosis since 2004. The clinical development program has focused on 7 mg and 14 mg doses of teriflunomide. A closely related drug product, leflunomide (marketed as tradename Arava), was approved in 1998 for the treatment of rheumatoid arthritis. Leflunomide is converted to its only active metabolite, teriflunomide, through which it mediates essentially all of its clinical activity.

After consultation with FDA concerning the acceptability and adequacy of the teriflunomide clinical development program for monotherapy of MS, initially informally in the context of a meeting concerning planned adjunctive therapy studies, and later in the context of a formal submission to FDA outlining the sponsor's planned approach followed by a formal pre-NDA meeting, FDA agreed in principle to an NDA supported by one apparently robust primary study with additional supportive evidence.

As primary support for the proposed indication, the sponsor presents the results from one controlled Phase 3 efficacy study (EFC6049 or TEMSO). TEMSO evaluated the effect of 7 mg and 14 mg of teriflunomide in patients with MS on a variety of outcomes. In addition, as further support, the sponsor presents the results of a controlled Phase 2 monotherapy study (study 2001), the results of two controlled Phase 2 adjunctive therapy studies (PDY6045 and PDY6046), interim results of an ongoing additional Phase 3 study (TOWER) similar to TEMSO, and interim safety results from the ongoing extension studies of the aforementioned completed studies as well as from other ongoing Phase 3 trials.

Two meetings with the sponsor focused on this submission took place. The first was a Type C meeting on 9/14/10, and the second was a pre-NDA meeting on 3/28/11. There are no significant outstanding issues from these meetings.

3. CMC/Device

Dr. Shiromani reviewed this submission and found it acceptable.

Dr. Chen reviewed this submission and found it acceptable.

There are no outstanding CMC issues. There are no CMC post-approval recommendations.

4. Nonclinical Pharmacology/Toxicology

Dr. Houghtling reviewed this submission and found it acceptable. He (along with his supervisor, Lois Freed, PhD) has labeling recommendations concerning teratogenicity and pregnancy.

Dr. Jackson reviewed this submission and found it acceptable.

There are no outstanding nonclinical issues. There are no nonclinical post-approval recommendations.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Tandon, Dr. Lee, Dr. Kraft, and Dr. Ng reviewed this submission and found it acceptable.

Detailed labeling recommendations are found in the clinical pharmacology review, including specific mention of teriflunomide's effects on urate and its interaction with certain immunosuppressants.

The clinical pharmacology review notes, as discussed above, that "teriflunomide is the active, predominant metabolite of leflunomide (Arava) and the major circulating moiety." With a relative bioavailability of teriflunomide when given as Arava of 70%, "the exposure after 14 mg teriflunomide tablet is equivalent to that of a 20 mg Arava tablet." (Note that 20 mg is the approved dose of Arava.)

There are no outstanding clinical pharmacology issues. The clinical pharmacology review team recommends imposition of a post-marketing requirement for an in vivo drug-drug interaction study with rosuvastatin.

Pharmacokinetics
Teriflunomide exhibits linear pharmacokinetics in doses ranging from 7-20 mg in single dose studies. Tmax is achieved in 1 to 4 hours. Bioavailability is essentially 100%, and it is nearly completely protein bound. Teriflunomide has a "limited" volume of distribution of 11 liters. Teriflunomide is not extensively metabolized, with unchanged teriflunomide being the only major component detected in the circulation and only small amounts of other minor

(presumably inactive) metabolites being formed mostly via hydrolysis. The median terminal half-life (14 mg dose) in MS patients was 19.4 days, with steady state reached in approximately 3 months. Given this long half-life, a rapid elimination procedure using either cholestyramine or activated charcoal administered for 7 to 11 days reduces the terminal half-life to approximately 2 to 3 days. Unchanged teriflunomide is excreted almost exclusively in the feces with various metabolites being excreted in the urine.

Food effect
There was no significant food effect.

Pharmacodynamics
The key pharmacodynamic effect of teriflunomide appears to be inhibition of dihydroorotate dehydrogenase, an enzyme required for de novo pyrimidine synthesis in proliferating cells, leading to anti-inflammatory effects.

Intrinsic factors
Age and race – no meaningful conclusions can be drawn due to a lack of patient variability.

Gender – no dose adjustments are recommended.

Renal impairment – no dose adjustments are recommended.

Hepatic impairment – no dose adjustments are recommended for mild and moderate hepatic impairment. Dosing in severe hepatic impairment is not recommended (consistent with leflunomide).

Drug-drug interactions
The clinical pharmacology team recommends monitoring and caution when administering teriflunomide with warfarin, oral contraceptives, and drugs metabolized by CYP2C8 (teriflunomide inhibits) and CYP1A2 (teriflunomide induces). Teriflunomide is a substrate and inhibitor of BCRP, and an inhibitor of OATP1B1 and OAT3 (leading to the recommendation for the in vivo interaction study with rosuvastatin above).

Thorough QT study
Teriflunomide did not show any potential for prolonging the QTcF interval compared with placebo.

Pharmacometrics
Dr. Lee conducted exposure-response analyses for efficacy and safety and found a clear relationship for efficacy (based on relapse rate and MRI data) but no clear dose relationship for safety (based on ALT increase). Dr. Lee concludes that the proposed 14 mg dose is appropriate.

Pharmacogenomics
Dr. Kraft reviewed the genotyping analyses provided by the sponsor in order to characterize any teriflunomide PK variability and found no clinically relevant genetic effects.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Dr. Green and Dr. Yan reviewed this submission. Both recommend approval.

