# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 202992Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# EXCLUSIVITY SUMMARY

NDA # 202992 SUPPL # HFD #

Trade Name Aubagio

Generic Name Teriflunomide

Applicant Name Sanofi-Aventis, Inc

Approval Date, If Known 9/12/2012

## PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐ ! NO ☐
Explain: ! Explain:

| Investigation #2 | ! |
|---|---|
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: LCDR Hamet Touré
Title: Regulatory Project Manager
Date: 25 April 2012

Name of Office/Division Director signing form: Russell Katz, MD
Title: Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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HAMET M TOURE
09/18/2012

ERIC P BASTINGS
09/19/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, September 11, 2012 1:33 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

For the clinical pharmacology drug interaction PMR, we have the final report submission date. We do not need the protocol/trial submission dates that we asked for yesterday.

For the pregnancy registry PMR, we suggested yesterday that you allow for at least 3 months to come to agreement on the protocol, and we suggested that the final protocol submission date be 12/12 (giving an extra 3 months). Please provide new milestone dates for that PMR. In addition, please provide milestone dates for the annual interim reports.

Please provide milestone dates for the following additional PMR: 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.

We request your response for the milestone dates by close of business today.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
09/12/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, September 10, 2012 10:10 AM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** RE: NDA 202992: Request for Meeting - Follow up to Voice Mail Message

Dear Dr. Psaras,

We have the following information request:

1. Please note that your summary of CV deaths is missing patient LTS6050/3009/0016.
2. Please submit the autopsy results for patient LTS650/3203/0010.

We request your response as soon as possible and preferably before this morning's teleconference.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Friday, September 07, 2012 4:41 PM
**To:** Toure, Hamet
**Subject:** RE: NDA 202992: Request for Meeting - Follow up to Voice Mail Message

Dear Dr. Touré,

Thank you for agreeing to have a discussion with our team on Monday, September 10, 2012 between 11 AM and 12 PM. In addition to comments embedded in boxes in the attached labeling, we would like to discuss the following topics with your team.

- Section 8.1 pertaining to male mediated toxicity
- cases of cardiovascular deaths for which I have attached narratives as well as one translated autopsy report
- to maintain consistency of information and clinically meaningful information provided to prescribers, we reviewed labels of previously approved products in the same class and have revised Table 2 in Section 14 accordingly. Further explanation of the changes to this table is provided in boxed text below the table.

We are sensitive to FDA's concerns about differentiating certain safety information based on indication alone but we included the reference to rheumatoid arthritis for leflunomide where we believed it was relevant and appropriate.

We look forward to finalizing the label on Monday.

Kind regards,

Cynthia

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**From:** Psaras, Cynthia R&D/US
**Sent:** Friday, September 07, 2012 1:35 PM
**To:** 'Toure, Hamet'
**Subject:** RE: NDA 202992: Request for Meeting - Follow up to Voice Mail Message

Dear Dr. Touré,

Monday, September 10, 2012, between 11 and noon is fine. Yes, you can use the same call in number.

Later this afternoon, I will be sending our comments on the label you sent yesterday and a list of topics to be discussed on Monday. Thank you.

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Friday, September 07, 2012 12:01 PM
**To:** Psaras, Cynthia R&D/US
**Subject:** RE: NDA 202992: Request for Meeting - Follow up to Voice Mail Message

Dear Dr. Psaras,

My computer crashed earlier and you may not have received my earlier message.

We prefer to meet on Monday. Would your team be available on Monday, September 10, 2012, between 1100 and noon? If yes, can we use the same call in number?

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration

Office of Drug Evaluation – Division of Neurology Products
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10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Friday, September 07, 2012 10:14 AM
**To:** Toure, Hamet
**Subject:** NDA 202992: Request for Meeting - Follow up to Voice Mail Message

Dear Dr. Touré,

Based on the labeling you sent us yesterday, we have accepted most of your team's comments, in particular those related to safety. However, we have a few very important remaining points in section 14 that needs urgent clarification and discussion particularly in view of FDA's proposed broader indication. We would like a few minutes of your team's time as soon as possible today. I would anticipate a smaller group on our side. With the action date next week, it is very important that we speak to your team today. Please send me an email with the time your team can be available today. Thank you.

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
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/s/

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HAMET M TOURE
09/10/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, September 10, 2012 3:11 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** 202992_Advice

Dear Dr. Psaras,

We refer to NDA 202992. Please find below our proposed language for the Drug Interactions section of the label:

***Drug Interactions***:

Teriflunomide is not metabolized by Cytochrome P450 or flavin monoamine oxidase enzymes. Based on *in vitro* studies, teriflunomide is a substrate of the efflux transporter Breast Cancer Resistant Protein (BCRP). BCRP inhibitors (such as cyclosporine, eltrombopag, gefitinib) may increase exposure of teriflunomide.

*In vitro* and *in vivo* studies suggested teriflunomide is an inhibitor of CYP2C8. An *in vivo* study with caffeine indicated that it induces CYP1A2. Teriflunomide is also an inhibitor of BCRP, hepatic uptake transporter (OATP1B1) and renal uptake transporter (OAT3). *In vivo* studies to confirm transporter based interaction have not been conducted.

*Potential of Other Drugs to Affect AUBAGIO:*

Potent CYP and transporter inducers: Rifampin did not affect the pharmacokinetics of teriflunomide..

*Potential of AUBAGIO to Affect Other Drugs:*
Teriflunomide did not affect the pharmacokinetics of bupropion (a CYP2B6 substrate), midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), omeprazole (a CYP2C19 substrate) and metoprolol (a CYP2D6 substrate).

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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/s/

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HAMET M TOURE
09/10/2012
Sent at request of CTDL

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, September 08, 2011 3:07 PM
**To:** Cynthia.Psaras@sanofi-aventis.com
**Cc:** 'Nilda.Ramos@sanofi-aventis.com'; Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

Please submit the final version of the pivotal PROTOCOL Study HMR 1726D/EFC6049 to the NDA.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
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/s/

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HAMET M TOURE
09/08/2011

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202992

**PROPRIETARY NAME REQUEST**
**CONDITIONALLY ACCEPTABLE**

sanofi-aventis U.S., LLC
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

ATTENTION: Cynthia Psaras, PhD
Director, Global Regulatory Affairs

Dear Dr. Psaras:

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

We refer to your correspondence, dated and received June 11, 2012, requesting review of your proposed proprietary name, Aubagio. We also refer to your correspondence, dated and received June 13, 2012, amending your request to review the proposed proprietary name, Aubagio. We have completed our review of the proposed proprietary name, Aubagio and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your June 11, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hamet Toure at (301) 796-7534.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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LAURIE A KELLEY
09/07/2012

CAROL A HOLQUIST
09/07/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, September 06, 2012 3:51 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Psaras,

We have revised the PMR for the deferred pediatric study 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-remitting multiple sclerosis.

Additionally, it is acceptable to place Germany as the country of origin on your labeling.

Thanks,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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10903 New Hampshire Ave
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hamet.toure@fda.hhs.gov

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**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Thursday, September 06, 2012 10:02 AM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Touré,

With regard to the deferred pediatric study under PREA (first item below), we have proposed a study duration of (b) (4) in the latest PPSR while the PMR states 24 months. The team just wants to know if our proposal was taken into consideration for the PMR.

Additionally, we have not received any feedback on the PLAIR for the 7 mg tablets. In fact, I was told that we did not even receive notification of receipt of the request. It was sent to the FDA mailbox that you mentioned as were all the previous PLAIRs.

Thank you for all you assistance.

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Wednesday, September 05, 2012 9:29 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Psaras,

The first PMR is for a deferred pediatric study under PREA.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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10903 New Hampshire Ave
Silver Spring, MD 20993
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Wednesday, September 05, 2012 9:26 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Touré,

Can you please clarify the first PMR? Thank you.

Best regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Wednesday, September 05, 2012 5:57 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following PostMarketing Requirements. Please provide milestone dates:

A 24-month, 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-remitting multiple sclerosis.

Final Protocol Submission: MM/YY
Study/Trial Completion: MM/YY
Final Report Submission: MM/YY

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.

Final Protocol Submission: MM/YY
Study/Trial Completion: MM/YY
Final Report Submission: MM/YY

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.

Final Protocol Submission: MM/YY
Study/Trial Completion: MM/YY
Final Report Submission: MM/YY

We request your response by Monday, September 10, 2012, noon. Kindly provide your response by email and follow with an identical archival submission to NDA 202992.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration

Office of Drug Evaluation – Division of Neurology Products
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/s/

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HAMET M TOURE
09/06/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, September 06, 2012 2:01 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** 202992_Proposed label

**Attachments:** 202992_FDA proposed PI and medication guide_090612.doc

Dear Dr. Psaras.

We refer to NDA 202922. Please find enclosed our proposed labeling. This was not completely checked for typographical and formatting issues, although they were corrected when seen. You should feel free to include such corrections, as necessary, in your next proposal.

202992_FDA
oposed PI and med

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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/s/

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HAMET M TOURE
09/06/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, September 05, 2012 5:57 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following PostMarketing Requirements. Please provide milestone dates:

A 24-month, 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-remitting multiple sclerosis.

Final Protocol Submission: MM/YY
Study/Trial Completion: MM/YY
Final Report Submission: MM/YY

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.

Final Protocol Submission: MM/YY
Study/Trial Completion: MM/YY
Final Report Submission: MM/YY

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.

Final Protocol Submission: MM/YY
Study/Trial Completion: MM/YY
Final Report Submission: MM/YY

We request your response by Monday, September 10, 2012, noon. Kindly provide your response by email and follow with an identical archival submission to NDA 202992.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
09/06/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, August 31, 2012 1:51 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have reviewed your proposed 7 mg carton and container labeling and we have the following comments:

**28 Tablet Wallet Blister-Front (Inside):**

Please revise the 28 tablet wallet blister-front for the 7 mg strength so the proprietary and established names are given more prominence by increasing the font size and relocating the proprietary and established names to the left side of the tablets similar to the 14 mg wallet blister-front presentation.

Please also clarify whether you are proposing a 5 tablet count or only the 28 tablet count for the 7 mg dose.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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/s/

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HAMET M TOURE
08/31/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, August 29, 2012 5:29 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** 202992_Advice memo

**Attachments:** 202992_Patient labeling comments_082912.pdf

Dear Dr. Psaras,

We refer to NDA 202992. We have completed our review of the medication guide and we have the attached comments.

202992_Patient labeling commen...

Please incorporate your proposed changes to the medication guide and provide your response in the version of the label you will send to us tomorrow.

We request that you note in a tracked version any changes (additions, deletions, and revisions) that you have made to our proposed patient labeling language.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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HAMET M TOURE
08/29/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, August 24, 2012 2:10 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** Proposed label

**Attachments:** 202992_FDA proposed label_24 August 2012.DOC

Dear Dr. Psaras,

We refer to NDA 202992. Please find enclosed our proposed label.

202992_FDA
roposed label_24 A.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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/s/

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HAMET M TOURE
08/24/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, August 03, 2012 2:05 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Nilda.Ramos@sanofi.com; Toure, Hamet
**Subject:** 202992_Advice

Dear Dr. Psaras,

We refer to NDA 202992. We also refer to your August 3, 2012, submission providing updated carton and container labeling. Your latest revisions to the 5 tablet and 28 tablet blister cards are acceptable.

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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/s/

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HAMET M TOURE
08/03/2012
Sent at request of DMEPA

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, August 02, 2012 12:40 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet; Nilda.Ramos@sanofi.com
**Subject:** 202992_Advice

Dear Dr. Psaras,

We refer to NDA 202992. We have reviewed your July 16, 2012, carton and container labeling proposal and we have the following additional comments regarding the 28 tablet wallet blister:

**28 Tablet Wallet Blister Front (Inside):**

The current design of the wallet blister card allows for the possibility of each of the (b) (4) blister cards to be separated from wallet. If any panel containing tablets were to be separated from the wallet, they will only be labeled with the 8 point proprietary name and the 6 point established name.

DMEPA has concerns regarding the small size of the proprietary name and established name particularly in regards to readability with this scenario. Due to the space limitations on the wallet blister front, we accept the rationale provided by the Applicant. However, if the blister card panels will contain any perforated edges that allows for the potential to separate the blister cards from the wallet, we recommend removing these perforations from the wallet card design, or revising the design or location of the proprietary and established name statements on the wallet panels which contain tablets.

We request your response to these comments at your earliest convenience. Provide your response as an archival submission to NDA 202992. Please let me know if you have questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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/s/

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HAMET M TOURE
08/02/2012

## Toure, Hamet

**From:** Chen, Lana Y
**Sent:** Wednesday, July 25, 2012 2:55 PM
**To:** Nilda.Ramos@sanofi.com
**Cc:** Toure, Hamet; Bradley, Nicole; Chen, Lana Y; Kelley, Laurie
**Subject:** FW: NDA 202992 Update - Carton and Container Submission

Hi Nilda,

Below are some additional comments to regarding the 28 tablet wallet blister (front).

**28 Tablet Wallet Blister Front:**

Increase the size and prominence of the proprietary name and strength statement, as they are currently presented in a font size that is difficult to read (8 point and 6 point), especially considering that the intended patient population for this product may experience visual problems, and it is the most important information on the label. Ensure the established name is at least half the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).

thanks,

Lana

(for Dr. Hamet Toure)

**********

Lana Y. Chen, R.Ph., CAPT-USPHS
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
Phone 301-796-1056
Fax 301-796-9842
Email: **lana.chen@fda.hhs.gov**

---

**From:** Nilda.Ramos@sanofi.com [mailto:Nilda.Ramos@sanofi.com]
**Sent:** Tuesday, July 24, 2012 11:13 AM
**To:** Chen, Lana Y
**Cc:** Toure, Hamet; Cynthia.Psaras@sanofi.com; Bradley, Nicole; Kelley, Laurie
**Subject:** RE: NDA 202992 Update - Carton and Container Submission

Captain Chen,

Can you please advise if the carton and container labeling that we submitted on 16 July 2012 have been reviewed and if we should be expecting additional comments.

Thanks to reply to me since Dr. Psaras is currently out of the office.

