

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202992Orig1s000

Trade Name: Aubagio

Generic Name: Teriflunomide Film-Coated Tablets

Sponsor: Sanofi-Aventis

Approval Date: 9/12/2012

Indications: For the treatment of patients with relapsing forms of multiple sclerosis

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APPROVAL LETTER



NDA 202992

NDA APPROVAL

Sanofi-aventis U.S. Inc.
Attention: Cynthia Psaras, Ph.D.
Director, Global Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Psaras:

Please refer to your New Drug Application (NDA) dated August 12, 2011, received August 12, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aubagio (teriflunomide) 7 mg and 14 mg tablets.

We acknowledge receipt of your amendments dated August 12, 2011, August 18, 2011, August 19, 2011 (2), September 2, 2011, September 9, 2011, September 19, 2011, September 30, 2011 (3), October 21, 2011, October 31, 2011 (2), November 15, 2011, November 16, 2011, November 18, 2011, November 22, 2011, November 30, 2011, December 1, 2011, December 2, 2011 (2), December 9, 2011, December 14, 2011, December 16, 2011, December 29, 2011, January 5, 2012, January 11, 2012 (2), January 12, 2012, January 18, 2012, January 31, 2012, February 8, 2012, February 14, 2012 (2), February 17, 2012, February 21, 2012, March 8, 2012 (2), March 9, 2012, March 13, 2012, March 15, 2012, March 20, 2012 (2), March 23, 2012, March 30, 2012, April 6, 2012 (2), April 10, 2012, April 12, 2012, April 13, 2012 (3), April 16, 2012 (2), April 17, 2012 (2), April 20, 2012 (2), April 24, 2012, April 26, 2012, April 30, 2012, March 1, 2012, March 3, 2012, March 9, 2012, June 8, 2012, June 11, 2012, June 12, 2012, June 13, 2012, June 19, 2012, June 29, 2012, July 16, 2012, August 3, 2012, August 31, 2012, September 6, 2012, September 11, 2012, and September 12, 2012.

This new drug application provides for the use of Aubagio (teriflunomide) 7 mg and 14 mg tablets for the treatment of patients with relapsing forms of multiple sclerosis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert and Medication Guide. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to your carton and immediate container labels submitted on September 6, 2012, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 202992.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Aubagio (teriflunomide) 7 mg and 14 mg tablets was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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 FDCA 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 FDCA. This required study is listed below.

1924-1 Deferred pediatric trial under PREA: A randomized, controlled, parallel group superiority trial to evaluate the single and multiple dose pharmacokinetics of teriflunomide, and the safety and efficacy of teriflunomide compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

Final Protocol Submission:	05/13
Trial Completion:	07/17
Final Report Submission:	12/17

Submit the clinical protocol(s) to your IND, with a cross-reference letter to this NDA. Submit the final report as a supplement to this NDA.

Submit the draft protocol at least 3 months prior to the final protocol submission date to allow for review and agreement on the protocol design.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of teratogenicity in humans, as suggested by evidence of a risk of teratogenicity and embryoletality in nonclinical studies.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1924-2** 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.

The timetable you submitted on September 11, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/12
1 st interim report	09/14
2 nd interim report	09/15
3 rd interim report	09/16
4 th interim report	09/17
5 th interim report	09/18
Study Completion:	06/19
Final Report Submission:	12/19

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess unexpected serious risks of effects on bicarbonate, magnesium, and calcium levels and acute renal failure and to assess the risk of potential for drug interactions

between Aubagio (teriflunomide) 7 mg and 14 mg tablets and substrates of the transporters OATP1B1 and BCRP when in vitro studies show a risk for interaction.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1924-3 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.

The timetable you submitted on September 11, 2012, states that you will conduct this trial according to the following schedule:

Final Report Submission: 12/12

1924-4 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/Guidance/UCM292362.pdf> for more detailed recommendations regarding transporter-based drug-drug interactions.

The timetable you submitted on September 11, 2012, states that you will conduct this trial according to the following schedule:

Final Report Submission: 10/12

Submit draft protocols for these postmarketing requirements at least 3 months prior to the final protocol submission date to allow for review and agreement on the protocols.

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated August 12, 2011, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Aubagio (teriflunomide) 7 mg and 14 mg tablets to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

ONGOING TRIALS/STUDIES AND POSTMARKETING SURVEILLANCE

Information on the effect of Aubagio (teriflunomide) 7 mg and 14 mg tablets on bicarbonate, magnesium, and calcium levels was not available in the clinical trials. Assessments of these laboratory values should be included in ongoing trials and studies. In addition, evaluation of acute renal failure should be performed in ongoing trials and studies, and monitored in postmarketing surveillance. Other areas of interest in postmarketing surveillance include pancreatic toxicity, hemorrhage, thrombosis, cardiac events, and serious or opportunistic infections.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call LCDR Hamet Touré, PharmD MPH, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
09/12/2012