As discussed by Dr. Green and Dr. Yan, the sponsor submitted one adequate and well-controlled pivotal efficacy study, TEMSO. As primary supportive evidence, the sponsor submitted study 2001 (a phase 2 study with a 36 week double-blind phase using an MRI primary outcome measure). Interim descriptive results from the TOWER study (an ongoing study very similar to TEMSO) were also submitted during the review period as they became available.

TEMSO was a multi-center, multi-national, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of two doses of teriflunomide (7 mg and 14 mg) in patients with relapsing multiple sclerosis (RMS).

Enrollment criteria for TEMSO were typical of MS trials including the following notable key inclusion criteria: Diagnosis (per 2005 revised McDonald criteria) of either RRMS, SPMS, or PRMS (collectively RMS) with EDSS $\leq$ 5.5, and at least 1 relapse over the preceding year or 2 relapses over the preceding 2 years and no relapses in the 60 days prior to randomization.

The primary efficacy endpoint was the annualized relapse rate (ARR) over a 2 year treatment period. This is widely used in multiple sclerosis studies.

The "key" secondary efficacy endpoint was time to disability progression (defined as the time to an increase from baseline of at least 1 point on EDSS if the baseline EDSS score was < 5.5, or the time to an increase from baseline of at least 0.5 points on EDSS if the baseline EDSS score was > 5.5, with the respective increase in EDSS score sustained for at least 12 weeks).

Additional important secondary efficacy endpoints included change from baseline in the total score of the fatigue impact scale (FIS) at 2 years, the total number of gadolinium-enhancing T1 lesions per MRI scan over the treatment period, and the change from baseline in MRI burden of disease (BOD) at 2 years.

The above primary and secondary endpoints were analyzed in a hierarchical fashion that controlled for overall Type I error.

Dr. Green and Dr. Yan have provided a discussion of these various measurements and the statistical approach used in their analyses. Their use in this trial is acceptable.

A total of 1086 patients were randomized and treated as follows:

363 subjects to placebo
365 subjects to 7 mg
358 subjects to 14 mg

Patients were enrolled from 126 centers in 21 countries in Europe and the Americas, including 4 centers from the United States that enrolled and treated 8 (0.7%) patients. Overall, patients were distributed widely throughout Europe and the Americas. Given the low enrollment of Americans, it is worth noting that 17% of enrolled patients were Canadian, the highest enrolling country.

290 patients, well balanced across all three treatment groups, did not complete the study. In addition, 40 patients were unblinded. The high discontinuation rate and instances of unblinding were discussed and considered by both Dr. Green and Dr. Yan. While a cause for concern, neither concluded that they called the results of the study into question.

Demographic and baseline characteristics of the patients were well-matched. As is typical for MS trials, most patients were relatively young white women. Relapsing-remitting, secondary progressive, and relapsing progressive MS subtypes were all included, though most (about 90%) had RRMS.

The results for the primary outcome in the standard ITT population (assigned treatment at randomization with at least 1 day of study medication exposure), presented by the sponsor and confirmed by the review team, are below:

	ARR	relative risk reduction compared to placebo	p-value
7 mg	0.370	31.2%	0.0002
14 mg	0.369	31.5%	0.0005
Placebo	0.539		

Dr. Yan conducted analyses of all relapses (including unconfirmed relapses), the per protocol population, and the unblinded patients (excluding them) and found the results remained robust and minimally changed in all cases.

The results for the secondary outcome concerning disability progression in the standard ITT population, presented by the sponsor and confirmed by the review team, are below:

	progression probability at year 2	p-value	hazard ratio	p-value
7 mg	21.7%	0.0835	0.762	0.0962
14 mg	20.2%	0.0279	0.702	0.0337
Placebo	27.3%			

Dr. Yan conducted an analysis of the per protocol population and the unblinded patients (excluding them) and found the results remained robust and minimally changed. An analysis

of progression sustained for 24 weeks (rather than 12) revealed no significant treatment effect in either teriflunomide group.

Dr. Yan conducted an analysis of the change in EDSS score from baseline at 1 year and 2 years and found little change between groups (Dr. Yan's review, Table 8). She argues that this diminishes the significance of the 14 mg group's improvement in the probability of progression.

Dr. Yan performed an additional subgroup analysis on the Americas population in TEMSO in order to further evaluate disability progression. She found that in this population of about 80 patients per treatment group, both teriflunomide groups progressed notably more than the placebo group, with the placebo group experiencing virtually no progression. There was no baseline imbalance in the EDSS scores to potentially explain this subgroup finding.

An analysis of another clinical secondary endpoint, the FIS, was not significant for either dose of teriflunomide, though it did trend in favor of 14 mg.

An analysis of the total number of gadolinium-enhancing T1 lesions per MRI scan over the treatment period strongly favors both 7 mg and 14 mg:

	Gd T1 lesions	relative risk compared to placebo	p-value
7 mg	0.57	0.43	<0.0001
14 mg	0.26	0.20	<0.0001
Placebo	1.33		

An analysis of BOD on MRI scan over the treatment period favors both 7 mg and 14 mg, the 14 mg dose more strongly:

	BOD	difference compared to placebo	p-value
7 mg	0.072	-0.053	0.0317
14 mg	0.045	-0.089	0.0003
Placebo	0.111		

Dr. Yan points out that the above two analyses may not be viewed as statistically valid due to the failure of the 7 mg dose to significantly differ from placebo in disability progression.

Both Dr. Yan and Dr. Green evaluated the interim results of the TOWER study. We requested this interim analysis in order to determine whether descriptive results of the primary endpoint were trending in a similar manner as TEMSO.