Nilda

---

**From:** Ramos, Nilda R&D/US
**Sent:** Monday, July 16, 2012 11:09 AM
**To:** Bradley, Nicole; Kelley, Laurie
**Cc:** 'Toure, Hamet'; Psaras, Cynthia R&D/US; Chen, Lana Y
**Subject:** NDA 202992 Update - Carton and Container Submission

Dear Dr. Bradley and Commander Kelly,

As requested by Dr. Toure in his email below, you are being provided with the attached electronic copy of the carton and container submission which was dispatched via the Electronic Submissions Gateway (ESG) today.

Regards,

Nilda RAMOS
Sr. Manager, Global Regulatory Affairs
Sanofi US
TEL.: 908.981-3574
MOBILE: 215-200-3437
55C, D-2, 2448 Mail Code 55D 225A
BRIDGEWATER – New Jersey 08807

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Friday, July 13, 2012 11:29 AM
**To:** Psaras, Cynthia R&D/US
**Cc:** Ramos, Nilda R&D/US; Chen, Lana Y; Bradley, Nicole; Kelley, Laurie
**Subject:** RE: IND 067476 and NDA 202992 Update

Dear Dr. Psaras,

I will be on leave later today and will return to the office on July 30, 2012. Please contact Dr. Bradley and Captain Chen for urgent issues or responses to information requests:

Dr. Bradley - covering from 7/13 to 7/20

CAPT Chen - covering from 7/23 to 7/27

Regarding your July 16, 2012, carton and container comments, please email an electronic copy of your submission to Commander Kelley and Dr. Bradley at the time of your archival submission. Please also provide the sequence number of the archival submission to them. We will send comments after our review of your submission.

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Thursday, July 12, 2012 2:17 PM
**To:** Toure, Hamet
**Cc:** Nilda.Ramos@sanofi.com
**Subject:** IND 067476 and NDA 202992 Update

Dear Dr. Touré,

I just wanted to make you aware of two upcoming submissions. We had stated that the audited nonclinical study report, JUV0024, which supports our pediatric development program, would be submitted to the IND on July 13, 2012. Due to the additional endpoints requested by the Agency we had to out source the study. The audited report will be submitted to the IND on July 31, 2012.

Our response to your Advice Memo received July 3, 2012 pertaining to cartons and containers will be submitted to the NDA on Monday, July 16, 2012. As you mentioned previously, you would like the packaging review completed prior to the labeling review. Should the Agency have any comments on the upcoming submission, will someone forward their comments to us in your absence? If so, since I will be out of the office as well, please have them copy Nilda Ramos on the request so that the team can promptly address any issues. Will we also be notified if the revised packaging is acceptable? Thank you in advance and have a great vacation.

Best regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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/s/

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HAMET M TOURE
08/02/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, July 03, 2012 5:29 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** 202992_Advice memo

Dear Dr. Psaras,

We refer to NDA 202992. We also refer to your June 29, 2012, submission providing a response to our June 5, 2012, Carton and Container comments.

We have reviewed your submission and we have the following comments:

**28 Tablets Wallet Sleeve:**

1. Ensure the lot number and expiration date are printed on the label per 21 CFR 201.17 and 21 CFR 201.18.

**28 Tablet Wallet Blister Front:**

1. Increase the size and prominence of the proprietary name and strength statement, as it currently appears that the manufacturer statement is of a larger size than that of the proprietary name, established name and strength statements. Ensure the established name is at least half the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).

**5 Tablet Wallet Blister Front:**

1. (b) (4)

2.

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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HAMET M TOURE
07/03/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, July 02, 2012 3:38 PM
**To:** Cynthia.Psaras@sanofi.com
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We acknowledge receipt of a follow up safety report for MFR# 2012SA002196 (pneumonia and lung abscess). Please confirm that the culture for tuberculosis is still pending.

Please respond by COB July 6, 2012.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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Silver Spring, MD 20993
Office: 301-796-7534
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hamet.toure@fda.hhs.gov

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HAMET M TOURE
07/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug
Administration Silver
Spring MD 20993

NDA 202992

**PROPRIETARY NAME REQUEST WITHDRAWN**

sanofi-aventis U.S., LLC
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

ATTENTION: Cynthia Psaras, PhD
Director, Global Regulatory Affairs

Dear Dr. Psaras:

Please refer to your New Drug Application (NDA) dated and received August12, 2011, submitted under section 505 of the Federal Food, Drug, and Cosmetic Act for Teriflunomide Tablets, 14 mg.

Please also refer to teleconference discussions on May 30, 2012 as well as June 4, 2012.

We acknowledge receipt of your correspondence, dated and received June 8, 2012, notifying us that you are withdrawing your April 16, 2012 request for a review of the proposed proprietary name Aubagio. This proposed proprietary name request is considered withdrawn as of June 8, 2012.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Laurie Kelley, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0558. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Hamet Toure at (301) 796-7534.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh
Director, Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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LAURIE A KELLEY
06/18/2012

CAROL A HOLQUIST
06/18/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, June 11, 2012 4:50 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

We request additional tables of baseline demographic information for each of the three regions (Eastern Europe, Western Europe, and the Americas) similar to what you have already provided for the whole randomized trial population in the HMR 1726 EFC 6049 clinical trial. Specifically, please provide a set of tables similar to:

1. Table 14 on page 74/184 of the Clinical Study Report entitled "Demographics and patient characteristics at baseline-randomized population"
2. Table 2 on page 28/38 Section 15.1 entitled "Baseline disease characteristics-randomized population"

Please provide these additional tables by June 22, 2012.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
06/11/2012
Sent at request of team leader

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, June 07, 2012 11:24 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

Table 6 of the ISS (Patient disposition in Pool 1, safety population) shows that 7.8% , 9.3% and 11.1% of patients on placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively, discontinued treatment due to adverse events. However, Table 22 of the ISS (Patients with treatment emergent adverse events leading to permanent discontinuation) shows that 7.6%, 9.1% and 11.8% in the placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively discontinued due to adverse events. Please clarify the discrepancy. Please respond by 6/8/12.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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/s/

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HAMET M TOURE
06/07/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, June 05, 2012 4:53 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Advice memo

Dear Dr. Psaras,

We refer to NDA 202992. We have reviewed your carton and container labeling proposal and have the following comments:

A. 28 Tablets Blister Card Wallet

1. Ensure that the proprietary name will be presented in title case, such as Tradename instead of TRADENAME. The use of all upper case letters is a form of tallman lettering, and the use of tallman lettering is reserved for drug name pairs that have been confused.

2. Revise the established name so that it is at least half the size of the proprietary name. Ensure that the established name has a prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).

3. Revise the strength statement “14mg” to read “14 mg” (space) “per Tablet”.

4. The [redacted] (b) (4) graphic is overly prominent and distracts from more important information on the label. We recommend removing the graphic, or minimizing and moving the graphic away from the proprietary name so that it does not compete with the prominence of the proprietary name, established name, and product strength.

5. The “Rx Only” statement is overly prominent. Debold the “Rx Only” statement.

6. The net quantity statement is overly prominent and competes with the product strength. Debold and decrease the prominence of the net quantity statement.

7. [redacted] (b) (4)

B. 5 Tablets Blister Card Wallet

1. See comments A.1 and A.6 above.

2. [redacted] (b) (4)

C. Carton Labeling (28 Tablets, 5 Tablets)

1. See comments A.1 to A.6 above.
2. The active ingredient statement, "Each tablet contains 14 mg teriflunomide," is on the side panel [redacted] (b) (4)

A. 28 Tablets Wallet Sleeve

1. See comments A.1 to A.6 above.
2. Ensure the lot number and expiration date are printed on the label per 21 CFR 201.17 and 21 CFR 201.18.

Please address these comments and provide your response as an amendment to NDA 202992.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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HAMET M TOURE
06/05/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, May 29, 2012 2:25 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. In reference to the IND safety report # 2012sa035825, 31 year old male who presented with myocardial infarction 7 years into teriflunomide treatment, please provide full narrative, ECG and electrolyte evaluations at baseline, at the time of hospitalization for MI and during the study. Submit the information by June 12, 2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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/s/

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HAMET M TOURE
05/29/2012
Sent at request of Safety Deputy Director

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, May 07, 2012 12:10 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 2020992. Our request #2 of April 20, 2020, read as follows:

> "As per Table 7 of your 4/17/12 response, 10 patients in the teriflunomide groups did not recover from ALT elevation ≥3xULN (8 who underwent washout and 2 who did not). Please provide the listing of these patients, including the date of last dose of study drug and the date of the last available follow up laboratory evaluation."

Please note that the intent of the request was to quickly evaluate whether the lack of normalization of liver enzymes was related to short follow up or to a true irreversible teriflunomide effect on liver enzymes.
Your response dated 4/23/12 includes the listing of patients with links to the narratives, and refers the reviewer to the laboratory listings were submitted as part of Amendment 11.
To expedite the reviewer's review, please submit the following information for patients who had ALT elevation ≥3xULN whose ALT values were not normal at the time of last laboratory follow up (including patients on placebo and teriflunomide treated patients), in Pool 1. Please respond by 5/9/12.

| Patient ID | Date of last ALT value >3x ULN | Date of drug discontinuation | Date of washout | Date of latest laboratory evaluation in which ALT was still above normal |
|---|---|---|---|---|
| Placebo | | | | |
| Teriflunomide 7 | | | | |
| Teriflunomide 14 | | | | |

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
05/07/2012
Sent at request of Acting Safety Deputy Director

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, May 01, 2012 3:35 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

**Attachments:** Picture (Enhanced Metafile); Picture (Enhanced Metafile)

Dear Dr. Psaras,

We refer to NDA 202992. Please respond to the following requests by COB on Thursday, May 3. In the future, please double check to make sure that the information provided in the responses is consistent throughout your submissions. This will assist in the review of this information and reduce the need for subsequent clarifying requests.

**1. We request clarification of the following discrepant counts regarding the number of Pool 1 subjects with serum potassium levels > 6 mmol/L. The discrepancies were found among three different documents, itemized in 1a, 1b, and 1c, below.**

1a. In Table 44, Titled "Electrolytes - Number of patients with abnormalities (CTCAE) according to baseline status - Safety population - Pool 1," on page 309 of the ISS, the total number of Pool 1 subjects with serum potassium levels >6 mmol/L was listed as 5 subjects in placebo, 5 subjects in teriflunomide 7 mg, and 7 subjects in teriflunomide 14 mg.

| Laboratory parameter<br>Baseline<br>by CTCAE criteria n/N1 (%) | Placebo<br>(N=421) | teriflunomide<br>7 mg<br>(N=429) | teriflunomide<br>14 mg<br>(N=415) |
|---|---|---|---|
| Potassium (hyperkalemia) | | | |
| Total[a] | | | |
| >ULN - ≤5.5 mmol/L | 16/420 (3.8%) | 18/428 (4.2%) | 12/413 (2.9%) |
| >5.5 - ≤6.0 mmol/L | 23/420 (5.5%) | 19/428 (4.4%) | 18/413 (4.4%) |
| >6.0 - ≤7.0 mmol/L | 2/420 (0.5%) | 1/428 (0.2%) | 3/413 (0.7%) |
| >7.0 mmol/L | 3/420 (0.7%) | 4/428 (0.9%) | 4/413 (1.0%) |

1b. On page 7 of the Sanofi response document sent by e-mail on April 11, 2012, the following text was listed:

> "for the 23 patients in the placebo-controlled pool 1, elevations above 6.0 mmol/L were balanced across treatment groups (9 patients in placebo, 7 patients in teriflunomide 7mg and 7 patients in teriflunomide 14mg)."

1c. No narratives for subjects in Study 2001 were submitted in response to the Agency request for narratives with data on "all subjects in Pool 1, Pool 2, and ongoing studies who had a serum potassium levels ≥ 6.0 mmol/L." Thus, all Pool 1 narratives should be from EFC6049 study subjects. From EFC6049, we received narratives for 6 subjects from placebo, 12 subjects from 7 mg teriflunomide, and 4 subjects from 14 mg teriflunomide. These narratives included subjects with a serum potassium measurement = 6.0 mmol/L, but this does not account for all of the differences between these counts and those listed in items 1a and 1b above.

**2. Related to item 1, we request any necessary revisions to the response to agency questions regarding serum potassium levels, sent on April 11, 2012 (response document and narratives).**

**3. Provide the following:**

3a. A table of Pool 1 subjects with serum potassium measurements > 6.0 mmol/L, stratified by treatment arm, that includes the subject numbers for each group, using the following table format:

| **Subject** | **Arm** | **Highest Pre-treatment K** | **Highest Post-treatment K** |
|---|---|---|---|
| **14 mg teriflunomide** | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| **7 mg teriflunomide** | | | |
| | | | |
| | | | |
| **placebo** | | | |
| | | | |
| | | | |

3b. A table of Pool 1 subjects with serum potassium measurements ≥ 6.0 mmol/L, stratified by treatment arm, that includes the subject numbers for each group, using the following table format:

| **Subject** | **Arm** | **Highest Pre-treatment K** | **Highest Post-treatment K** |
|---|---|---|---|
| **14 mg teriflunomide** | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| **7 mg teriflunomide** | | | |
| | | | |
| | | | |
| **placebo** | | | |
| | | | |
| | | | |

3c. A table of Pool 1 subjects with **treatment-emergent** serum potassium measurements > 6.0 mmol/L (i.e. exclude subjects who had a pre-treatment serum potassium measurement >5.4 mmol/L), stratified by treatment arm, that includes the subject numbers for each group, using the following table format:

| **Subject** | **Arm** | **Highest Pre-treatment K** | **Highest Post-treatment K** |
|---|---|---|---|
| **14 mg teriflunomide** | | | |
| | | | |
| | | | |

| | | | |
|---|---|---|---|
| | | | |
| | | | |
| **7 mg teriflunomide** | | | |
| | | | |
| | | | |
| **placebo** | | | |
| | | | |
| | | | |

3d. A table of Pool 1 subjects with **treatment-emergent** serum potassium measurements ≥6.0 mmol/L (i.e. exclude subjects who had a pre-treatment serum potassium measurement >5.4 mmol/L), stratified by treatment arm, that includes the subject numbers for each group, using the following table format:

| **Subject** | **Arm** | **Highest Pre-treatment K** | **Highest Post-treatment K** |
|---|---|---|---|
| **14 mg teriflunomide** | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| **7 mg teriflunomide** | | | |
| | | | |
| | | | |
| **placebo** | | | |
| | | | |
| | | | |

**4. Provide information requested in the table below.**

Table 1. Requests regarding Pool 1 subjects with serum potassium measurements ≥ 6.0 mmol/L

| Subject (treatment arm) | Request |
|---|---|
| EFC6049-2203-0014 (placebo) | We request specific results for UA micro results listed as "positive". |
| EFC6049-2600-0006 (14 mg) | - We request specific results for UA micro results listed as "positive".<br>- Why was a renal ultrasound ordered? We request the results of any kidney-related assessments in this subject. |
| EFC6049-2809-0002 (placebo) | Were this subject's repeatedly high potassium levels evaluated? What is the etiology of this subject's high potassium levels? |
| EFC6049-2809-0003 (14 mg) | Elevated potassium (b) (6) occurred during AE "Right inguinal hernia" for which he was hospitalized. This was not mentioned in the narrative. Did this subject receive surgery during this hospitalization? If yes, provide the dates. Is the cause of this subject's elevated potassium level known? |
| EFC6049-3008-0006 (14 mg) | We request specific results for UA micro results listed as "positive" or missing. |
| EFC6049-3204-0009 (7.mg) | We request specific results for UA micro results listed as "positive" or missing. |

| | |
|---|---|
| EFC6049-3205-0001 (7 mg) | What was the reason for this subject's unscheduled visit on 10/26/2005? What were the results of the urine micro exam on that date? |
| EFC6049-3508-0001 (placebo) | We request specific results for UA micro results listed as "positive" or missing. |
| EFC6049-3508-0001 (7 mg) | We request specific results for UA micro results listed as "positive" or missing. |
| EFC6049-3801-0008 | We request specific results for UA micro results listed as "positive" or missing. |

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
05/03/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, May 01, 2012 11:27 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following requests:

Please provide the listing of absolute eosinophil count and eosinophil count percentage (of total WBC) for patients with absolute eosinophil count >0.5 Giga/L in Pools 1 and 2.

