CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202992Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, M.D.
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	202992
Applicant Name	Sanofi-Aventis
Date of Submission	8/12/2011
PDUFA Goal Date	9/12/2012
Proprietary Name / **Established (USAN) Name**	Aubagio/Teriflunomide
Dosage Forms / Strength	7, 14 mg oral tablet
Proposed Indication(s)	Treatment of patients with relapsing forms of multiple sclerosis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Clinical (Efficacy) Review	Jody Green, MD
Clinical (Safety) Review	Lourdes Villalba, MD and Evelyn Mentari, MD
Statistical Review	Sharon Yan, PhD
Nonclinical Pharmacology Review	Richard Houghtling, PhD
Nonclinical (Carcinogenicity) Review	Matthew Jackson, PhD
Clinical Pharmacology Review	Veneeta Tandon, PhD
Clin. Pharm. Pharmacometrics Review	Joo Yeon Lee, PhD
Clin. Pharm.(Pharmacogenomics Rev.	Jeffrey Kraft, PhD
Clin. Pharmacology (IRT-TQT) Rev.	Moh Jee Ng, MD
CMC Review/OBP Review	Prafull Shiromani, PhD
CMC Biopharmaceutics Review	Tien-Mien Chen, PhD
DSI	Antoine El-Hage, PhD
CDTL Review	Billy Dunn, MD
Division Director	Russell Katz, MD
OSE/DMEPA	Jung E. Lee, RPh
OSE/DRISK	Yasmin Choudhry, MD
DMPP	Robin Duer, RN
PMHS (Maternal)	Upasana Bhatnagar, MD
PMHS (Pediatric)	Elizabeth Durmowicz, MD
Controlled Substance Staff	Katherine Bonson, PhD
Office of Prescription Drug Promotion	Meeta Patel, PharmD; Quynh-Van Tran, PharmD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

CMC= Chemistry, Manufacturing Control
DMPP=Division of Medical Policy Programs
PNHS=Pediatric and Maternal Health Staff

I. Introduction

The Division clinical reviewers (Drs. Katz, Dunn, Green, Villalba, and Mentari) as well as all other reviewers (Chemistry Manufacturing and Control, Pharmacology-Toxicology, Clinical Pharmacology, and Office of Safety Evaluation) recommend approval of teriflunomide for treatment of relapsing forms of multiple sclerosis (MS), and I concur. The basis for this recommendation is well described in the Cross-Disciplinary Team Leader and Division Director memos of Drs. Dunn and Katz. The effectiveness data are well-described by Drs. Green and Yan, and summarized by Drs. Dunn and Katz. On the primary endpoint in the study, the annual relapse rate (ARR), the critical controlled trial, TEMSO, a large (n>1000) study in relapsing MS (RMS) [primarily relapsing, remitting MS (RRMS), as is usually the case in RMS studies] showed substantial effects of both the 7 and 14 mg doses, about a 30% reduction, similar to the effect of interferon and copoxone, and very highly statistically significant.

In what follows I will discuss several aspects of the evidence of effectiveness and choice of dose, as well as a few safety issues.

II. Effectiveness

1. Substantial Evidence

As explained in Dr. Green's review, we initially told Sanofi-Aventis that two controlled effectiveness studies would be needed (i.e., the usual standard for substantial evidence), TEMSO and TOWER (a second large study, of one year's duration), but we subsequently explained (Green, July 13, 2012 review, p. 22, and letter to sponsor dated Dec. 20, 2010) that TEMSO, if its findings were robust, with supportive data on MRI lesions from Study 1726/2001 could support effectiveness; TOWER interim data would be provided.

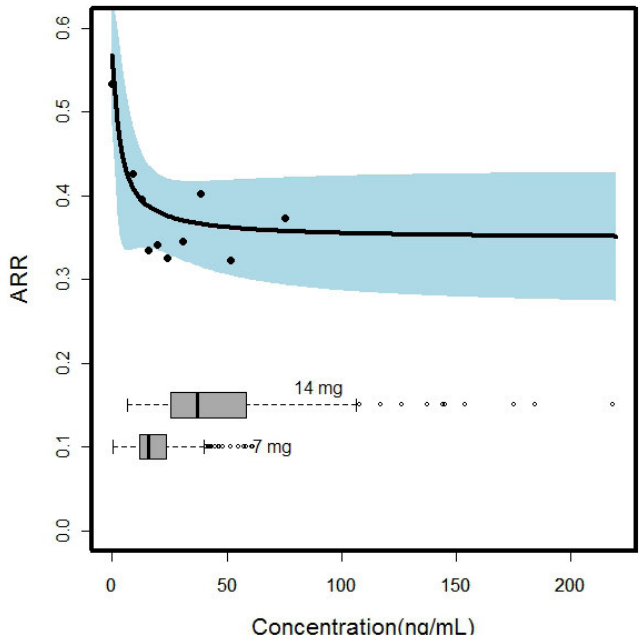
In our Clinical Evidence Guidance we consider a number of possible bases for approval based on a single adequate and well-controlled study. The two principal bases are: 1) Evidence from other studies that supports the primary controlled study, including studies in different populations, and studies of related endpoints; and 2) The single study is statistically very strong and shows internal consistency, multiple effects, etc. In this case both bases are present. Study 2001 MRI data strongly support the clinical outcome in TEMSO, providing evidence that the MRI neurologic lesions are reduced by teriflunomide. In addition, a small study adding teriflunomide to interferon (Study 6045) also showed substantial reductions of MRI lesions compared to placebo. Moreover, TEMSO, apart from its statistically strong 30% reduction of annual relapse rate (ARR), with p-values of 0.0002 (7 mg dose) and 0.0005 (14 mg dose), includes an element of replication (i.e., both doses) of the basic finding (not quite replication, however, as there is only one placebo group). TEMSO also showed 30% decreased likelihood of progression (an endpoint distinct from ARR) with the 14 mg dose (p=0.034), with a favorable trend with the 7 mg dose, and