TOWER is fundamentally similar to TEMSO. It differs in duration. As Dr. Yan states, "The treatment duration was 48 weeks from the last patient recruited. The treatment period had a fixed end for all patients so that all patients were to have the end-of- treatment (EOT) visit within 6 weeks prior or 6 weeks after the EOT visit for the last patient randomized. The minimum duration on treatment for any patient not withdrawing prematurely was 48 weeks."

For this interim analysis, the minimum treatment period was 3 months with an expected average exposure of 1 year.

TOWER also differs from TEMSO in its inclusion of American patients. About 20% of the 1092 enrolled and treated patients at the time of the interim analysis are from the United States, the greatest percentage from any enrolling country. TOWER has a similarly high discontinuation rate (about 20%) as TEMSO.

As Dr. Yan describes, she performed an analysis of ARR for TOWER using the same methods as TEMSO:

	ARR	relative risk reduction compared to placebo	p-value
7 mg	0.371	30.2%	0.0072
14 mg	0.321	39.6%	0.0002
Placebo	0.531		

Dr. Green evaluated the study providing primary supportive evidence to TEMSO, study 2001.

Study 2001 was a randomized, double-blind, placebo-controlled, parallel-group phase 2 study to evaluate the efficacy and safety of two doses of teriflunomide (7 mg and 14 mg) in patients with RMS. Diagnosis of patients was made by the Poser criteria rather than the 2005 McDonald criteria (this study was conducted from 2001 to 2003). The double-blind period of the trial lasted for 36 weeks, preceded by a 4 week treatment free period, and followed by a 6-week post double-blind observational period leading to a final MRI.

The primary efficacy endpoint was the average number of unique active lesions per MRI scan for the double-blind portion of the trial, calculated as the sum of uniquely new active lesions and unique persistent active lesions for all scans divided by the number of scans on which the sum was based during the double-blind treatment period.

Secondary efficacy endpoints included other MRI findings and various clinical outcomes including EDSS and relapse rate.

A total of 179 patients were randomized and treated as follows:

61 subjects to placebo
61 subjects to 7 mg
57 subjects to 14 mg

Patients were enrolled from 10 Canadian centers and 6 French centers. 65% of the patients were enrolled at 4 of the Canadian centers.

Of the 179 randomized patients, 160 completed the study and 19 discontinued. The discontinuations were unbalanced with more patients (12) in the 14 mg group discontinuing than in the 7 mg group (3) or in the placebo group (4). Only one patient was prematurely unblinded following the completion of data collection.

Demographic and baseline characteristics of the patients were well-matched. Again, most patients were relatively young white women, though in this trial the placebo group was unbalanced with respect to gender, with a somewhat increased number of males. Relapsing-remitting and secondary progressive MS subtypes were included, with most (about 88%) having RRMS. Relapsing progressive patients were not included.

An analysis of the primary efficacy endpoint (unique active lesions) per MRI scan over the double-blind treatment period in the "efficacy-evaluable" population favors both 7 mg and 14 mg:

	Unique active lesions	p-value
7 mg	0.98	0.0234
14 mg	1.06	0.0052
Placebo	2.69	

Sensitivity analyses of this primary endpoint using the ITT, per protocol, and completer populations largely confirmed the results above, as may be see in this table from the Study 2001 CSR (Dr. Green's review, page 92):

Population/ time period	Adjusted mean (±SEM)			Comparison			
	Placebo	Teriflunomide		7 mg – placebo		14 mg – placebo	
		7 mg	14 mg	p-value [a]	(95% CI)	p-value [a]	(95% CI)
Efficacy-evaluable	**N = 61**	**N = 60**	**N = 56**				
Screening period	**2.22 (0.62)**	**1.21 (0.60)**	**2.44 (0.61)**	**0.2312**	**(-2.70, 0.68)**	**0.9972**	**(-1.49, 1.94)**
Treatment period	**2.69 (0.39)**	**1.06 (0.38)**	**0.98 (0.39)**	**0.0234**	**(-2.70, -0.55)**	**0.0052**	**(-2.79, -0.63)**
Intent-to-treat	N = 61	N = 60	N = 56				
Screening period	2.22 (0.62)	1.21 (0.60)	2.44 (0.61)	0.2312	(-2.70, 0.68)	0.9972	(-1.49, 1.94)
Treatment period	2.62 (0.39)	1.04 (0.37)	0.98 (0.38)	0.0291	(-2.64, -0.53)	0.0092	(-2.71, -0.58)
Completer	N = 57	N = 58	N = 45				
Screening period	2.20 (0.70)	1.22 (0.64)	2.57 (0.72)	0.5074	(-2.80, 0.84)	0.9906	(-1.58, 2.31)
Treatment period	2.37 (0.40)	0.98 (0.37)	0.69 (0.41)	0.0476	(-2.44, -0.34)	0.0069	(-2.79, -0.56)
Per-protocol	N = 53	N = 51	N = 43				
Screening period	2.15 (0.69)	1.20 (0.65)	2.46 (0.71)	0.2622	(-2.78, 0.88)	0.9485	(-1.60, 2.22)
Treatment period	2.89 (0.48)	1.04 (0.45)	1.00 (0.49)	0.1099	(-3.12, -0.58)	0.0490	(-3.21, -0.57)

The calculation of the p-value for the comparison between treatment groups is based on a rank analysis of covariance. Clinical Study Report HMR 1726/2001 page 103