Please direct the reviewer to the location of the analyses of coagulation parameters (descriptive statistics and PCSA) in Pools 1 and 2.

We request your response by 5/3/12.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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/s/

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HAMET M TOURE
05/01/2012
Sent at request of Deputy Director for Safety

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

**PROPRIETARY NAME REQUEST WITHDRAWN**

Sanofi-Aventis U.S., LLC
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

ATTENTION: Cynthia Psaras, PhD
Director, Global Regulatory Affairs

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 for teriflunomide tablets, 14 mg.

We acknowledge receipt of your correspondence, dated and received April 16, 2012, notifying us that you are withdrawing your December 2, 2011, request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of April 16, 2012.

We also acknowledge your correspondence, dated and received April 16, 2012, requesting review of your proposed proprietary name, Aubagio.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hamet Toure at (301) 796-7534.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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LAURIE A KELLEY
05/01/2012

CAROL A HOLQUIST
05/01/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, April 26, 2012 2:09 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dr. Psaras,

You are correct. Please kindly provide your response by COB Tuesday, May 1.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Wednesday, April 25, 2012 7:32 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Touré,

Just to be clear, adverse event reported term with the words "loin" and "pain" means both terms must be used by the investigator. Is this correct?

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

---

**From:** Psaras, Cynthia R&D/US
**Sent:** Wednesday, April 25, 2012 4:51 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Touré,

What is the timeline for this additional information since the original request is due tomorrow?

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Wednesday, April 25, 2012 4:41 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Psaras,

We have the following addendum to question 3 below:

In addition to the subjects listed in Question 3, we request patient files for any additional subject in completed or ongoing trials of teriflunomide who had an adverse event mapped to any of the following:

- Adverse event reported term with the words "loin" and "pain"
- Lower Level Terms Loin pain or Loin pain hematuria syndrome
- Preferred term Flank pain
- SMQ Acute Renal Failure

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
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10903 New Hampshire Ave
Silver Spring, MD 20993
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Toure, Hamet

**Sent:** Friday, April 20, 2012 2:58 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request this information by April 26, 2012.

1. Regarding LTS6050 subject 3803-0003, who had an increased creatinine level and was hospitalized:
   - On what date were her symptoms of nausea and vomiting documented to have started? Where was this information documented?
   - Laboratory results from 26 September 2008 were submitted in the response to Question 7, dated April 10, 2012. Is it known whether these labs were drawn before or after she received intravenous saline?

2. Did the urine microscopic examinations in teriflunomide studies (submitted 4/10-11/2012) evaluate for urine eosinophils?

3. We request patient files for the following subjects with an adverse event of flank pain or loin pain (without a clearly stated reason such as a fall), an adverse event of renal failure, or an adverse event of azotemia.

| USUBJID | Study/Arm | AE Preferred Term |
|---|---|---|
| 002001-124-0015-0011 | LTS6048/7 mg teri | Renal failure |
| 006049-250-2403-0008 | EFC6049/7 mg teri | Azotaemia |
| 006049-124-1209-0048 | EFC6049/placebo | Flank pain |
| 006049-124-1209-0045 | EFC6049/7 mg teri | Flank pain |
| 006049-124-1205-0010 | EFC6049/7 mg teri | Flank pain |
| 006049-826-2602-0001 | EFC6049/7 mg teri | Back pain* |

* This subject had two adverse events with AE reported terms of right sided loin pain and left sided loin pain, both of which were mapped to the MedDRA Preferred Term of Back pain.

The patient files should include, but not be limited to the following:

a. Age
b. Sex
c. Dates of screening, randomization and starting therapy
d. Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e. Narrative evaluating the listed adverse event, as well as any related adverse events
f. A list of other adverse events ( reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
g. Whether the subject had a history of renal or urologic disease.
h. Whether each subject had a history of urinary lithiases
i. Prior medications and concomitant medications with dates of start and end
j. Tables of the following laboratory results (sorted by date, with reference ranges): serum creatinine, creatinine clearance, BUN, uric acid, serum phosphorus, serum potassium, serum bicarbonate, any urine studies (including uric acid, creatinine, or **specific results of any urine microscopic exam**)*
k. Full reports for radiologic studies, pathology results, and special studies used to evaluate the adverse event (with dates and reference ranges) *
l. Whether the increase adverse event was preceded by dehydration, exercise, or an increase in physical activity in the 30 days prior to the adverse event.
m. Whether the cause of the adverse event was assessed. If yes, what was the likely cause, according to the treating physician(s) and/or investigator?
n. Whether the subject received any treatment or corrective action

* Relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, should be included in each patient file. Available baseline study results should also be included.

We request that you explicitly state pertinent negatives. (For example, if a subject did not have symptoms with

the increase in creatinine, this should be explicitly stated.) If information could not be obtained, we request that you explicitly state this.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
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/s/

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HAMET M TOURE
04/26/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, April 25, 2012 4:41 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Psaras,

We have the following addendum to question 3 below:

In addition to the subjects listed in Question 3, we request patient files for any additional subject in completed or ongoing trials of teriflunomide who had an adverse event mapped to any of the following:

- Adverse event reported term with the words "loin" and "pain"
- Lower Level Terms Loin pain or Loin pain hematuria syndrome
- Preferred term Flank pain
- SMQ Acute Renal Failure

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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Silver Spring, MD 20993
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hamet.toure@fda.hhs.gov

---

**From:** Toure, Hamet
**Sent:** Friday, April 20, 2012 2:58 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request this information by April 26, 2012.

1. Regarding LTS6050 subject 3803-0003, who had an increased creatinine level and was hospitalized:
   - On what date were her symptoms of nausea and vomiting documented to have started? Where was this information documented?
   - Laboratory results from 26 September 2008 were submitted in the response to Question 7, dated April 10, 2012. Is it known whether these labs were drawn before or after she received intravenous saline?

2. Did the urine microscopic examinations in teriflunomide studies (submitted 4/10-11/2012) evaluate for urine eosinophils?

3. We request patient files for the following subjects with an adverse event of flank pain or loin pain (without a clearly stated reason such as a fall), an adverse event of renal failure, or an adverse event of azotemia.

| USUBJID | Study/Arm | AE Preferred Term |
|---|---|---|
| 002001-124-0015-0011 | LTS6048/7 mg teri | Renal failure |
| 006049-250-2403-0008 | EFC6049/7 mg teri | Azotaemia |
| 006049-124-1209-0048 | EFC6049/placebo | Flank pain |
| 006049-124-1209-0045 | EFC6049/7 mg teri | Flank pain |
| 006049-124-1205-0010 | EFC6049/7 mg teri | Flank pain |
| 006049-826-2602-0001 | EFC6049/7 mg teri | Back pain* |

* This subject had two adverse events with AE reported terms of right sided loin pain and left sided loin pain, both of which were mapped to the MedDRA Preferred Term of Back pain.

The patient files should include, but not be limited to the following:

a. Age
b. Sex
c. Dates of screening, randomization and starting therapy
d. Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e. Narrative evaluating the listed adverse event, as well as any related adverse events
f. A list of other adverse events ( reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
g. Whether the subject had a history of renal or urologic disease.
h. Whether each subject had a history of urinary lithiases
i. Prior medications and concomitant medications with dates of start and end
j. Tables of the following laboratory results (sorted by date, with reference ranges): serum creatinine, creatinine clearance, BUN, uric acid, serum phosphorus, serum potassium, serum bicarbonate, any urine studies (including uric acid, creatinine, or **specific results of any urine microscopic exam**)*
k. Full reports for radiologic studies, pathology results, and special studies used to evaluate the adverse event (with dates and reference ranges) *
l. Whether the increase adverse event was preceded by dehydration, exercise, or an increase in physical activity in the 30 days prior to the adverse event.
m. Whether the cause of the adverse event was assessed. If yes, what was the likely cause, according to the treating physician(s) and/or investigator?
n. Whether the subject received any treatment or corrective action

* Relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, should be included in each patient file. Available baseline study results should also be included.

We request that you explicitly state pertinent negatives. (For example, if a subject did not have symptoms with the increase in creatinine, this should be explicitly stated.) If information could not be obtained, we request that you explicitly state this.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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/s/

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HAMET M TOURE
04/25/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, April 25, 2012 4:37 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request.

1. Please provide short narratives of patients who experienced drug overdose in the teriflunomide program.

2. Section 6.1.4 of your original ISS (analyses of AE by intrinsic factors, weight and body mass index) describes PK differences between subjects in the 25th and 75th percentile, but analyses of AE by BMI. Please provide analyses of AE similar to those provided by BMI (Appendix 1.5.3.3.36), but by weight (<25th percentile and ≥25th percentile) in Pool 1.

3. Table 31 of the original ISS shows analyses of neutrophil and lymphocyte values by CTCAE criteria. The reviewer has not been able to locate the analyses of hematologic parameters by PCSA criteria in the ISS or TEMSO clinical study report.

    a. Please direct the reviewer to the location of the analyses or submit the analyses by PCSA criteria for <u>all</u> hematologic values (not only neutrophils and leukocytes) in Pool 1 and 2.
    b. Provide a listing of patients who had elevated eosinophil count by PCSA criteria in Pool 1 and 2, along with the list of adverse events or other concurrent laboratory abnormalities presented by these patients.

Respond by COB 4/30/12.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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/s/

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HAMET M TOURE
04/25/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, April 20, 2012 3:01 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Request for information

Dear Dr. Psaras,

We refer to NDA 202992. We acknowledge receipt of your 1/19/12 response regarding ALT elevation in Pool 1, in Table 7 of your 4/17/12 response and Appendix 1.6.3.4.121 of the ISS.

1. You state that "The 4 patients in Table 7, but not counted in the 21 patients under teriflunomide 14 mg in Appendix 1.6.3.4.121 under "occurred during treatment" are actually the 4 counted under "occurred during washout" a little lower in this same appendix." Of note, the number of patients with ALT≥3xULN on placebo and teriflunomide 7 in Table 7 of your 1/17/12 response is the same as the number of patients with ALT >3xULN on treatment in Appendix 1.6.3.4.121 of the ISS. Please clarify whether any of patients in the placebo and teriflunomide 7 mg groups ALT >3ULN "during washout" (9 and 11 patients respectively), are also included among the patients in the "during treatment" (17 and 14, respectively) in Appendix 1.6.3.4.121.

2. As per Table 7 of your 4/17/12 response, 10 patients in the teriflunomide groups did not recover from ALT elevation ≥ 3xULN (8 who underwent washout and 2 who did not). Please provide the listing of these patients, including the date of last dose of study drug and the date of the last available follow up laboratory evaluation.

3. As per Table 4 of your 4/17/12 response, some patients had ALT≥3xULN at least twice in both the treatment and washout periods. However, for placebo, the overall number of patients (16)exceeds the sum of the individual periods (7 during treatment, 8 during washout). Please clarify the number of patients who had ALT≥3xULN at least twice in the placebo group.

We request your response by April 24, 2012.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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/s/

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HAMET M TOURE
04/21/2012
Sent at request of Safety Deputy Director

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, April 20, 2012 2:58 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request this information by April 26, 2012.

1. Regarding LTS6050 subject 3803-0003, who had an increased creatinine level and was hospitalized:
   - On what date were her symptoms of nausea and vomiting documented to have started? Where was this information documented?
   - Laboratory results from 26 September 2008 were submitted in the response to Question 7, dated April 10, 2012. Is it known whether these labs were drawn before or after she received intravenous saline?

2. Did the urine microscopic examinations in teriflunomide studies (submitted 4/10-11/2012) evaluate for urine eosinophils?

3. We request patient files for the following subjects with an adverse event of flank pain or loin pain (without a clearly stated reason such as a fall), an adverse event of renal failure, or an adverse event of azotemia.

| USUBJID | Study/Arm | AE Preferred Term |
|---|---|---|
| 002001-124-0015-0011 | LTS6048/7 mg teri | Renal failure |
| 006049-250-2403-0008 | EFC6049/7 mg teri | Azotaemia |
| 006049-124-1209-0048 | EFC6049/placebo | Flank pain |
| 006049-124-1209-0045 | EFC6049/7 mg teri | Flank pain |
| 006049-124-1205-0010 | EFC6049/7 mg teri | Flank pain |
| 006049-826-2602-0001 | EFC6049/7 mg teri | Back pain* |

* This subject had two adverse events with AE reported terms of right sided loin pain and left sided loin pain, both of which were mapped to the MedDRA Preferred Term of Back pain.

