CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Memo

Date:	August 28, 2012
Reviewer(s):	Yasmin Choudhry, M.D., Medical Officer, Division of Risk Management (DRISK) Kendra Worthy, Pharm. D., Team Leader, DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	Teriflunomide (proposed tradename Aubagio)
Therapeutic Class:	Immunomodulator with anti-proliferative and anti-inflammatory activity
Indication(s):	Treatment of patients with relapsing remitting multiple sclerosis (b) (4)
Dosage and Route:	14 mg (Tablet) orally once daily
Application Type/Number:	NDA 202992
Applicant/sponsor:	Sanofi Aventis
OSE RCM #:	2011-3090

1 INTRODUCTION

This is a review of Sanofi-Aventis's proposed Risk Evaluation and Mitigation Strategy (REMS) voluntarily submitted with NDA 202992 to the Division of Neurology Products (DNP) for teriflunomide (proposed name Aubagio) on August 12, 2011. The Applicant's proposed REMS consists of a Medication Guide and a timetable for submission of assessment at 18 months, 3 years, and 7 years from the date of the approval of the REMS.

Teriflunomide, an immunomodulating agent, is the active metabolite of leflunomide (Arava). Leflunomide was approved on September 10, 1998 for the treatment of active rheumatoid arthritis. The proposed indication for teriflunomide is (b) (4) in patients with relapsing forms of multiple sclerosis (MS). The recommended dosage is 14 mg orally once daily.

1.1 MATERIALS REVIEWED

- Applicant's proposed REMS submitted on August 12, 2011
- Clinical review by Lourdes Villalba, M.D., and Evelyn Mentari, M.D., M.S., dated July 12, 2012
- Draft clinical review by Jody E. Green, M.D., dated July 13, 2012
- Hepatotoxicity safety review by Dr. John R. Senior, M.D., dated December 9, 2011

1.2 OVERVIEW OF CLINICAL PROGRAM

Teriflunomide 14 mg/day was found to be efficacious in reducing the frequency of relapses and delaying the accumulation of physical disability in patients with relapsing MS in the pivotal trial TEMSO and other supportive trials. The TEMSO trial was conducted in 1088 patients with relapsing MS with 7 mg and 14 mg doses; both doses had robust results for reducing the annualized relapse rate. Statistically significant reduction in disability progression (compared with placebo) was seen with the 14 mg dose but not with the 7 mg dose. The 14 mg dose, which is the recommended dose, also demonstrated a strong effect on magnetic resonance imaging parameters, reducing the number of gadolinium-enhanced T1 and T2 lesions[1].

Teriflunomide is the active metabolite of leflunomide (Arava). Leflunomide has 2 million patient-years of exposure in patients with active rheumatoid arthritis for which it was approved in 1998. There is no evidence that teriflunomide is less or more toxic than leflunomide.

[1] Clinical review (DRAFT) Teriflunomide NDA 202992 by Jody E. Green, M.D., dated july13, 2012

Major safety concerns[2] with leflunomide are severe liver injury and teratogenicity. The Arava label carries a box warning for these adverse effects. Leflunomide does not have a REMS.

Liver toxicity: Leflunomide has the potential to cause serious liver injury and death; as of September 2011, the rate of serious liver injury was 4 per 100,000 patient-years and the DNP safety reviewers believe that there is no evidence that the risk of severe liver injury with teriflunomide will be lower than that with leflunomide. Of the 3,100 patients exposed to teriflunomide there is one possible case of severe drug induced liver injury in a 35 year old Russian woman who recovered after stopping the drug; see Dr. John R. Senior's review[3].

Teratogenicity: There were 303 pregnancy exposures to leflunomide reported in the periodic safety report (PSUR) dated November 14, 2003. There were 85 live births among the 164 known pregnancy outcomes; 7 of the 85 pregnancies (8%) resulted in live births with major malformations. The data from leflunomide (PSUR) indicates an increased risk of major malformations from the background risk of 3-4%.

As of March 20, 2012, 64 pregnancies occurred in patients in the teriflunomide clinical program. There were 10 live births reported but only 4 of the patients had exposure to teriflunomide during pregnancy. The exposure to teriflunomide in patients of the other 6 live births was either unknown or had no exposure. The maternal health team reviewer concluded that data from the exposed pregnancies with teriflunomide is insufficient to counsel patients regarding the effects of in utero exposure on the human fetus. Based on the multiple developmental effects seen in animal studies and lack of data about use in human pregnancies, teriflunomide will be labeled pregnancy category X[4]. Leflunomide is also pregnancy category X.

Other major toxicities seen with leflunomide and teriflunomide include bone marrow toxicity with potential for long term immunosuppression, opportunistic infections, and malignancies. These are addressed in the Arava label and will be similarly addressed in the teriflunomide labeling.