The sponsor also presented analyses of multiple other MRI parameters in this table from the Study 2001 CSR (Dr. Green's review, page 93) that largely favored teriflunomide at both doses:

Type of lesion	Adjusted mean (±SEM)			Comparison			
	Placebo	Teriflunomide		7 mg – placebo		14 mg – placebo	
	(N = 61)	7 mg (N = 60)	14 mg (N = 56)	p-value [a]	(95% CI)	p-value [a]	(95% CI)
T1 lesions							
Newly enhancing	1.83 (0.25)	0.73 (0.24)	0.72 (0.25)	0.0410	(-1.78, -0.41)	0.0108	(-1.80, -0.42)
Persistently enhancing	0.44 (0.11)	0.16 (0.11)	0.10 (0.11)	0.1362	(-0.58, 0.01)	0.0173	(-0.64, -0.04)
Combined T1	2.27 (0.33)	0.89 (0.32)	0.79 (0.33)	0.0331	(-2.29, -0.48)	0.0123	(-2.39, -0.56)
T2 lesions							
New	1.07 (0.19)	0.29 (0.18)	0.42 (0.19)	0.0033	(-1.30, -0.27)	0.0078	(-1.17, -0.14)
Newly enlarging	0.37 (0.06)	0.12 (0.05)	0.22 (0.06)	0.0080	(-0.41, -0.10)	0.0874	(-0.31, 0.00)
Persistently enlarging	0.07 (0.02)	0.02 (0.02)	0.04 (0.02)	0.3514	(-0.11, 0.02)	0.5541	(-0.09, 0.04)
Combined T2	1.51 (0.24)	0.44 (0.23)	0.68 (0.24)	0.0029	(-1.72, -0.42)	0.0184	(-1.49, -0.18)
Unique newly active lesions (T1 and T2)	2.16 (0.31)	0.88 (0.30)	0.84 (0.30)	0.0312	(-2.12, -0.44)	0.0051	(-2.17, -0.47)
Unique persistently active lesions (T1 and T2)	0.53 (0.12)	0.18 (0.11)	0.16 (0.12)	0.0409	(-0.66, -0.03)	0.0700	(-0.69, -0.05)
Unique active lesions (T1 and T2)	Primary efficacy variable *(see Section 7.1 Analysis of primary efficacy variable* (pg. 000103))						

Clinical study Report HMR 1726/2001 page 105

A descriptive analysis of relapse rate in Study 2001 is below:

	% with relapse
7 mg	35
14 mg	23
Placebo	38

A descriptive analysis of progression on EDSS in Study 2001 is below:

	% with progression
7 mg	29
14 mg	7
Placebo	21

Dr. Green also briefly discusses the efficacy results of two open-label extension trials (LTS 6048 and LTS 6050) that the sponsor presented primarily to provide additional safety data. Although the results are not discouraging, the nature of these trials precludes the drawing of any meaningful conclusions regarding efficacy.

Finally, Dr. Green mentions three other trials that mainly contribute to the safety database (PDY 6045, PDY 6046, and LTS 6047) and were not designed to assess efficacy. They were pilot trials with an open-label extension and she does not feel they can be used in support of the efficacy analysis in this application.

In summary, Dr. Yan feels that efficacy has been sufficiently demonstrated for both 7 mg and 14 mg of teriflunomide to support approval. She feels that the disability findings in TEMSO, while promising, require further confirmation (b) (4). Dr. Green feels that the totality of the evidence argues for approval of the 14 mg dose and there is little to recommend an approval of the 7 mg dose, although she agrees that the data supporting an effect of the 7 mg dose is robust.

8. Safety

Dr. Villalba and Dr. Mentari reviewed this submission and found no obstacles to approval related to safety.

As noted above, though teriflunomide has not been previously approved, leflunomide, the active and primary metabolite of which is teriflunomide, is an approved drug for the treatment of rheumatoid arthritis. As Dr. Villalba discusses, major safety concerns with leflunomide include liver toxicity (with a boxed warning), teratogenicity (with a boxed warning), potential for immunosuppression, skin reactions, and peripheral neuropathy. The safety reviewers (including the safety team leader, Dr. Sally Yasuda), along with the entire review team for this application, determined early in the course of the review that teriflunomide and leflunomide were fairly viewed, based on the totality of the data, as essentially identical for the purposes of determining the relevance of various safety findings with leflunomide. Accordingly, the analysis of safety performed by the review team incorporates not only data from the teriflunomide clinical development program, but known data regarding leflunomide, as well.

As Dr. Villalba and Dr. Yasuda discuss, the safety database for teriflunomide exceeds standard ICH guidelines for the characterization of common adverse events. At the time of the safety update on 2/7/12, approximately 2600 patients had been exposed to 7 mg or 14 mg, with about 650 patients exposed for 6 months or more, about 500 patients exposed for 1 year or more, and about 350 patients exposed for 2 years or more. Leflunomide's approved dose of 20 mg, equivalent to 14 mg of teriflunomide, also contributes relevant exposure prior to and since its approval in 1998.

DEATHS

There were 9 deaths in the teriflunomide clinical development program, of which 1 occurred on placebo (suicide). Of the other 8 deaths, 5 occurred on 7 mg and 3 occurred on 14 mg of teriflunomide. None of these deaths occurred in the two main controlled studies presented in support of the drug's effectiveness. Rather, they occurred in the uncontrolled extension portion of these trials or in the ongoing TOWER trial. Of the 8 deaths, Dr. Villalba considers 6 possibly related (including 3 deaths of unknown cause), with 2 of these 6 dying for cardiac

reasons, and 1 dying of sepsis. The other 2 deaths were due to suicide and motor vehicle accident and are unlikely to be related to teriflunomide. Dr. Villalba points out that the 3 deaths of unknown cause occurred in patients with significant MS brainstem lesions.