The patient files should include, but not be limited to the following:

a. Age
b. Sex
c. Dates of screening, randomization and starting therapy
d. Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e. Narrative evaluating the listed adverse event, as well as any related adverse events
f. A list of other adverse events ( reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
g. Whether the subject had a history of renal or urologic disease.
h. Whether each subject had a history of urinary lithiases
i. Prior medications and concomitant medications with dates of start and end
j. Tables of the following laboratory results (sorted by date, with reference ranges): serum creatinine, creatinine clearance, BUN, uric acid, serum phosphorus, serum potassium, serum bicarbonate, any urine studies (including uric acid, creatinine, or **specific results of any urine microscopic exam**)*
k. Full reports for radiologic studies, pathology results, and special studies used to evaluate the adverse event (with dates and reference ranges) *
l. Whether the increase adverse event was preceded by dehydration, exercise, or an increase in physical activity in the 30 days prior to the adverse event.
m. Whether the cause of the adverse event was assessed. If yes, what was the likely cause, according to the treating physician(s) and/or investigator?
n. Whether the subject received any treatment or corrective action

* Relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, should be included in each patient file. Available baseline study results should also be included.

We request that you explicitly state pertinent negatives. (For example, if a subject did not have symptoms with the increase in creatinine, this should be explicitly stated.) If information could not be obtained, we request that you explicitly state this.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
04/21/2012
Sent at request of Safety Deputy Director

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, April 18, 2012 11:37 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. In reference to the analyses of ALT elevations in teriflunomide studies submitted on 4/17/12:

Table 7 (ALT elevations in Pool 1) includes 14 patients on teriflunomide 14 mg with ALT elevation > or = 3x ULN. However, Appendix 1.6.3.4.121 of the ISS includes 21 patients on teriflunomide 14 mg with ALT >3xULN. Please clarify why there are more patients with ALT >3x ULN than with ALT > or = 3x ULN in the teriflunomide 14 mg group.

Also, Table 1 includes patients with ALT elevation > or = 3x or 5x ULN only once, and Table 4 includes patients with ALT > or = 3x ULN at least twice. Please submit a table of ALT > or = 3x ULN and ALT > or = 5x ULN at least once (which would include patients who had it only once and patients who had it more than once).

Please respond by 4/19/12.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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HAMET M TOURE
04/18/2012
Sent at request of Acting Deputy Director for Safety

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

**REVIEW EXTENSION – MAJOR AMENDMENT**

Sanofi-aventis U.S. Inc.
Attention: Cynthia Psaras, Ph.D.
Director, Global Regulatory Affairs
200 Crossing Blvd
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, for Teriflunomide 14 mg tablets.

On April 13, 2012, we received your April 13, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 12, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 1, 2012.

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

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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RUSSELL G KATZ
04/18/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, April 16, 2012 12:01 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. Please note that our request of April 9, 2012 referred to analyses of ALT elevation equal to or greater than 3 fold the upper limit of normal. The analyses you submitted are increases greater than 3 fold the upper limit of normal. Please submit analyses as requested on April 9, 2012 by April 17, 2012.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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/s/

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HAMET M TOURE
04/16/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, April 11, 2012 11:03 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Request for information

Dear Dr. Psaras,

We refer to NDA 202992. We have the following request for information.

Appendix 1.7.2.1 of your ISS includes analyses of potentially clinically significant abnormalities (PCSA) in systolic and diastolic BP in Pool 1. It shows that the percentage of patients with such events was greater with teriflunomide as compared to placebo. Please provide a summary table or short narratives of the patients who fulfilled PCSA criteria for increased blood pressure by treatment group in Pool 1. Specifically, include the following information: prior history of HTN, need for new treatment or modification of treatment, any symptoms associated with increased BP, action taken with drug and outcome (resolved or not; long term outcome -did any of these patients had a CV event/death?).

Provide response by COB 4/16/12.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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/s/

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HAMET M TOURE
04/11/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, April 11, 2012 11:01 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

Table 5 of the ISS lists the definition of AESI. Most of them refer to MedDRA Narrow SMQs. Please provide the full list of preferred terms used in the search for each AESI.
Provide by COB today.

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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HAMET M TOURE
04/11/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, April 10, 2012 6:03 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following request.

In reference to the TEMSO trial please prepare an analysis of time to relapse after drug discontinuation including Kaplan-Meier curves and an analysis of number of patients with relapse after drug discontinuation, both for all three treatment arms. Please do two separate analyses for those who received washout with cholestyramine/charcoal after drug discontinuation and for those that did not.

Please do the same analysis for the Interim data from the TOWER trial as well.

Please submit by COB 4/20/2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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HAMET M TOURE
04/11/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, April 10, 2012 5:11 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Subject:** RE: 202992_Information request

Dear Dr. Psaras,

We were referring to 3009/0016.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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10903 New Hampshire Ave
Silver Spring, MD 20993
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Tuesday, April 10, 2012 4:38 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Touré,

Our pharmacovigilence database has been down and we are unable to obtain the information you requested. We are trying to obtain the information from other sources but due to the time difference we were unable to obtain it by 4:30 PM. In the mean time, I would like to clarify the second patient listed below. Is it patient 3009/0015 or 3009/0016? The latter patient was a death in LTS6050 and was on placebo in EFC6049 and teriflunomide 7 mg in LTS6050.

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Monday, April 09, 2012 11:14 AM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

Please provide treatment group for the following cases by COB tomorrow 4/10/12.

8510/0005. Destructive tuberculosis of right lung (TOPIC).

3009/0015. Found dead (LTS6050).

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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HAMET M TOURE
04/10/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, April 09, 2012 12:57 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

**Attachments:** Picture (Enhanced Metafile)

Dear Dr. Psaras,

We refer to NDA 202992. We have the following request:

Table 1.6.2.3.6 on page 7942 of the ISS says that **6** of 587 subjects who received 7 mg of teriflunomide in Pool 2 experienced an increase in serum creatinine > or = to 100% of baseline. However, it appears that we have received narratives for **7** subjects who received 7 mg of teriflunomide in Pool 2 and who experienced an increase in serum creatinine > or = to 100% of baseline.

TEMSO
1209-0023
2406-0007
3003-0022
3208-0004
3508-0007

LTS6050
1201-0002
3803-0003

Please clarify whether this table needs to be corrected.

1.6.2.3.6 Renal function - Number of patients with abnormalities (PCSA) according to baseline status - Safety population - Pool 2

| Laboratory parameter<br>Baseline<br>by PCSA criteria n/N1 (%) | teriflunomide<br>7 mg<br>(N=587) | <br>14 mg<br>(N=548 |
|---|---|---|
| Creatinine | | |
| Total[a] | | |
| ≥150 µmol/L | 5/585 (0.9%) | 5/546 ( |
| ≥30% change from baseline | 45/585 (7.7%) | 42/546 ( |
| ≥100% change from baseline | 6/585 (1.0%) | 6/546 ( |
| >3*Baseline or >3 ULN | 4/585 (0.7%) | 3/546 ( |
| >6 ULN | 0/585 | 1/546 ( |

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Please provide your response by your response by April 11, 2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products

Bldg. 22, Room 4395
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HAMET M TOURE
04/10/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, April 09, 2012 12:22 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Request for information

Dear Dr. Psaras,

We refer to NDA 202992. We have the following request:

Patient 840074/004, who died in a motor vehicle accident (b) (6) days into teriflunomide 7 mg treatment in TOWER was diagnosed with Brugada syndrome on Day 1 of teriflunomide treatment. Please provide information about what was the basis for the diagnosis of Brugada syndrome in this patient by COB 4/10/12.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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HAMET M TOURE
04/09/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, April 09, 2012 11:20 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request this information by April 12, 2012.

1. Please provide analyses of ALT elevation ≥ 3xULN x1 and ≥ 5xULN x1 in Pool 1 and Pool 2, TOWER and TENERE by treatment group, overall and separated by treatment period (whether they occurred during the active treatment period or during washout).
2. Provide the same analyses for patients who had ≥ 3xULN twice.
3. Provide analyses of frequency of ALT normalization among patients discontinued because of ≥ 3xULN or had ALT ≥3xULN at the time of discontinuation/completion of study drug in Pool 1, similar to that provided in Appendix 1.6.3.4.121 of the ISS. Clarify whether any of those patients did not undergo washout with cholestyramine or charcoal.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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HAMET M TOURE
04/09/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, April 09, 2012 11:14 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

Please provide treatment group for the following cases by COB tomorrow 4/10/12.

8510/0005. Destructive tuberculosis of right lung (TOPIC).

3009/0015. Found dead (LTS6050).

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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/s/

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HAMET M TOURE
04/09/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, April 06, 2012 8:43 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request this information by April 11, 2012.

1. Eleven subjects in the TEMSO trial had serum potassium levels listed as 14.6 mmol/L. We request your assessment of these potassium levels. Was there any documentation of specimen hemolysis associated with these measurements?

2. For all subjects in Pool 1, Pool 2, and ongoing studies who had a serum potassium levels ≥ 6.0 mmol/L, we request narratives assessing the high potassium level of each subject, including, but not limited to, the following information:

a. Age
b. Sex
c. Dates of screening, randomization and starting therapy
d. Whether the subject had a high serum potassium level at baseline
e. Whether the patient completed or did not complete the study, with dates and reason for withdrawal
f. Adverse events ( reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
g. Whether the subject had a history of renal or urologic disease.
h. Assess any factors contributing to increased serum potassium level, including but not limited to: increase in potassium intake, hemolysis, decrease in renal function, concomitant electrolyte abnormality, leukocytosis, or thrombocytosis
i. Prior medications and concomitant medications with dates of start and end
j. Tables of the following laboratory results (sorted by date, with reference ranges): serum creatinine, creatinine clearance, BUN, uric acid, serum phosphorus, serum potassium, serum bicarbonate, any urine studies (including uric acid, creatinine, or specific results of any urine microscopic exam)*
k. Whether the subject received any treatment or corrective action, including but not limited to intravenous fluids, medications, emergency room evaluation and treatment, hospitalization, or hemodialysis
l. We request copies of all available ECGs in these subjects, as well as any related ECG reports, interpretations, or assessments

* Relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, should be included in each patient file. Available baseline study results should also be included.

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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/s/

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HAMET M TOURE
04/06/2012
Sent at request of Team Leader

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, April 04, 2012 3:38 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

**Attachments:** 202992_Information request_040412.doc

Dear Dr. Psaras,

We refer to NDA 202992. We have the enclosed information request:

202992_Informatio
n request_040...

Please let me know if you have any questions. We request your response by Monday, April 9, 2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

We request this information by Monday, April 9, 2012.

1. Confirm whether the following subjects received any treatment or corrective action, including but not limited to intravenous fluids, emergency room treatment, hospitalization, or hemodialysis for their increased creatinine. This information was requested, but was not included in the narratives submitted March 9, 2012. We request that you explicitly state pertinent negatives. (For example, if a subject did not have treatment with the increase in creatinine, this should be explicitly stated.) If information could not be obtained, we request that you explicitly state this.

TEMSO

- 1211-0008
- 2406-0007
- 3003-0022
- 3207-0004
- 3207-0010
- 3208-0004
- 4602-0007
- 4802-0002

LTS6048

- 0014-0050

LTS6050

- 1201-0002
- 3803-0003

2. For subjects with >100% in serum creatinine from baseline, provide specific results of urine microscopic exams. Information that the exam was “Positive” is not sufficient.

3. In the patient files submitted March 9, 2012, some subjects in the TEMSO study had electrolyte measurements, including serum potassium levels, missing on the day of the measured creatinine increase. For the subjects and dates below, we request that you provide the missing laboratory measurements.

Provide an explanation of why these results were missing from the March 9, 2012 patient files.

| **Subject** | **Date** |
|---|---|
| 1211-0008 | 2007-02-01 |
| 2406-0007 | 2005-08-18 |
| 3207-0010 | 2008-06-18 |
| 3508-0007 | 2008-05-26 |

4. TEMSO subjects 1209-0023 and 4802-0002 both had serum potassium levels listed as14.6 mmol/L on the day of their creatinine increases. We request your assessment of these potassium levels. Was there any documentation of specimen hemolysis associated with these measurements?

5. In the TEMSO trial, what standard procedures were in place to address critical laboratory values, such as the high serum potassium levels that were recorded? Were these procedures followed in subjects who had high serum potassium levels recorded?

6. Were any EKGs performed in subjects with >100% in serum creatinine from baseline with high serum potassium measurements? We request all available EKGs in these subjects, as well as any related interpretations or assessments.

7. The narrative for LTS6050 subject 3803-0003 says the following:

> "On Day 1286 ([redacted] (b) (6)), the patient had an elevated level of serum creatinine of 248 micromol/L (normal range 31-101 micromol/L) with elevated serum uric acid at 1297micromol/L (normal range 125-428 micromol/L), elevated urea at 53.6 (normal range 1.4-8.6 mmol/L), elevated serum phosphorus at 2.36 mmol/L (normal range 0.71-1.65 mmol/L), and normal serum potassium."
>
> "The abnormal creatinine result was considered as erroneous."

The narrative for EFC10531 subject 616005006 says the following:

> "On Day 433 [redacted] (b) (6) the patient had an elevated serum creatinine value of 292 micromol/L (normal range 31-101 micromol/L) with BUN at 14.3 mmol/L, and serum phosphorus at 1.96 mmol/L (normal range 0.71-1.65 mmol/L)."
>
> "Regarding the abnormal serum creatinine value, the site reported an incorrect sample handling that explained the creatinine value peak."

Several teriflunomide-treated subjects, including the two subjects listed above, experienced multiple, concurrent laboratory abnormalities that were: 1) consistent with changes seen with acute renal failure; and 2) markedly different from baseline.

We request an explanation of what type of laboratory error could cause multiple erroneous results consistent with acute renal failure.

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/s/

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HAMET M TOURE
04/04/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, April 02, 2012 4:33 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. Please provide the following information:

1. Patient 6049-276-2003-0002, 41 yo F, on teriflunomide 7 mg discontinued because of fatigue and vomiting during the extension study. There is no mention of any laboratory measurements in the narrative. Did she have a work up to rule out hepatitis or renal failure. Please provide laboratory evaluations and outcome of this patient.