Two cases of progressive multifocal leukoencephalopathy (PML) were identified with leflunomide in the postmarketing setting; both cases were confounded by prior use of immunosuppressants; the PML cases are not included in the Arava label. No cases of PML have been identified with teriflunomide.

Two new signals identified with teriflunomide that were not seen with leflunomide were cardiovascular deaths and reversible acute renal failure.

Of the total 9 deaths reported from completed and ongoing teriflunomide studies, 8 deaths occurred in teriflunomide-treated patients (in phase 2/3 studies, n=2600) and 1 death (a suicide) in a patient on placebo. Five of the 8 deaths were cardiovascular (CV)/unknown cause of death. According to the clinical safety reviewer, a causal

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[2] Clinical review by Lourdes Villalba, M.D., and Evelyn Mentari, M.D., M.S., dated July 12, 2012

[3] Hepatotoxicity Safety Review by Dr. John R. Senior, M.D., dated December 9, 2011.

[4] Maternal Health Team Review, Teriflunomide NDA 202992 by Melissa S. Tassinari, Ph.D., dated August 8, 2012.

relationship between teriflunomide and the deaths could not be ruled out. A total of 10 patients with acute renal failure based on renal function evaluation were identified; all ten patients were on teriflunomide for over 3 years and in each case re-test showed creatinine values within the normal range[5].

1.3 RISK MANAGEMENT PROPOSED BY APPLICANT

The Applicant proposed a REMS with a Medication Guide and a timetable for submission of assessments of the REMS at 18 months, 3 years, and 7 years from the date of the approval of the REMS.

2 DISCUSSION

MS is a chronic demyelinating disorder of the central nervous system that can lead to progressive neurological disability. Treatment goals for MS are to shorten the duration and severity of symptoms associated with relapses, prevent the incidence of relapses, and delay the accumulation of disability[6]. Teriflunomide, an oral formulation, at 14 mg dose was found efficacious in reducing the frequency of clinical exacerbations as well as delaying the accumulation of physical disability. There is only one other approved oral drug, Gilenya (fingolimod).

Teriflunomide is the active metabolite of leflunomide. It is not known whether teriflunomide is more or less toxic than leflunomide. The drug safety profile of teriflunomide from clinical trials appears to be similar to leflunomide. The main safety concerns with both drugs are liver toxicity and teratogenicity, which for leflunomide are addressed in the boxed warning in the label. The teriflunomide label will also carry a boxed warning for these toxicities.

However, the two new signals identified with teriflunomide, acute renal failure and CV deaths that were not seen with leflunomide are of concern. Even though it is difficult to determine the exact cause of death in these patients, the safety reviewer indicates several possible mechanisms such as increase in blood pressure and atrial and ventricular arrythmias; both adverse events were seen with teriflunomide in clinical trials and it is difficult to attribute these relatively common events to the drug. As for the acute renal failure, the safety reviewer stated that uric acid nephropathy is a likely explanation for these cases as renal failure has been seen with other drugs that cause hyperuricosuria as well as in patients with hereditary hyperuricosuria. Since there is limited information available at this time, we believe (as also suggested by the safety reviewer) that in addition to appropriate labeling both of these signals should be carefully monitored and closely followed in the postmarketing period. At this time a REMS is not required to address these adverse events.

[5] Clinical review by Lourdes Villalba, M.D., and Evelyn Mentari, M.D., M.S., dated July 12, 2012

[6] Clinical review (DRAFT) Teriflunomide NDA 202992 by Jody E. Green, M.D., dated july13, 2012

3 CONCLUSION

DRISK and DNP agree that a REMS for teriflunomide is not necessary at this time; routine pharmacovigilance measures and postmarketing requirements/commitments are acceptable.

We agree with the clinical reviewers recommendations which include the following:

- An observational study to evaluate CV death and arrythmia in patients exposed to leflunomide
- Systemic collection of additional information in subjects with reported acute renal failure or elevated serum creatinine ≥ 100% of baseline in ongoing studies and postmarketing cases; and comprehensive evaluation of cases of loin or flank pain in ongoing studies and in postmarketing setting.
- Evaluation of the effect of teriflunomide on bicarbonate, magnesium, and calcium levels
- An updated integrated summary of safety pooling the TOWER completed study with Study 6049

The clinical review team concluded that there were no safety concerns that would preclude approval of teriflunomide in patients with MS. The label for teriflunomide will also include a box warning with teratogenicity and liver toxicity. A Medication Guide will also be part of the labeling. Should DNP identify additional safety information that warrants risk mitigation measures, please send a consult to DRISK.

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/s/

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08/28/2012

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