SERIOUS ADVERSE EVENTS (SAEs)

In the controlled trials (referred to in the safety reviews as "Pool 1" – i.e., the two main placebo controlled studies, 2001 and TEMSO), the overall rate of SAEs was similar between the two doses of teriflunomide and placebo. The type and distribution of these SAEs was not significantly concerning, as seen in Table 14 taken from Dr. Villalba's review:

Primary System Organ Class	**Placebo (N=421) n(%)**	**7 mg (N=429) n(%)**	**14 mg (N=415) n(%)**
Any class	54 (12.8)	55 (12.8)	65 (15.7)
Infections and infestations	9 (2.1)	6 (1.4)	9 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.2)	2 (0.5)	3 (0.7)
Blood and lymphatic system disorders	1 (0.2)	2 (0.5)	3 (0.7)
Metabolism and nutrition disorders	1 (0.2)	0	0
Psychiatric disorders	4 (1.0)	4 (0.9)	2 (0.5)
Nervous system disorders	6 (1.4)	5 (1.2)	7 (1.7)
Ear and labyrinth disorders	1 (0.2)	0	1 (0.2)
Cardiac disorders	2 (0.5)	0	0
Vascular disorders	0	2 (0.5)	4 (1.0)
Respiratory, thoracic and mediastinal disorders	0	0	2 (0.5)
Gastrointestinal disorders	1 (0.2)	8 (1.9)	8 (1.9)
Hepatobiliary disorders	2 (0.5)	9 (2.1)	2 (0.5)
Skin and subcutaneous tissue disorders	1 (0.2)	1 (0.2)	1 (0.2)
Musculoskeletal and connective tissue disorders	4 (1.0)	5 (1.2)	4 (1.0)
Renal and urinary disorders	0	0	2 (0.5)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0	3 (0.7)
Reproductive system and breast disorders	2 (0.5)	6 (1.4)	2 (0.5)
General disorders and administration site conditions	0	0	1 (0.2%)
Investigations	13 (3.1)	9 (2.1)	12 (2.9)
Injury, poisoning and procedural complications	4 (1.0)	5 (1.2)	9 (2.2)
Surgical and medical procedures	0	1 (0.2)	0

Dr. Villalba points out that in the uncontrolled "Pool 2" that included the extension studies, the SAE rates increased (24% and 21% for the 7 mg and 14 mg groups, respectively), as expected given the longer exposures in this group.

Given the major safety concerns with leflunomide, it is worth noting that infections, skin reactions, neurological disorders, and pregnancy issues were essentially unremarkable.

Dr. Villalba extensively discusses hepatobiliary issues, while Dr. Yasuda summarizes this information, and both conclude that, while there were isolated cases of liver injury that may have been related to teriflunomide, numbers were small and causality was not clear. Despite this lack of clarity, the case for drug induced liver injury is reasonable in several cases. In addition, the cases of liver injury on teriflunomide tended to suffer from incomplete evaluations, while the cases of liver injury on placebo tended to have alternative explanations. Both feel that leflunomide's boxed warning regarding hepatotoxicity is appropriate for teriflunomide.

ADVERSE EVENTS (AEs) LEADING TO STUDY DISCONTINUATION

The incidence of AEs leading to discontinuation in the controlled trials was similar amongst all groups at approximately 8%, 9%, and 12% for placebo, 7 mg, and 14 mg, respectively. The type and distribution of these AEs is seen in Table 35 taken from Dr. Villalba's review:

Primary System Organ Class	**Placebo (N=421) n (%)**	**7 mg (N=429) n (%)**	**14 mg (N=415) n (%)**
Any class	32 (7.6)	39 (9.1)	49 (11.8)
Infections and infestations	4 (1.0)	1 (0.2)	5 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.0)	0	1 (0.2)
Psychiatric disorders	3 (0.7)	1 (0.2)	2 (0.5)
Nervous system disorders	2 (0.5)	2 (05)	2 (0.5)
Vascular disorders	0	0	1 (02)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.2)
Gastrointestinal disorders	1 (0.2)	6 (1.4)	5 (1.2)
Hepatobiliary disorders	2 (0.5)	1 (0.2)	1 (0.2)
Skin and subcutaneous tissue disorders	0	4 (0.9)	13 (3.1)
Musculoskeletal and connective tissue disorders	0	2 (0.5)	2 (0.5)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	1 (0.2)	4 (1.0)
Reproductive system and breast disorders	0	1 (0.2)	0
General disorders and administration site conditions	0	1 (0.2)	0
Investigations	15 (3.6)	18 (4.2)	13 (3.1)

Injury, poisoning and procedural complications	0	1(0.2)	0

Aside from skin disorders, accounted for primarily by alopecia that was reversible upon drug discontinuation, there is no marked imbalance between the groups.

AEs leading to discontinuation in the uncontrolled trials were also well-balanced.

Dr. Villalba and Dr. Yasuda discuss the specifics of the various AEs leading to discontinuation in detail and do not conclude that there are any specific unique concerns in this group.

COMMON AEs

Table 67 from Dr. Villalba's review shows common (>= 5% and >placebo) adverse events in teriflunomide controlled trials.