2. Three patients were found dead in extension studies with teriflunomide. Sudden death has been reported in patients with MS and brainstem involvement. Did these patients have brainstem involvement? Please provide full brain MRI reports of these patients.

3. Patient 8400086007 in TOWER, is listed as developing renal artery stenosis on Day 67 of the study. However, she was known to have renal artery stenosis before entering the study. For two days preceding the hospitalization she had intermittent chest pressure radiated to the left arm consistent with unstable angina. The narrative says that the patient discontinued on Day 65 due to “other reasons”. Nothing is said of the workup on Day 67. Please clarify the course of events with this patient.

4. Patient 804117008, in TOWER was diagnosed with chronic renal failure on day 18. She was seen by a nephrologist and hospitalized. Event resolved on Day 31. Please provide a patient file, using the format detailed in the agency request dated February 25, 2012. Please ensure that all available laboratory evaluations (including those collected during the hospitalization) are included, as well as the nephrologist's evaluation and hospital discharge summary.

5. Patient 002001-124-0015-0020 was diagnosed with connective tissue disorder on Day 260 of treatment, and discontinued on Day 1030 because of connective tissue disorder. There is no explanation as to what kind of symptoms she had, how was the diagnosis made and what event specifically led to study discontinuation on Day 1030. Was there respiratory involvement? Please provide additional information about this case.

6. Patient 006049-152-3801-0006 was diagnosed with rheumatoid arthritis on Day 35 of teriflunomide treatment leading to drug discontinuation. Please provide additional information regarding signs, symptoms and work up that led to such diagnosis. Additionally, a patient had a serious AE of rheumatoid arthritis in the TOPIC study. Please proved additional information about this patient.

7. Patient 6049-840-1037-0001 developed confusion 2 days into teriflunomide 7 mg treatment. The narrative does not mention vital signs (such as hypertension) or any evaluations such as laboratory measurements to rule out a metabolic encephalopathy, CT scan to rule out a stroke, EEG to rule out a seizure or CSF analysis to rule out infection. Please clarify whether this patient had any work up done to identify the cause of the confusion.

8. Several patients were found to have hemangioma of the liver, fibro nodular hyperplasia of the liver or hepatomegaly in teriflunomide studies on routine abdominal ultrasound. Please provide a summary table listing the patient ID number/study; treatment group; whether baseline US was available prior to starting drug and whether finding was present on baseline US or not as well as the relative day of diagnosis of the event and action taken with the drug, including events that occurred in ongoing studies.

9. Your 120-day SUR does not include adverse events datasets that would allow replication of your analyses in Pool 2a. Please submit the 120-day updated ISS AE datasets.

10. Patient 6049/1209/0005 is reported to have had grade 3 anemia treated with iron and vitamin B12. The narrative for this patient refers to an event of hepatic steatosis, but does not provide information about the type of anemia she had, values for WBC and platelets or what kind of work up she had, if she had any. Please provide available information about the diagnosis of anemia in this patient. Did any of the patient with anemia grade 3 have a work up to identify the type of anemia associated with teriflunomide?

11. Patient 6049-124-1201-0002 was diagnosed with posterior reversible encephalopathy with no evidence of hypertension 4 years into teriflunomide treatment. She did have CSF cultures and JC virus testing back in August 2011. Cultures were said to be negative and results of JC virus testing was pending at the time of the initial report. Please clarify which cultures were done and provide final results of JC virus testing.

    Additionally, please provide the following information. (It is possible that you responded to some of these requests already, however, the reviewer is not able to locate that information).

12. There were only 8 patients from the US in the ISS. At the preNDA meeting the DNP requested Sanofi to provide justification for the applicability of teriflunomide data to U.S. patients, given the majority of subjects in Study EFC6049/TEMSO are from non-U.S. locations. Have you submitted a justification of applicability of the data?

13. Please clarify whether patient # 006049-643-3210-0003 had syphilis reactivation or not.

Please submit responses by April 12, 2012.

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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HAMET M TOURE
04/02/2012
Sent at request of Team Leaders

**Bouie, Teshara**

**From:** Bouie, Teshara
**Sent:** Friday, March 30, 2012 2:31 PM
**To:** 'cynthia.psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** NDA 202992 - Information Request

**Importance:** High

Hi Cynthia,

The proposed dissolution acceptance criterion of "Q = (b) (4) in 30 minutes" for teriflunomide tablets is not supported by the provided dissolution data. The provided data from the clinical, stability, and commercial batches clearly indicate that a mean amount dissolved of at least (b) (4) is achieved in 20 minutes. However, we acknowledge that several batches may require Stage 2 or Stage 3 testing at the 20 minutes timepoint; therefore, we are willing to accept a criterion of Q = (b) (4) at 30 minutes for your product. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing.

Accordingly, please revise the dissolution acceptance criterion for Teriflunomide IR 14 mg tablets to "Q = (b) (4) in 30 minutes" and provide the revised specification table for your teriflunomide film-coated 14 mg tablet drug product.

We request a response as soon as possible.

Thanks,

*Teshara G. Bouie, MSA, OTR/L*
CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

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TESHARA G BOUIE
03/30/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, March 28, 2012 5:11 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Request for information

Dear Dr. Psaras,

We are in agreement and we have no additional comments.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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10903 New Hampshire Ave
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Wednesday, March 28, 2012 7:51 AM
**To:** Toure, Hamet
**Subject:** RE: 202992_Request for information

Dear Dr. Touré,

I do not believe we have received a response from your team for this clarification. Please let us know if your team is in agreement. Thank you.

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Friday, March 02, 2012 12:23 PM
**To:** Psaras, Cynthia R&D/US
**Subject:** RE: 202992_Request for information

Dear Dr. Psaras,

I will share your response with the review team.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Thursday, March 01, 2012 5:18 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Request for information

Dear Dr. Touré

Below is an excerpt from email exchanges between Dr. Sarah Ji and you concerning Question 1 in the Agency's pre-NDA meeting minutes.

On April 22, 2011, Dr. Sarah Ji sent you an email requesting clarification of the Agency's pre-NDA meeting minutes pertaining to Question 1.

"In addition, after reviewing Agency's minutes, the sponsor would like to ask Agency's clarification concerning the required presentation of efficacy data for Study EFC10531/TOWER interim analysis under Question 1.

The sponsor confirms that no futility analysis is planned on EFC10531/TOWER, and thus we appreciate your agreement in the minutes for Question 1 that the following descriptive data for ARR will suffice:

- Estimate and 95% confidence interval for ARR by treatment group for confirmed, on treatment relapses (primary)
- Estimate and 95% confidence interval for ARR by treatment group for all on treatment relapses (confirmed and non confirmed as supportive)

- ARR estimates and 95% confidence intervals within pre-defined subgroups

Regarding the evaluation of treatment response by treatment duration, we will provide the Nelson-Aalen mean cumulative function plot which provides the cumulative hazard over time. "

On May 12, 2011, you sent an Advice email to Dr. Ji with the following comment on Question 1:

"We have the following comments regarding your post-meeting follow-up clarifications regarding the March 28, 2011 pre-NDA meeting.

**Question 1:**
**FDA Comments to Sponsor's Post-Meeting Follow-Up:**

Descriptive data will suffice."

Based on this response from the Agency, no separate table was produced for efficacy by time period for the NDA submission.

As agreed, the Nelson-Aalen mean cumulative function plot which provides the cumulative hazard over time (see appendix 14.2.6.1.2 for confirmed relapses and appendix 14.2.6.1.4 for confirmed and non-confirmed relapses in the TOWER interim clinical study report) was provided for the evaluation of treatment responses by treatment duration.

Please let me know if you have any comments.

Kind Regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Wednesday, February 29, 2012 12:02 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Request for information

Dear Dr. Psaras,

We refer to NDA 202992. Please let us know if in the NDA the efficacy analysis for the TOWER study was presented not only in the aggregate but in bins of various duration and where this might be found in the application. See Question 1 below from the preNDA meeting.

***Question 1:*** *Does the agency agree with the proposed presentation of efficacy data from the placebo-controlled studies of teriflunomide (7 mg and 14 mg once daily) in the treatment of relapsing forms of multiple sclerosis?*
***FDA Preliminary Response***

We agree with the proposed presentation of data from EFC6049 (TEMSO) and HMR1726/2001. For EFC10531 (TOWER), please make clear in your interim analysis the duration of treatment (both in aggregate and in bins of various duration) of subjects with trial medication.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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hamet.toure@fda.hhs.gov

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HAMET M TOURE
03/30/2012
Sent at request of Team Leader

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, March 28, 2012 12:05 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

> Teriflunomide is associated with low serum uric acid and phosphorus levels in clinical trials. You have attributed the low uric acid levels to uricosuria due to inhibition of urate transport through the apical urate/anion exchanger. However, you have not provided an explanation for the effects on phosphorus. Your proposed label for teriflunomide states [redacted] (b) (4)
>
> Please clarify the mechanism of hypophosphatemia and whether the effects of hypophosphatemia and hypouricemia are independent or not.

Please respond by April 6, 2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
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/s/

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HAMET M TOURE
03/28/2012
Sent at request of team leaders

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, March 28, 2012 11:08 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: NDA 202992: Request for Feedback on Changes to Packaging

Dear Dr. Psaras,

Please send your revised carton and container labeling now. This will prevent duplicate work at the end of the review cycle.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Wednesday, March 28, 2012 7:47 AM
**To:** Toure, Hamet
**Subject:** NDA 202992: Request for Feedback on Changes to Packaging

Dear Dr. Touré,

Our team is considering changing the artwork on our packaging for teriflunomide. Does your team recommend that we do this now or during labeling negotiations? Thank you in advance for your feedback.

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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HAMET M TOURE
03/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992 **INFORMATION REQUEST**

Sanofi-aventis U.S. LLC
Attention: Cynthia Psaras, Director
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Ms. Psaras:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Teriflunomide Tablets, 14 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

FDA, Division of Pharmaceutical Analysis (DPA) have evaluated your HPLC methods for the identity, determination of assay and uniformity of content of teriflunomide, and determination of degradation products in film-coated tablets (Sanofi Aventis U. S., Method ID QUA-FR-2011-04280 –EN-1.0, 3.2.P.5.2 Analytical Procedure). We have the following comments pertaining to the method:

1. The system suitability test for the determination of degradation products (Sec 4.2.2) states the signal to noise ratio (S/N) (b) (4) (b) (4) should be (b) (4). The (b) (4) concentration (b) (4) in the test solution corresponds to the release criteria concentration of (b) (4) given in the specification, Teriflunomide-film coated tablets-14 mg (QUA-FR-2011-00700 –EN-1.0). The signal to noise ratio for the Limit of Quantitation (LOQ) should be greater than or equal to 10 according to the ICH Q2B guideline. Thus, the signal to noise ratio of (b) (4) for the release criteria concentration is below the ICH Limit of Quantitation. Modify the method, as suggested in 2a below so as to conform to ICH Q2B.

2. The method specified the amount of (b) (4) in the sample be less than or equal to (b) (4) DPA calculated the LOQ by the ICH Q2B procedure based on the standard deviation and the slope of the calibration curve. The Limit of Detection (LOD) and LOQ were determined to be (b) (4), respectively. Thus, the specification for the content (b) (4) is too close to the LOQ.

   a. Therefore, increase the sample concentration by changing the second dilution in the sample preparation (b) (4). The peak area of the teriflunomide would still be within the linear range.

3. The method states the disregard limit for degradation products is (b) (4) which is above the (b) (4) specification for (b) (4). The method should state the disregard limit for degradation products other that (b) (4) is (b) (4).

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

---

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/s/

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RAMESH K SOOD
03/27/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, March 19, 2012 12:06 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

> ECG data in the interim analysis from TOWER includes only 60-75 patients per treatment group (out of the approximately 350 randomized per group) and is limited to tables of outlier analyses. Please clarify if 60-75 is the number of patients evaluated with ECG or the number of patient with available post baseline ECG at the time of cut-off date in the TOWER study. The cut-off date for the analyses included in TOWER was November 2010. It is our understanding that the TOWER study is complete. Please provide updated, standard ECG analyses of all patients with available ECG data.
> Similarly, provide updated, standard analyses of pulmonary function tests for all patients with available PFT data in the TOWER study.

Submit information by April 13, 2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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10903 New Hampshire Ave
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HAMET M TOURE
03/19/2012
Sent at request of acting safety deputy director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992 **INFORMATION REQUEST**

Sanofi-aventis U.S. LLC
Attention: Cynthia Psaras, Director
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Ms. Psaras:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Teriflunomide Tablets, 14 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The provided dissolution data do not support the proposed acceptance criterion of Q= (b) (4) at 45 minutes for your product. Your dissolution data from clinical batches, commercial batches with development image, and commercial batches with final image (Module 3.2.P.2, Figures 21 and 22 and Tables 28-31 on page Nos. 53-35), clearly indicate that (b) (4) of teriflunomide is dissolved in 20 min. Therefore, please revise the dissolution acceptance criterion for your proposed product to Q= (b) (4) at 20 minutes and submit the updated specifications table for your drug product.

We request a response by March 23, 2012.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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RAMESH K SOOD
03/16/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, March 14, 2012 2:57 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. The reviewers have not been able to locate all the narratives for pregnancies in the NDA. Please provide the location of the narratives for each of the pregnancies in the Teriflunomide program. If possible, provide a single list with all pregnancies with hyperlinks to each narrative or provide a single document with all the narratives. Please respond by COB 3/20/12.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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HAMET M TOURE
03/14/2012
Sent at request of Acting Safety Deputy Director

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, March 09, 2012 4:53 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. In reference to IND safety report MFR# 2012SA002518 and your response to the FDA request for information submitted 3/8/12, the patient was neutropenic. Please provide hemoglobin and platelet count. We look forward to seeing the EBV serology as soon as available.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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HAMET M TOURE
03/09/2012
Sent at request of Acting Safety Deputy Director

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, March 05, 2012 12:25 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. In reference to the IND safety report MFR# 2012SA002518 submitted on 3/1/12, from Study HMR1726D/EFC6260(3005, Investigator 6201, Patient 0005:

1. Was there any imaging (chest X-ray, CT scan) done in September 2011 when she complained of shortness of breath, and was diagnosed with asthma despite normal spirometry?
2. As per the report, she did have a history of asthma prior to entering the study. Please clarify for how long and how it was treated prior to entering the study.
3. Please provide ALT, AST, bilirubin and alkaline phosphatase values during hospitalization in (b) (6) and a copy of laboratory testing supporting the diagnosis of mononucleosis by Epstein barr.
4. Did she receive cholestyramine washout?