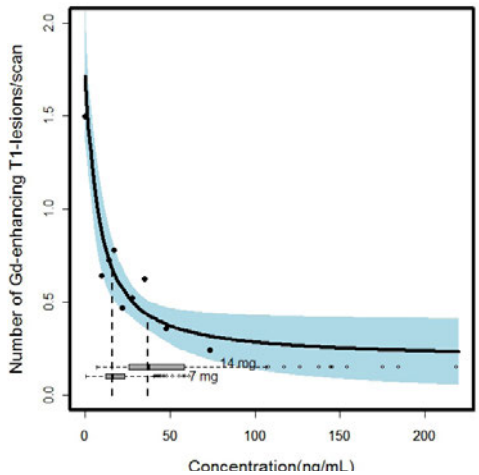
very strong MRI findings for reducing gadolinium-enhancing T_1 lesions and reduced burden of disease (BOD) on MRI, all of which support the primary endpoint finding. Finally, the preliminary interim TOWER results appear essentially identical to TEMSO, although these, of course, have not been fully reviewed.

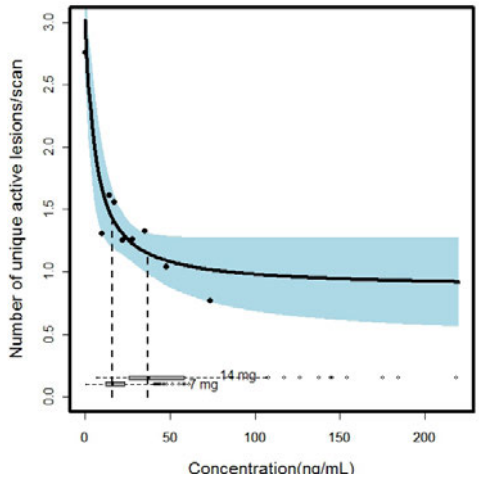
I believe the strong findings on 2 doses and several distinct endpoints in TEMSO, supported by Study 2001, provide substantial evidence that teriflunomide is effective. I note also that TEMSO had almost no US patients (but substantial Canadian representation); TOWER has a large US contingent.

2. Choice of Dose

Whether both 7 and 14 mg should be approved has been a matter of considerable discussion. Dr. Green, impressed by the effect on progression of the 14 mg dose in TEMSO, thought only the 14 mg dose should be approved. My own initial view was that the ARR effects of both doses were identical and that the effects on progression of 7 and 14 mg in TEMSO seemed very similar, despite nominal significance only with the 14 mg dose, so that only the 7 mg dose should be recommended. Drs. Dunn and Katz support approval of both doses, with labeling noting both in D and A, and with data on clinical effects shown in Section 14 of the package insert, allowing the physician to note the somewhat greater effect of the 14 mg dose on disability and MRI and decide which to choose. There is no assertion in labeling of superiority of the higher dose. It is hardly unusual for dose-response to plateau and show only modest differences between doses at the high end. The Pharmacometric analysis is informative here. It shows the relationship of serum concentrations to effects on ARR and MRI findings (p. 14-15 of Clinical Pharmacology review). There is a very flat concentration response curve over the range of concentrations obtained with 14 mg dose, but the lower end of the concentration range obtained with the 7 mg dose is on the part of the C/R curve that is rising steeply toward less effect, especially for MRI effects.







I am therefore satisfied that there is reason to consider both the 7 mg and the 14 mg doses.

3. Safety

Like any immunomodulator, teriflunomide has a variety of toxicity concerns. Most of these are well understood because it is the active metabolite of leflunomide, a drug marketed since 1998 for treatment of rheumatoid arthritis at a dose equivalent to the 14 mg dose of teriflunomide. Labeling for leflunomide (ARAVA) has important warnings:

1) Boxed warning on teratogenesis and liver toxicity;

2) Warnings and precautions about immunosuppression and bone marrow suppression;

3) Adverse reactions, including diarrhea, abnormal liver tests, alopecia, rash.

All of these are included in teriflunomide labeling.

Findings specifically with teriflunomide are presented in detail by Dr.Villalba and summarized by Dr. Katz, who notes no overall increase in serious liver injury or increase in abnormal liver enzymes, but 2 cases of liver injury and jaundice (one each on 7 and 14 mg). Alopecia was an important cause of drug discontinuation. Teriflunomide caused an increased rate of GI adverse reactions (diarrhea, nausea).

Teriflunomide is a uricosuric agent and, like all such agents, can cause acute renal failure and did so in 10 patients (with at least doubling of serum creatinine), sometimes with marked elevations of serum K The failure was transient (normalized at next assessment (5 to 48 days) in all cases but deserves attention (listed in Warnings and Precautions).

A major concern, given that the treatment population includes many women of child-bearing potential, is teriflunomide's striking pre-clinical teratogenicity and embryolethality, which gives it a pregnancy category X, like leflunomide. The possibility of various REMS approaches was considered, but given the long history of use of leflunomide in a similar population, we, with OSE, concluded that labeling and a Medguide represented the best approach to risk mitigation.

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/s/

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09/12/2012

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09/12/2012