Primary System Organ Class Preferred Term n(%)	**Placebo (N=421)**	**Teri 7 mg (N=429)**	**Teri 14 mg (N=415)**
Any class	377 (89.5%)	390 (90.9%)	382 (92.0%)
Infections and infestations	**242 (57.5%)**	**256 (59.7%)**	**256 (61.7%)**
Influenza	39 (9.3%)	41 (9.6%)	49 (11.8%)
Urinary tract infection	40 (9.5%)	34 (7.9%)	44 (10.6%)
Bronchitis	24 (5.7%)	18 (4.2%)	30 (7.2%)
Sinusitis	16 (3.8%)	19 (4.4%)	24 (5.8%)
Gastroenteritis	21 (5.0%)	22 (5.1%)	23 (5.5%)
Nervous system disorders	**189 (44.9%)**	**194 (45.2%)**	**187 (45.1%)**
Paraesthesia	33 (7.8%)	41 (9.6%)	44 (10.6%)
Cardiac disorders	**13 (3.1%)**	**20 (4.7%)**	**17 (4.1%)**
Palpitations	5 (1.2%)	13 (3.0%)	8 (1.9%)
Gastrointestinal disorders	**145 (34.4%)**	**170 (39.6%)**	**188 (45.3%)**
Diarrhoea	35 (8.3%)	60 (14.0%)	72 (17.3%)
Nausea	29 (6.9%)	40 (9.3%)	59 (14.2%)
Abdominal pain	24 (5.7%)	20 (4.7%)	25 (6.0%)
Abdominal pain upper	19 (4.5%)	21 (4.9%)	22 (5.3%)
Skin and subcutaneous tissue disorders	**92 (21.9%)**	**124 (28.9%)**	**154 (37.1%)**
Alopecia	18 (4.3%)	48 (11.2%)	61 (14.7%)
Rash	17 (4.0%)	20 (4.7%)	23 (5.5%)
General disorders and administration site conditions	**115 (27.3%)**	**117 (27.3%)**	**112 (27.0%)**
Pain	4 (1.0%)	10 (2.3%)	9 (2.2%)
Investigations	**107**	**138 (32.2%)**	**125**

	(25.4%)		**(30.1%)**
ALT increased	30 (7.1%)	54 (12.6%)	58 (14.0%)

These findings are consistent with the analyses of SAEs and AEs leading to discontinuation and do not raise particular additional concern.

LABORATORY DATA

Teriflunomide was associated with several abnormal laboratory findings discussed in detail by Dr. Villalba and Dr. Mentari and thoroughly summarized by Dr. Yasuda. Please refer to their reviews for additional details. Clinically relevant findings will be addressed below.

VITAL SIGNS

In the controlled trials, blood pressure (BP) was increased from baseline on teriflunomide 14 mg by 3.9 mmHg systolic and 2.3 mmHg diastolic as compared to placebo. The difference was less pronounced in the 7 mg group. As Dr. Villalba points out, 5.6% of patients on 14 mg and 1.9% of patients on placebo had at least one measurement of systolic BP ≥ 160 mmHg and ≥ 20 mmHg higher than baseline, while 1.4% of patients on 14 mg and 0.5 % of patients on placebo had at least one measurement of diastolic BP ≥ 110 mmHg AND ≥ 10 mmHg higher than baseline.

Heart rate was little affected.

OTHER SAFETY ISSUES OF CONCERN

Hepatotoxicity – as noted above, liver injury is a concern with leflunomide. In the teriflunomide database, liver injury that did occur was difficult to assign to an effect of teriflunomide due to the presence of other contributing factors, but teriflunomide's role in the injuries is possible and consistent with leflunomide. In addition to the liver injury above, several cases of focal nodular hyperplasia (all in teriflunomide patients) have been reported, a finding not described thus far with leflunomide.

Acute renal failure – this unexpected safety finding was recognized during the course of the review. Dr. Mentari and Dr. Villalba present a detailed discussion of this issue in their review and Dr. Yasuda presents a detailed summary of this issue in her memo which I will briefly discuss here. The review team observed that 10 teriflunomide patients in the controlled trials, evenly divided between the two doses, experienced at least a doubling of their serum creatinine, some much higher, while none on placebo experienced this degree of creatinine increase. This observation prompted a detailed analysis by Dr. Mentari. Of the 10 patients, 7 had a creatinine clearance of less than 30 ml/min. Additional analysis of contemporaneous laboratory tests confirmed the diagnosis of acute renal failure. Serum potassium was markedly elevated (6.7 – 7.3 mmol/L) in 3 of these patients, and the potassium value was missing in 4 of the patients. In all cases, the next available set of laboratory tests (ranging from 6-48 days later) demonstrated resolution of the findings. This unexpected acute renal failure occurred in both men and women across a wide range of ages (19-51) and duration of exposure (12 weeks-

2 years after first exposure). Ultimately, 3 additional patients in the uncontrolled trials with a similar presentation were recognized. Given the clinical course and findings, Dr. Mentari believes these patients experienced acute uric acid nephropathy causing transient renal failure. Teriflunomide (and leflunomide) is a recognized uricosuric agent, and such agents are known to cause transient renal failure of this sort. Given the significance of these findings and the possible consequences of the physiologic abnormalities, Dr. Mentari recommends including information in the label with an appropriate warning about the renal failure and hyperkalemia that may occur when taking teriflunomide. She also recommends increased surveillance and management plans for these events in clinical trials and postmarketing surveillance.

Peripheral neuropathy – this is a recognized complication of leflunomide and is contained in its label. In the controlled trials, there was a slightly higher risk of developing events of polyneuropathy, mononeuropathy and neuralgia in the teriflunomide treatment groups, particularly at the 14 mg dose. The leflunomide labeling concerning peripheral neuropathy appears relevant to teriflunomide.