Please submit information by COB 3/8/12.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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HAMET M TOURE
03/05/2012
Sent at request of acting safety deputy director

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, March 02, 2012 5:25 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We cannot locate the narrative for patient 2001-124-0029, a 43 year old female diagnosed with sarcoidosis during teriflunomide treatment. Please provide the location of the narrative or submit the narrative, including the results of the bronchoscopy/lung biopsy, by COB 3/6/12.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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HAMET M TOURE
03/02/2012
Sent at request of safety deputy director

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, March 01, 2012 2:55 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request - Serum Creatinine

Dear Dr. Psaras,

We request that you submit the information as requested. The short paragraph summaries that were provided are not adequate to characterize these episodes of increased creatinine. In Pool 1 there were 7 subjects with severe decreases in creatinine clearance <30 cc/minute, all of whom were treated with teriflunomide.

We are concerned that these are cases of acute renal failure caused by teriflunomide-induced hyperuricosuria. Exercise-induced acute renal failure has been documented in patients with hereditary defects in uric acid handling, which also cause hypouricemia and hyperuricosuria. In patients with these hereditary defects, the acute renal failure can be severe, sometimes requiring hemodialysis.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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10903 New Hampshire Ave
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hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Wednesday, February 29, 2012 3:49 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request - Serum Creatinine

Dear Dr. Touré,

After a review of the data for an increase in serum creatinine ≥ 100% from baseline for all subjects in Pool 1, Pool 2, and ongoing studies, we identified approximately 30 cases. In the vast majority of these cases, the increases occurred only once with no associated clinical signs. In these cases, we propose to provide short paragraph summaries as we did for a subset of these patients from Study EFC6049 / TEMSO in previous submissions (SN0024 [pertaining to creatinine clearance] and SN0026 [pertaining to increases in serum creatinine in Pool 1]) plus the creatinine laboratory data. Does the FDA team

agree?

Best regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Saturday, February 25, 2012 5:29 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request this information by March 9, 2012.

1. For all subjects in Pool 1, Pool 2, and ongoing studies who had an increase in serum creatinine ≥100% from baseline, we request patient files including, but not limited to, the following information:

a. Age
b. Sex
c. Dates of screening, randomization and starting therapy
d. Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e. Adverse events ( reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
f. Whether the subject had a history of renal or urologic disease.
g. Whether each subject had a history of urinary lithiases
h. Prior medications and concomitant medications with dates of start and end
i. Tables of the following laboratory results (sorted by date, with reference ranges): serum creatinine, creatinine clearance, BUN, uric acid, serum phosphorus, serum potassium, serum bicarbonate, any urine studies (including uric acid, creatinine, or specific results of any urine microscopic exam)*
j. Full reports for radiologic studies, pathology results, and special studies used to evaluate renal disease (with dates and reference ranges) *
k. Whether the increase in serum creatinine level was preceded by exercise or an increase in physical activity in the 30 days prior to the creatinine increase. Provide details of the physical activity, as well as details of the timing. See item 2a for a request to summarize this information. §
l. Whether there were any signs or symptoms associated with the increased serum creatinine level(s). If yes, what were they? §
m. Whether the cause of the increased creatinine level(s) was assessed. If yes, what was the likely cause, according to the treating physician(s) and/or investigator?
n. Whether the subject received any treatment or corrective action, including but not limited to intravenous fluids, emergency room treatment, hospitalization, or hemodialysis

* Relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, should be included in each patient file. Available baseline study results should also be included.

§ If information for items k and l was not collected, we request that you contact each subject who had an

increase in serum creatinine ≥100% from baseline and obtain this history. (This information may be submitted, as an addendum to the main response, by March 14, 2012.)

We request that you explicitly state pertinent negatives. (For example, if a subject did not have symptoms with the increase in creatinine, this should be explicitly stated.) If information could not be obtained, we request that you explicitly state this.

2. We also request summary information regarding subjects in Pool 1, Pool 2, and ongoing studies who had an increase in serum creatinine ≥100% of baseline. For each subject pool treatment group we request:

a. A summary of whether subjects had a history of exercise or increased physical activity before the increase in creatinine, using the following categories: i) number of subjects with a positive history; ii) number of subjects with a negative history; iii) number of subjects who could not recall whether there was a history; and iv) number of subjects whom the sponsor did not contact.

b. The median, range, and interquartile range of:
   i. Subject age at the time of the increased creatinine.
   ii. The number of days from first treatment to the time of the increased creatinine
   iii. The duration of the increased creatinine (days)
   iv. Nadir creatinine clearance

c. Summaries of the following parameters:
   i. Subject sex
   ii. Number of subjects who had symptoms associated with the increase in creatinine
   iii. Number of subjects with a history of urinary lithiases
   iv. Number of subjects with a known history of renal disease
   v. Number of subjects who received treatment or corrective action for the increase in creatinine

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
03/01/2012
Sent at request of safety team leader

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

**PROPRIETARY NAME REQUEST**
**CONDITIONALLY ACCEPTABLE**

Sanofi-Aventis U.S., LLC
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, New Jersey 08807

ATTENTION: Cynthia Psaras, PhD
Director, Global Regulatory Affairs

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 for Teriflunomide Tablets, 14 mg.

We also refer to your correspondence, dated and received December 2, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, (b) (4) will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 2, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hamet Toure at (301) 796-7534.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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LAURIE A KELLEY
02/29/2012

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
02/29/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, February 29, 2012 12:02 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Request for information

Dear Dr. Psaras,

We refer to NDA 202992. Please let us know if in the NDA the efficacy analysis for the TOWER study was presented not only in the aggregate but in bins of various duration and where this might be found in the application. See Question 1 below from the preNDA meeting.

***Question 1:*** *Does the agency agree with the proposed presentation of efficacy data from the placebo-controlled studies of teriflunomide (7 mg and 14 mg once daily) in the treatment of relapsing forms of multiple sclerosis?*

***FDA Preliminary Response***

We agree with the proposed presentation of data from EFC6049 (TEMSO) and HMR1726/2001. For EFC10531 (TOWER), please make clear in your interim analysis the duration of treatment (both in aggregate and in bins of various duration) of subjects with trial medication.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
02/29/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, February 29, 2012 11:56 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. In attempting to confirm the efficacy findings of your studies, our results differ somewhat from those you have reported. In order to confirm the results you obtained, we request the following:

For both TEMSO and TOWER studies:

(1) Relapse data in one dataset with only those variables included in the primary model (subjid, armn, stratumn, region, rscount, rsdurn and logtm); (2) Provide SAS program that runs on these variables and produces the reported results.

For TEMSO only:

(1) MRI data (burden of disease only) in one dataset with the variables included in the primary model and these variables only (usubjid, armn, stratumn, region, visit or visitnum, baseline value, cubic root transformed baseline, and the response variable and cubic transformed response variable); (2) Provide SAS program that runs on these variables and produces the reported results; (3) Disability progression data in one dataset with the variables needed in the log rank and Cox models only (subjid, stratumn, armn, edttfp12, and censoring indicator) and SAS programs that runs on these variables to produce the reported results.

Please provide details of the 40 patients for whom the blind was broken. At a minimum, submit reasons for the unblinding, relative study day of unblinding, whether or not the patient was discontinued at the unblinding, and relative study day of discontinuation.

We request your response by March 8, 2012 COB. Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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/s/

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HAMET M TOURE
02/29/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, February 27, 2012 6:26 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: NDA 202992: Follow-up to Request for Clarification from February 17, 2012
**Attachments:** 067476_Pediatric Inadequate PPSR.pdf

Dear Dr. Psaras,

Regarding item 1 below, I will clarify tomorrow.

Regarding item 2, you may add the sentence that an investigator may consider local labeling for leflunomide to the teriflunomide IB. For US centers, however, we request that you also attach the ARAVA USPI.

Regarding item 3, please find attached our response to the second PPSR.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Friday, February 24, 2012 4:32 PM
**To:** Toure, Hamet
**Subject:** NDA 202992: Follow-up to Request for Clarification from February 17, 2012

Dear Dr. Touré,

This email is a follow-up to the voicemail message that I left on your telephone at 2:05 PM today. I called to follow-up on the items below:

1. Financial Disclosure: We are waiting for feedback from your team based on our request for clarification sent in an email on Friday, February 17, 2012. We are unable to make the submission until we hear from you on the required content of the submission with respect to requested information on those investigators for whom we do not have a Financial Disclosure form.

2. Additional amendment to the IB: We are waiting for feedback on another request for clarification sent in an email on Friday, February 17, 2012. Although the submission is due on Monday, February 27, 2012, we are unable to make the submission until we hear from you and your team with regard to our proposal to add to the IB that an investigator may consider the local labeling for leflunomide instead of including the ARAVA USPI or referring to the Black Box warning in that USPI.

2. Proposed Pediatric Study Request (PPSR): Have you received feedback from your team on our second PPSR which was submitted on October 21, 2011?

Thank you in advance for your responses to these topics.

Kind regards,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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/s/

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HAMET M TOURE
03/07/2012
Sent at request of team leader

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Saturday, February 25, 2012 5:29 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request this information by March 9, 2012.

1. For all subjects in Pool 1, Pool 2, and ongoing studies who had an increase in serum creatinine ≥100% from baseline, we request patient files including, but not limited to, the following information:

a. Age
b. Sex
c. Dates of screening, randomization and starting therapy
d. Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e. Adverse events ( reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
f. Whether the subject had a history of renal or urologic disease.
g. Whether each subject had a history of urinary lithiases
h. Prior medications and concomitant medications with dates of start and end
i. Tables of the following laboratory results (sorted by date, with reference ranges): serum creatinine, creatinine clearance, BUN, uric acid, serum phosphorus, serum potassium, serum bicarbonate, any urine studies (including uric acid, creatinine, or specific results of any urine microscopic exam)*
j. Full reports for radiologic studies, pathology results, and special studies used to evaluate renal disease (with dates and reference ranges) *
k. Whether the increase in serum creatinine level was preceded by exercise or an increase in physical activity in the 30 days prior to the creatinine increase. Provide details of the physical activity, as well as details of the timing. See item 2a for a request to summarize this information. §
l. Whether there were any signs or symptoms associated with the increased serum creatinine level(s). If yes, what were they? §
m. Whether the cause of the increased creatinine level(s) was assessed. If yes, what was the likely cause, according to the treating physician(s) and/or investigator?
n. Whether the subject received any treatment or corrective action, including but not limited to intravenous fluids, emergency room treatment, hospitalization, or hemodialysis

* Relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, should be included in each patient file. Available baseline study results should also be included.

§ If information for items k and l was not collected, we request that you contact each subject who had an increase in serum creatinine ≥100% from baseline and obtain this history. (This information may be submitted, as an addendum to the main response, by March 14, 2012.)

We request that you explicitly state pertinent negatives. (For example, if a subject did not have symptoms with the increase in creatinine, this should be explicitly stated.) If information could not be obtained, we request that you explicitly state this.

2. We also request summary information regarding subjects in Pool 1, Pool 2, and ongoing studies who had an increase in serum creatinine ≥100% of baseline. For each subject pool treatment group we request:

a. A summary of whether subjects had a history of exercise or increased physical activity before the increase in creatinine, using the following categories: i) number of subjects with a positive history; ii) number of subjects with a negative history; iii) number of subjects who could not recall whether there was a history; and iv) number of subjects whom the sponsor did not contact.

b. The median, range, and interquartile range of:
i. Subject age at the time of the increased creatinine.

ii. The number of days from first treatment to the time of the increased creatinine
iii. The duration of the increased creatinine (days)
iv. Nadir creatinine clearance

c. Summaries of the following parameters:
i. Subject sex
ii. Number of subjects who had symptoms associated with the increase in creatinine
iii. Number of subjects with a history of urinary lithiases
iv. Number of subjects with a known history of renal disease
v. Number of subjects who received treatment or corrective action for the increase in creatinine

Please let me know if you have any questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
02/25/2012
Sent at request of safety team leader

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, February 16, 2012 7:04 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

1. Has a usability study been conducted with the intended patient population for the blister card wallets? If so, please provide us the study results.

2. Is this product approved in other countries? If so, how is this product packaged in those countries? Is it similar to your proposed blister card wallet design for (b) (4)?

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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HAMET M TOURE
02/16/2012
Sent at request of DMEPA

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, February 10, 2012 9:38 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

1. In reference to MFR report 2012SA002177, 28 yo F in study EFC10891 (patient 011, investigator 610001) who developed ALT elevation 5 months into study drug and reached ALT of 426 U/L (around 10x ULN) approximately one month later, please provide all available information that would allow adequate evaluation of the case including but not limited to total bilirubin values, amylase and lipase at the time of peak ALT elevation, serologic evaluations to rule out infection, whether the patient was jaundiced, whether she received cholestyramne washout and what the outcome of the event was. Also, please unblind the case, if not already done.

2. As per information submitted on 1/6/12, patient 006049-643-3201-0009 who developed toxic hepatitis had a history of chronic cholecystits with abnormal abdominal ultrasound (US). However, as per the CRF, she had a normal abdominal US at baseline and no following US on file. Please provide documentation of an abnormal US preceding the use of teriflunomide.

3. Patient 006049-380-2812-0001 was diagnosed with CMV hepatitis, based on positive IgG and IgM antibodies. This appears to be a case of CMV reactivation. Do you have any evidence otherwise?

Submit information by COB 2/20/12.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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hamet.toure@fda.hhs.gov

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HAMET M TOURE
02/25/2012
Sent at request of safety team leader

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, February 03, 2012 2:44 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

1. Patient 1203 0017 was randomized to Teriflunomide 14 mg in TEMSO on November 12, 2007. He entered LTS650 on December 7, 2009. On Day 74 of the extension study, the patient was withdrawn from the study because he was found to have a renal carcinoma. Upon review of a previous abdominal US (during TEMSO, on Day -426 of the extension study), the cystic kidney lesion was already present, although it did not appear to be malignant at that time. The patient underwent left partial nephrectomy. Was there a baseline abdominal US before entering TEMSO?