Hypertension- as noted above, BP is increased in association with teriflunomide use, especially at 14 mg. Given the 5 deaths that may have been related to cardiovascular causes, appropriate language in labeling warning of this effect is needed.

Bone marrow suppression - teriflunomide is associated with a decrease in neutrophils, lymphocytes, hemoglobin, and platelets. Though these findings resolve and do not appear to be associated with serious infections, leflunomide's warning regarding these effects is appropriate.

Infection – there is a slight excess in the overall risk of infection in teriflunomide patients in the controlled trials.

Hypersensitivity – there is s slight excess in the overall risk of hypersensitivity reactions, primarily skin rash and cough, in teriflunomide patients in the controlled trials.

Alopecia – this was the leading cause of discontinuations in the teriflunomide treatment groups.

Cardiovascular death/arrhythmia – there were two cardiovascular deaths in the uncontrolled trials, and three additional deaths of unknown cause, though difficult to ascribe to teriflunomide.

9. Advisory Committee Meeting

N/A

10. Pediatrics

Teriflunomide was discussed at a PeRC/PREA Subcommittee meeting on May 2, 2012. The Division presented a request for partial waiver for patients 0-9 years and deferral for patients 10 to 17 years of age. PeRC agreed with the Division.

The following language is being considered:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth through nine years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

Additionally, we are deferring submission of your pediatric study for ages 10 through 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

Deferred pediatric trial under PREA: A randomized, placebo-controlled, parallel group superiority trial to evaluate the single and multiple dose pharmacokinetics of teriflunomide, and the safety and efficacy of teriflunomide compared to placebo for the treatment of relapsing forms of multiple sclerosis.

11. Other Relevant Regulatory Issues

This application was filed in October 2011. During the course of the review process, a major amendment was submitted by the sponsor in April 2012 and the review clock was extended to its current action date of 9/12/12.

The Division requested an inspection of investigators from the TEMSO study, as data from this study are essential to the approval process. As noted by Dr. El-Hage in his review, three foreign clinical investigators were chosen for inspection of the protocol due to their enrollment of a relatively large number of subjects and significant effect on the primary efficacy results of the study. Although violations were noted for two of the three investigators (see Dr. El-Hage's

review for details), the inspections revealed no significant problems that would adversely impact data acceptability.

The sponsor proposed a Risk Evaluation and Mitigation Strategy (REMS) in the form of a Medication Guide. Dr. Choudhry has reviewed the proposal and does not feel that a REMS is necessary at this time.

Dr. Bhatnagar reviewed this application and has several recommendations regarding maternal health issues. She recommends that teriflunomide be labeled pregnancy category X due to multiple developmental effects seen in animal studies and lack of data about use in human pregnancies. She recommends that the sponsor consider ways to optimize post-marketing assessment of risk during pregnancy. Finally, she has multiple labeling recommendations.

Dr. Durmowicz reviewed this application and has several recommendations regarding the postmarketing pediatric study and the pediatric sections of labeling.

Dr. Bonson reviewed this application and did not find any evidence that teriflunomide has abuse-related central nervous system activity or has abuse potential. She does not recommend that teriflunomide be scheduled.

12. Labeling

The sponsor submitted proposed labeling. See the separate labeling document for the labeling negotiated with the sponsor.

Ms. Lee reviewed the final proposed trade name, Aubagio, and found it acceptable. She reviewed the proposed container labels, carton labeling, and insert labeling, and, after negotiation, found the final proposed versions acceptable.

Ms. Duer reviewed the proposed Medication Guide and, after negotiation, found it acceptable.

Dr. Tran reviewed the proposed prescribing information and has multiple labeling recommendations.

Dr. Patel reviewed the proposed Medication Guide, as well as Ms. Duer's recommendations, and has multiple labeling recommendations.

13. Recommendations/Risk Benefit Assessment

I recommend approval of this application.

The effectiveness of teriflunomide for the treatment of the relapsing forms of MS, based upon the results of the TEMSO and 2001 trials, appears compelling. The TEMSO trial is an adequate and well-controlled trial that demonstrates teriflunomide is effective in reducing the

frequency of clinical exacerbations and delaying the accumulation of physical disability. These effects are strongly supported by consistent findings on MRI-based markers of disease activity, both within TEMSO and in the independent 2001 trial. The 2001 trial also provides some degree of support for the robust clinical findings seen in TEMSO. Taken together, these findings represent the results of a single adequate and well-controlled trial supported by confirmatory evidence and meet the standard for substantial evidence of effectiveness.

The benefits of teriflunomide, in my opinion, outweigh its risks. The risks are not negligible, despite the relatively benign safety profile seen in its clinical development. It is, for all intents and purposes, indistinguishable from leflunomide. The review team, across many disciplines, has been clear in that understanding and approach. Accordingly, teriflunomide must inherit the known risks of leflunomide and, despite the fact that teriflunomide was developed independently from leflunomide, any assessments of its risks and benefits must take that into account. Even so, teriflunomide enjoys a favorable balance when considering its risks and benefits. MS is a serious disease, in need of effective therapies, and the joint risks of teriflunomide and leflunomide are manageable by adequate and effective labeling and continued pharmacovigilance. The risks include those associated with leflunomide, and reinforced by teriflunomide, most notably hepatotoxicity and teratogenicity, along with known additional risks including cardiovascular effects, bone marrow effects, peripheral neuropathy, and alopecia, amongst others, as well as new risks such as acute renal failure and hyperkalemia.