2. In addition to 1203 0017, two other patients developed renal carcinoma in Pool 2 (2001-124-0015-0014 and 2001-250-0024-0002.). Please comment on the fact that there were 3 cases of renal carcinoma in this database. Provide the pathology of these three cases. Clarify if there is any other case of renal cancer in any of the other completed or ongoing teriflunomide studies.

Please provide your response by February 13, 2012.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
02/03/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, February 01, 2012 12:43 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. Please submit an updated table of overall patient exposure in teriflunomide trials as of the time of the 120-day SUR, similar to that in Table 9 of the Clinical Overview of the original application. Please also provide total exposure to Teriflunomide 7 and 14 mg in patient-years.

Please provide your response by February 8, 2012.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
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hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
02/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

**METHODS VALIDATION MATERIALS RECEIVED**

Sanofi-Aventis U.S. LLC
Attention: Cynthia Psaras
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Cynthia Psaras:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aubagio (teriflunomide) Tablets, 14 mg and to our 10/6/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 1/12/2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

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JAMES F ALLGIRE
01/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-992 **INFORMATION REQUEST**

sanofi-aventis U.S. LLC
Attention: Cynthia Psaras, Director
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Ms. Psaras:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Teriflunomide Tablets, 14 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

### *S.2.2 Description of Manufacturing Process and Process Controls*

1. Provide details of the [redacted] (b) (4), operational parameters with ranges, and any in-process controls to ensure a particle size distribution of [redacted] (b) (4)

### *S.2.3 Control of Materials-Control of Starting Materials*

2. Verify if the spiking studies' on the impurities in the starting materials, [redacted] (b) (4) [redacted] were carried out for at least 6 consecutive pilot scale or 3 consecutive production scale batches. Provide such data for each batch. If this condition is not fulfilled, a routine test for these impurities in the drug substance specification is needed. This condition is stated in *EMA Guideline on the Limits of Genotoxic Impurities: CHMP/QWP/251344/2006 and Question & Answers Document EMA/CHMP/SWP/431994/2007, Rev. 3, Sept. 2010-Example 3*, which you have referred to in this section and in 'S.3.2-Impurities' in your submission. We are cognizant of the batch analysis (on several consecutive pilot and industrial batches) tables presented in section S.3.2; where in levels of [redacted] (b) (4) are given but not the levels of the potential genotoxic impurites in the starting materials.

### *S.7.1 Stability Summary and Conclusions*

3. The submitted 18- month primary stability data can qualify for a maximum of [redacted] (b) (4) retest period as per ICH Q1E and not a proposed [redacted] (b) (4) The guidance stipulates that the proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data. Therefore, include a 30-month test time point

in the stability protocol for the drug substance to confirm the potentially assignable retest period.

### *P.2.3 Manufacturing Process Development*

4. [redacted] (b) (4)

### *P.5.1 Specification(s)*

5. Provide data to show that [redacted] (b) (4) as per the maximum limit stated in the drug product specification. If the data shows that the [redacted] (b) (4) then the microbial contamination test in the drug product specification must be performed for every batch of the drug product.

### *FDA Regional Information 1.14.1.3 Draft Labeling Text*

6. The presentation of the strength (14) on one side of the tablet is incorrectly stated as being imprinted instead of engraved. Provide corrected description.

7. Provide the NDC code numbers for the various commercial blister cartons.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

---

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/s/

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RAMESH K SOOD
01/09/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Saturday, January 07, 2012 11:38 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. The analyses of blood pressure in the ISS and study reports refer to supine/sitting BP. Please clarify what that means. Respond by 1/9/11.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
01/07/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Saturday, January 07, 2012 10:52 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. Please provide a listing and numerical count of all investigators, subinvestigators, and radiologists reading study MRIs who participated in trials and provided financial disclosures contributing to this NDA. In addition, please provide their names, site numbers, and countries as well as number of subjects at their site and study name conducted at their site. Please provide a similar listing and numerical count for those investigators who did not provide a financial disclosure so that we may determine if a sizable number of investigators failed to disclose financial information. Please provide information on what attempts were made to collect this information and an explanation for those who failed to do so.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
01/07/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, January 03, 2012 11:14 AM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Psaras,

Please find below our answer to your questions:

1. Item #1 referred to hypophosphatemia <0.32 mmol/L. However, please provide the requested analyses for hypophosphatemia <0.6 mmol/L instead of <0.32 mmol/L.

2. Disregard item #7 (chloride by CTCAE in the TOWER study). The reviewer has found the analyses by PCSA.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

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hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Friday, December 23, 2011 2:10 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Touré,

We have two comments/questions on the items below.

For item 1, From CTCAE V4

Hypophosphatemia:

Grade 1 <LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L

Grade 2 <2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L

Grade 3 <2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L

Grade 4 <1.0 mg/dL; <0.3 mmol/L; lifethreatening consequences

Grade 5 Death

The request below to provide an analysis of patients with hypophosphatemia <32 mmol/L seems odd compared to the CTCAE values. Can you check on this?

For item 7, the CTCAE V4 does not have any criteria for chloride, what criteria do you want us to use?

Thank you in advance for your help.

Have a nice holiday,
Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Thursday, December 22, 2011 1:53 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992.

Teriflunomide is associated with increased renal excretion of phosphorus and uric acid. Please address the following questions.

1. Provide an analysis of patients with hypophosphatemia <32 mmol/L in Safety Pool 1, Pool 2 and TOWER, similar to the one conducted in Appendix 1.6.2.3 of original ISS. Provide narratives for those patients who also had adverse events.

2. Some drugs that increase phosphorus and uric acid excretion (e.g. ifosfamide, tetracyclines, antiviral agents), are associated with Fanconi syndrome (hyophosphatemia, hypouricemia, metabolic acidosis, glucosuria, amminoaciduria). Have you evaluated whether teriflunomide's renal tubular effects go beyond those on phosphorus and uric acid excretion?

3. More patients presented urinary tract infections and nephrolithiasis in the teriflunomide treatment groups as compared to placebo in the monotherapy studies as well as in the TOWER study. Have you examined what type of calculi the patients with lithiasis had?

Additional requests

4. Your ISS does not present analyses of calcium, magnesium and bicarbonate. Were these analytes measured in any of the teriflunomide studies? If so, please provide analyses of central tendency and outlier analyses similar to those provided for other electrolytes.

5. Appendix 1.6.2.3 of original ISS shows that 10 patients had an increase in creatinine of 100% (doubling of serum creatinine) in the teriflunomide treatment groups as compared to none on placebo. Please identify these patients in Pool 1. Clarify if any of them are the same who had serum creatinine clearance <30 ml/min. Provide narratives for patients who presented adverse events.

6. Provide phosphorus levels for patient 276002002 in study TENERE (patient had episode of hemolysis).

7. Provide analyses by CTCAE for chloride in the TOWER study (similar to those in Table 14.2.8.1.2 for sodium).

8. Were glucose, protein, electrolytes measured in urine in any of the teriflunomide studies? If so, please provide the results.

9. One patient had a subclavian vein thrombosis in the TOPIC study (patient 5401/0004). Please unblind this case. Did she have any workup for hypercoagulable state?

Provide this information by January 11, 2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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/s/

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HAMET M TOURE
01/03/2012

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, December 22, 2011 10:28 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Psaras,

Kindly send us your internal core safety data sheet for Arava so that we can determine which option is preferable.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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10903 New Hampshire Ave
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hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Wednesday, December 21, 2011 8:06 AM
**To:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Touré,

In our efforts to revise the teriflunomide Investigator Brochure (IB) to meet your expectations and since section 7.2 of the IB contains safety information for Arava, the team is considering appending the US labeling information or our internal core safety data sheet to the current IB. Since the IB is a global document, the addition of regional labeling may not be ideal but it is a consideration by our team if it meets your expectations within the timelines we have been given. Please let us know if appending either of these documents to the current IB is acceptable. Thank you for your time.

Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Monday, December 19, 2011 5:04 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Psaras,

We have the following responses to your questions:

Q1. DNP requests that you include information from the WARNINGS and PRECAUTIONS section of the ARAVA package insert (including the recently updated Boxed Warning related to hepatotoxicity) in the teriflunomide Investigator Brochure without delay rather than waiting until February.

Q2. Using updated data from the 120-day safety update is acceptable. Deferring submission of the narratives to early January is acceptable. Please be sure that the narratives include all the information mentioned in the December 15, 2011, request.

Q3. Thank you. We have found the hospital records.

Please let me know if you have any additional questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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10903 New Hampshire Ave
Silver Spring, MD 20993
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Friday, December 16, 2011 4:13 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Touré

Please see our comments below. We would appreciate your comments at your earliest convenience on Monday morning so our team can begin to prepare the submission for December 30, 2011. Thank you in advance for your time.

Have a nice weekend,
Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]

**Sent:** Thursday, December 15, 2011 11:15 AM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Advice and information request

Dear Dr. Psaras,

We refer you to NDA 202992 and IND 067476. We have the following comments:

1. Please revise your Investigator Brochure to better inform the investigators of the toxicity associated with leflunomide. Make it clear that teriflunomide is the principal metabolite of leflunomide and responsible for most of its effects. Clarify that ARAVA® carries a box WARNING for severe liver injury including fatal hepatic failure. Update the IB to reflect the major WARNINGS AND PRECAUTIONS recently added to the leflunomide label.

We had planned to amend the recently submitted Investigator Brochure (Edition 15, issued 15 November 2011; Serial No. 0467) in February 2012 based on our upcoming EU marketing application. In the February 2012 update, we will add the requested information on Arava®. Is this acceptable? If acceptable, the amended Investigator Brochure would be included in a submission to the Agency in mid-February 2012.

2. Please resubmit teriflunomide liver-related data in a format suitable for eDISH (Evaluation of Drug Induced Serious Hepatotoxicity in Clinical Studies) analysis, following the recommendations in the attached excel file (the eDISH requirements file). Please note that we need all the serial data, with dates blood drawn, laboratory normal ranges and values for the enzyme activities (ALT, AST, ALP) as numerical values in U/L and total bilirubin concentration TBL) in mg/dL for all subjects, for both routine and extra testing done, to plot the eDISH. The first step of eDISH is simple screening to identify subjects of special interest, particularly those who show ALT>3xULN **AND** TBL>2xULN. The eDISH program then allows displaying of the whole time course of all values for selected subjects of interest. From that second step, medical judgment is made about severity of liver **dysfunction** (not just ALT elevations) and more importantly, evaluation of supplemental clinical information to allow medical differential diagnosis of the probable or most likely cause. This third step requires clinical narrative data written and organized by a physician, rather than simply a reproduction of case report entries.

An eDISH plot of the peak ALT versus peak bilirubin for Pool 1 was submitted in the NDA in 2.7.4 Summary of Clinical Safety (Figure 5). However, we understand that the Agency wishes to perform a similar analysis so we plan to provide the appropriate datasets for all Phase 1-3 studies as requested for December 30, 2011. With your agreement, we will use data from the 120 day safety update since this is more current than what was provided in the NDA. In addition, for potential Hy's law cases , we propose to provide versions of narratives that conform to a SAS format in the submission for December 30, 2011.

We understand that the Agency would like supplemental clinical information from the clinical sites for potential Hy's law cases to assist in assessing the most likely cause of suspected hepatic injury. In the interest of obtaining data that is as complete as possible, we would appreciate if we could provide these additional narratives to the Agency in early January as many of the sites will be closed during the end of year holiday period. Please let us know if this is acceptable.

3. We acknowledge the follow-up information you have provided for patient #006049-643-3201-0009. We remind you that we have requested the hospital records for that patient.

The hospital records (including English translation) for patient #006049-643-3201-0009 were submitted in Amendment 22 on December 14, 2011 in Appendix A.

Please submit this information by December 30, 2011.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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/s/

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HAMET M TOURE
12/23/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, December 22, 2011 1:53 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992.

Teriflunomide is associated with increased renal excretion of phosphorus and uric acid. Please address the following questions.

1. Provide an analysis of patients with hypophosphatemia <32 mmol/L in Safety Pool 1, Pool 2 and TOWER, similar to the one conducted in Appendix 1.6.2.3 of original ISS. Provide narratives for those patients who also had adverse events.

2. Some drugs that increase phosphorus and uric acid excretion (e.g. ifosfamide, tetracyclines, antiviral agents), are associated with Fanconi syndrome (hyophosphatemia, hypouricemia, metabolic acidosis, glucosuria, amminoaciduria). Have you evaluated whether teriflunomide's renal tubular effects go beyond those on phosphorus and uric acid excretion?

3. More patients presented urinary tract infections and nephrolithiasis in the teriflunomide treatment groups as compared to placebo in the monotherapy studies as well as in the TOWER study. Have you examined what type of calculi the patients with lithiasis had?

Additional requests

4. Your ISS does not present analyses of calcium, magnesium and bicarbonate. Were these analytes measured in any of the teriflunomide studies? If so, please provide analyses of central tendency and outlier analyses similar to those provided for other electrolytes.

5. Appendix 1.6.2.3 of original ISS shows that 10 patients had an increase in creatinine of 100% (doubling of serum creatinine) in the teriflunomide treatment groups as compared to none on placebo. Please identify these patients in Pool 1. Clarify if any of them are the same who had serum creatinine clearance <30 ml/min. Provide narratives for patients who presented adverse events.

6. Provide phosphorus levels for patient 276002002 in study TENERE (patient had episode of hemolysis).

7. Provide analyses by CTCAE for chloride in the TOWER study (similar to those in Table 14.2.8.1.2 for sodium).

8. Were glucose, protein, electrolytes measured in urine in any of the teriflunomide studies? If so, please provide the results.

9. One patient had a subclavian vein thrombosis in the TOPIC study (patient 5401/0004). Please unblind this case. Did she have any workup for hypercoagulable state?

Provide this information by January 11, 2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration

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/s/

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HAMET M TOURE
12/22/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, December 20, 2011 5:12 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Psaras,

We are especially concerned about subjects with ALT>3 X ULN **AND** TBL > 2 X ULN, and somewhat less so for subjects with either ALT > 5xULN or TBL > 2xULN?

If time is linited, do the former cases first, and by physicians who are familiar with the medical differential diagnosis process.