Teriflunomide appears to substantially duplicate leflunomide's safety profile, as it should given their chemical relationship. The clinical experience with leflunomide, then, is relevant and allows some degree of reassurance that leflunomide's labeling is necessary and appropriate for the safe use of teriflunomide.

I recommend that both the 7 mg and 14 mg doses be approved. Both were clearly effective, with the 14 mg dose demonstrating a more robust effect on the outcomes assessed in the main trial. Indeed, the 7 mg and 14 mg doses were very nearly equal in treatment effect on clinical outcomes, differing in degree of statistical significance. On imaging outcomes, the 14 mg dose was not only more highly significant but also demonstrated a larger treatment effect than the still effective 7 mg dose. The imaging outcomes in the supportive trial demonstrate a largely similar picture. In short, there are two doses, each clearly effective when viewed independently, but with sufficient differential in their apparent effects to warrant inclusion of both in labeling. It is reasonable to envision a patient with relatively mild early disease without apparent progression who might opt for the 7 mg dose in order to minimize exposure to dose-related adverse events, while a patient with more advanced and progressive disease might opt for the slightly different effectiveness profile of the 14 mg dose.

I believe teriflunomide should be indicated for the treatment of relapsing forms of MS. The studies included patients with various relapsing forms, lending support to this approach, and this indicated population is consistent with our evolving Divisional thinking regarding MS, namely, that "relapsing forms" refers to a pathophysiological entity that is classical relapsing-remitting MS along with its initial presentation (popularly called clinically isolated syndrome) and its secondary forms.

The outcomes that support the drug's approval may be appropriately described in the clinical studies section of labeling and do not need to be recapitulated in the indication, and I recommend that approach. Such an approach does represent a small departure from what has been typical, but again, this is consistent with our evolving Divisional thinking. We believe that this somewhat simplified indication statement more closely reflects how physicians actually use these drugs when treating patients with MS. Further, it does not represent an elimination of information in labeling as all the same information may and will be described factually and accurately in the clinical studies section, providing the prescriber with the information needed to determine what dose to prescribe. Finally, this approach is more flexible, as demonstrated by this particular application. If the outcomes were tied inextricably to the indication, the opportunity to approve a clearly effective dose might be lost.

I recommend inclusion of relapse data, disability data, and imaging data in labeling. All have clinical relevance and meaning, as we have determined in previous approvals. Although Dr. Yan argues that disability progression should not be included in labeling due to its lack of substantiation, I believe it is reasonably well substantiated by the robust effect on relapse rate, a related clinical endpoint whose relationship to disability progression has been demonstrated with some consistency in previous approvals of drugs for the treatment of relapsing forms of MS, particularly in conjunction with robust imaging results.

I align with the rest of the review team concerning the need to incorporate the leflunomide experience and labeling language into the approved label for teriflunomide. We have been reassured by multiple members of the review team that these two drugs are fairly viewed as one and the same in terms of their effects. Accordingly, we should anticipate that what is seen in one clinical development program has direct relevance to the other. To the degree possible, the approved label for teriflunomide should include, and often duplicate, that of leflunomide.

A pediatric development program in pediatric patients 10-17 years of age will be required.

I agree with Dr. Bhatnagar that teriflunomide should be assigned a pregnancy category of X, consistent with leflunomide, for the reasons she has stated.

Although the sponsor has submitted a REMS as part of the application, I agree with Dr. Choudhry that a REMS is not necessary to ensure that the benefits of the drug outweigh the risks. Special mention must be made of teriflunomide's recommended pregnancy category, X, and appropriate risk mitigation, given its notable teratogenicity and embryolethality. The relevant members of the entire review team took place in several detailed discussions concerning these issues during the review process. Recognizing that the MS population includes a significant proportion of patients who may become pregnant, the possibility of instituting a REMS was considered carefully. Of substantial importance in this consideration was the fact that leflunomide has a long history of use without a specific REMS in a reasonably similar patient population. In addition, the potential burden that any given REMS would impose on the use of teriflunomide in the intended patient population was noted. Ultimately, the review team agreed upon and recommended an approach to risk mitigation

based upon prescriber and patient labeling without a formal REMS that echoed that used with the essentially identical category X drug leflunomide. I agree with this approach.

I agree with the review team that the following studies should be requested as PMRs:

1. (Preceded by standard introductory language in Section 10 above) Deferred pediatric trial under PREA: A randomized, placebo-controlled, parallel group superiority trial to evaluate the single and multiple dose pharmacokinetics of teriflunomide, and the safety and efficacy of teriflunomide compared to placebo for the treatment of relapsing forms of multiple sclerosis.

2. A prospective, observational exposure cohort study conducted in the United States that compares the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to teriflunomide during pregnancy to unexposed control populations (one with women with multiple sclerosis who have not been exposed to teriflunomide in pregnancy and the other in women without multiple sclerosis). The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes will be assessed through at least the first year of life. Annual interim reports are to be submitted to the Agency.

3. A summary analysis of the pooled safety results of the TOWER and Study 6049 clinical trials. The summary should include information on the effect of teriflunomide on bicarbonate, magnesium, and calcium levels and acute renal failure, as measured and evaluated in these trials.

4. A clinical trial to evaluate the effects of teriflunomide on plasma concentrations of rosuvastatin, a substrate of both OATP1B1 and BCRP. Refer to the Agency's Guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf for more detailed recommendations regarding transporter-based drug-drug interactions.

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/s/

WILLIAM H Dunn
09/11/2012