In regards to question 2 below, we request the narratives by January 5, 2012.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Tuesday, December 20, 2011 9:32 AM
**To:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Touré,

For further clarification to item 2 below, the first step of eDISH is to identify subjects of interest, particularly those who show ALT>3 X ULN **AND** TBL > 2 X ULN, followed by the second step which involves medical judgment of these cases and finally, the third step is the narrative. In the attachment you provided on eDISH, the third tab contains the following information.

It is not necessary to include all subjects in this patient narrative data set.
However, make sure to include narratives for subjects with either ALT > 5xULN or TBL > 2xULN.

Should the narratives be submitted for those cases in the text of your email, subjects with ALT>3 X ULN **AND** TBL > 2 X ULN, or subjects with either ALT > 5xULN or TBL > 2xULN? We would appreciate your response as soon as possible so the team can continue to work on the information requests.

The Sanofi Aventis offices will be closed from December 26, 2011 through January 2, 2012.

Thank you in advance for your time,
Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Thursday, December 15, 2011 11:15 AM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Advice and information request

Dear Dr. Psaras,

We refer you to NDA 202992 and IND 067476. We have the following comments:

1. Please revise your Investigator Brochure to better inform the investigators of the toxicity associated with leflunomide. Make it clear that teriflunomide is the principal metabolite of leflunomide and responsible for most of its effects. Clarify that ARAVA® carries a box WARNING for severe liver injury including fatal hepatic failure. Update the IB to reflect the major WARNINGS AND PRECAUTIONS recently added to the leflunomide label.

2. Please resubmit teriflunomide liver-related data in a format suitable for eDISH (Evaluation of Drug Induced Serious Hepatotoxicity in Clinical Studies) analysis, following the recommendations in the attached excel file (the eDISH requirements file). Please note that we need all the serial data, with dates blood drawn, laboratory normal ranges and values for the enzyme activities (ALT, AST, ALP) as numerical values in U/L and total bilirubin concentration TBL) in mg/dL for all subjects, for both routine and extra testing done, to plot the eDISH. The first step of eDISH is simple screening to identify subjects of special interest, particularly those who show ALT>3xULN **AND** TBL>2xULN. The eDISH program then allows displaying of the whole time course of all values for selected subjects of interest. From that second step, medical judgment is made about severity of liver **dysfunction** (not just ALT elevations) and more importantly, evaluation of supplemental clinical information to allow medical differential diagnosis of the probable or most likely cause. This third step requires clinical narrative data written and organized by a physician, rather than simply a reproduction of case report entries.

3. We acknowledge the follow-up information you have provided for patient #006049-643-3201-0009. We remind you that we have requested the hospital records for that patient.

Please submit this information by December 30, 2011.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
12/20/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, December 20, 2011 5:08 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Psaras,

Assuming you are running SAS 9.1 or newer, we would like to ask you to provide SAS datasets exactly formatted as specified in the eDISH-Data Specification Excel workbook, to be sent to us as desk copy (CD-ROM). For archiving purposes, please submit to us the XPT version with variable names and labels possibly truncated. This is the suggestion for LIVER and DEMO datasets.

We would like to emphasize that you should follow the explanations closely for the narrative SAS dataset and/or supplemental PDF file. Please also call attention to the medical doctor who will prepare the narratives. The narrative SAS dataset should be created using SAS version 9, allowing adequate length for the character variable, NARRATIVE, to hold possibly lengthy text strings. The not-truncated narrative SAS dataset should be submitted as part of the desk copy.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Monday, December 19, 2011 3:34 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Touré,

As a follow-up question to item 2, please see the following comment from our biostatistics team.

The variable names and labels that the FDA has specified for the data sets do not conform to the criteria for xpt files - maximum name length is 8 and maximum label length is 40. If they are longer than this, they get truncated in xpt.

So what data set format does the FDA want the data sets in? Do they want us to use the exact variable names and labels they provided? If they want xpt and we use the specs they provided, some will be truncated. Otherwise, we can revise the names and labels to be the 8, 40 length criteria or not send as xpt.

Can you let us know the format you want us to use for the data sets for eDISH? Thank you.

Have a nice afternoon,
Cynthia

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**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Thursday, December 15, 2011 11:15 AM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Advice and information request

Dear Dr. Psaras,

We refer you to NDA 202992 and IND 067476. We have the following comments:

1. Please revise your Investigator Brochure to better inform the investigators of the toxicity associated with leflunomide. Make it clear that teriflunomide is the principal metabolite of leflunomide and responsible for most of its effects. Clarify that ARAVA® carries a box WARNING for severe liver injury including fatal hepatic failure. Update the IB to reflect the major WARNINGS AND PRECAUTIONS recently added to the leflunomide label.

2. Please resubmit teriflunomide liver-related data in a format suitable for eDISH (Evaluation of Drug Induced Serious Hepatotoxicity in Clinical Studies) analysis, following the recommendations in the attached excel file (the eDISH requirements file). Please note that we need all the serial data, with dates blood drawn, laboratory normal ranges and values for the enzyme activities (ALT, AST, ALP) as numerical values in U/L and total bilirubin concentration TBL) in mg/dL for all subjects, for both routine and extra testing done, to plot the eDISH. The first step of eDISH is simple screening to identify subjects of special interest, particularly those who show ALT>3xULN **AND** TBL>2xULN. The eDISH program then allows displaying of the whole time course of all values for selected subjects of interest. From that second step, medical judgment is made about severity of liver **dysfunction** (not just ALT elevations) and more importantly, evaluation of supplemental clinical information to allow medical differential diagnosis of the probable or most likely cause. This third step requires clinical narrative data written and organized by a physician, rather than simply a reproduction of case report entries.

3. We acknowledge the follow-up information you have provided for patient #006049-643-3201-0009. We remind you that we have requested the hospital records for that patient.

Please submit this information by December 30, 2011.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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/s/

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HAMET M TOURE
12/20/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, December 19, 2011 5:14 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

1. Please provide for Trial EFC6049 and Trial EFC10531 a supportive analysis of all relapses, both confirmed and non-confirmed, as agreed to at the preNDA meeting, or advise us where in the submission these analyses can be located.

2. Please provide further information for Trial EFC6049 on the baseline MRI variables of the ITT population that were secondary endpoints or advise us where in the submission this information can be located rather than simply stating that all characteristics are well matched for treatment group (we can only locate baseline burden of disease and number of baseline gadolinium-enhanced lesions data). Please provide the associated p values.

3. There were 40 subjects who were unblinded in study EFC6049. Narratives can only be found for those who discontinued due to adverse events. Please list for each unblinded subject the patient identifier, the treatment group, the date that subject started treatment, the date that subject was unblinded, the date that study medication was discontinued, the number of days drug therapy was discontinued, as well as the reason(s) for unblinding and discontinuation.

Please submit a response to these questions by December 30, 2011.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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/s/

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HAMET M TOURE
12/20/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, December 19, 2011 5:04 PM
**To:** 'Cynthia.Psaras@sanofi.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Psaras,

We have the following responses to your questions:

Q1. DNP requests that you include information from the WARNINGS and PRECAUTIONS section of the ARAVA package insert (including the recently updated Boxed Warning related to hepatotoxicity) in the teriflunomide Investigator Brochure without delay rather than waiting until February.

Q2. Using updated data from the 120-day safety update is acceptable. Deferring submission of the narratives to early January is acceptable. Please be sure that the narratives include all the information mentioned in the December 15, 2011, request.

Q3. Thank you. We have found the hospital records.

Please let me know if you have any additional questions.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
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Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi.com [mailto:Cynthia.Psaras@sanofi.com]
**Sent:** Friday, December 16, 2011 4:13 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Advice and information request

Dear Dr. Touré

Please see our comments below. We would appreciate your comments at your earliest convenience on Monday morning so our team can begin to prepare the submission for December 30, 2011. Thank you in advance for your time.

Have a nice weekend,
Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Thursday, December 15, 2011 11:15 AM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Advice and information request

Dear Dr. Psaras,

We refer you to NDA 202992 and IND 067476. We have the following comments:

1. Please revise your Investigator Brochure to better inform the investigators of the toxicity associated with leflunomide. Make it clear that teriflunomide is the principal metabolite of leflunomide and responsible for most of its effects. Clarify that ARAVA® carries a box WARNING for severe liver injury including fatal hepatic failure. Update the IB to reflect the major WARNINGS AND PRECAUTIONS recently added to the leflunomide label.

We had planned to amend the recently submitted Investigator Brochure (Edition 15, issued 15 November 2011; Serial No. 0467) in February 2012 based on our upcoming EU marketing application. In the February 2012 update, we will add the requested information on Arava®. Is this acceptable? If acceptable, the amended Investigator Brochure would be included in a submission to the Agency in mid-February 2012.

2. Please resubmit teriflunomide liver-related data in a format suitable for eDISH (Evaluation of Drug Induced Serious Hepatotoxicity in Clinical Studies) analysis, following the recommendations in the attached excel file (the eDISH requirements file). Please note that we need all the serial data, with dates blood drawn, laboratory normal ranges and values for the enzyme activities (ALT, AST, ALP) as numerical values in U/L and total bilirubin concentration TBL) in mg/dL for all subjects, for both routine and extra testing done, to plot the eDISH. The first step of eDISH is simple screening to identify subjects of special interest, particularly those who show ALT>3xULN **AND** TBL>2xULN. The eDISH program then allows displaying of the whole time course of all values for selected subjects of interest. From that second step, medical judgment is made about severity of liver **dysfunction** (not just ALT elevations) and more importantly, evaluation of supplemental clinical information to allow medical differential diagnosis of the probable or most likely cause. This third step requires clinical narrative data written and organized by a physician, rather than simply a reproduction of case report entries.

An eDISH plot of the peak ALT versus peak bilirubin for Pool 1 was submitted in the NDA in 2.7.4 Summary of Clinical Safety (Figure 5). However, we understand that the Agency wishes to perform a similar analysis so we plan to provide the appropriate datasets for all Phase 1-3 studies as requested for December 30, 2011. With your agreement, we will use data from the 120 day safety update since this is more current than what was provided in the NDA. In addition, for potential Hy's law cases , we propose to provide versions of narratives that conform to a SAS format in the submission for December 30, 2011.

We understand that the Agency would like supplemental clinical information from the clinical sites for potential Hy's law cases to assist in assessing the most likely cause of suspected hepatic injury. In the interest of obtaining data that is as complete as possible, we would appreciate if we could provide these additional narratives to the Agency in early January as many of the sites will be closed during the end of

year holiday period. Please let us know if this is acceptable.

3. We acknowledge the follow-up information you have provided for patient #006049-643-3201-0009. We remind you that we have requested the hospital records for that patient.

The hospital records (including English translation) for patient #006049-643-3201-0009 were submitted in Amendment 22 on December 14, 2011 in Appendix A.

Please submit this information by December 30, 2011.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
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/s/

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HAMET M TOURE
12/20/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, December 15, 2011 11:15 AM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Advice and information request

**Attachments:** Copy of eDISHdataRequirement.xls

Dear Dr. Psaras,

We refer you to NDA 202992 and IND 067476. We have the following comments:

1. Please revise your Investigator Brochure to better inform the investigators of the toxicity associated with leflunomide. Make it clear that teriflunomide is the principal metabolite of leflunomide and responsible for most of its effects. Clarify that ARAVA® carries a box WARNING for severe liver injury including fatal hepatic failure. Update the IB to reflect the major WARNINGS AND PRECAUTIONS recently added to the leflunomide label.

2. Please resubmit teriflunomide liver-related data in a format suitable for eDISH (Evaluation of Drug Induced Serious Hepatotoxicity in Clinical Studies) analysis, following the recommendations in the attached excel file (the eDISH requirements file). Please note that we need all the serial data, with dates blood drawn, laboratory normal ranges and values for the enzyme activities (ALT, AST, ALP) as numerical values in U/L and total bilirubin concentration TBL) in mg/dL for all subjects, for both routine and extra testing done, to plot the eDISH. The first step of eDISH is simple screening to identify subjects of special interest, particularly those who show ALT>3xULN **AND** TBL>2xULN. The eDISH program then allows displaying of the whole time course of all values for selected subjects of interest. From that second step, medical judgment is made about severity of liver **dysfunction** (not just ALT elevations) and more importantly, evaluation of supplemental clinical information to allow medical differential diagnosis of the probable or most likely cause. This third step requires clinical narrative data written and organized by a physician, rather than simply a reproduction of case report entries.

Copy of SHdataRequirement

3. We acknowledge the follow-up information you have provided for patient #006049-643-3201-0009. We remind you that we have requested the hospital records for that patient.

Please submit this information by December 30, 2011.

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
12/15/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, December 15, 2011 1:47 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

1. Patient #006049-152-3803-0003. Patient was diagnosed with acute renal failure. Urine microscopic interpretation was read as “positive”. Please clarify what positive refers to (Cell casts? Crystals?).

2. Patients # 002001-124-0015-0014 and #002001-250-0024-0002, both on teriflunomide, were diagnosed with renal cell carcinoma. Did these patients have an abdominal ultrasound before entering study 2001 or the extension study?

3. Patient # 010531-840-0036-0006 developed thrombocytopenia, with a platelet count down to <10 Giga/L. She was diagnosed with autoimmune thrombocytopenia. Please provide evidence to support the diagnosis of autoimmunity, versus teriflunomide-induced thrombocytopenia.

4. Patient # 112104003, in TOWER, who presented mild ALT elevation during the trial, had a normal abdominal ultrasound at screening and was found to have mild steatosis on Day 262 of teriflunomide treatment. The finding was considered related to the drug by the investigator but drug was not discontinued. Is there any follow up information on this patient? Is the patient still in the trial?

5. Several narratives for hepatic related events in this NDA state that “liver serologies were not done”, “liver related serologies were negative" or "revealed past infection.” When serologies to rule out hepatitis are listed in this NDA, they unusually mention only Hepatitis A, B and C (and occasionally EBV or CMV). Could you please clarify what serologies are referred to when referring to “liver serologies”?

7. Patient # 006049-643-3210-0003 had a “false positive” reaction for syphilis 8 months into teriflunomide treatment. She discontinued drug due to polyneuropathy approximately 1 year into the study. A few months later an AE of latent syphilis was recorded and treated with penicillin. The CRF and narrative seem to be inconsistent. Please provide additional information about this patient. Did she or did she not have syphilis?

8. Table 1.6.2.3 of the original ISS (outliers for renal function laboratory abnormalities in Pool 1) shows that seven patients developed severe renal impairment (creatinine clearance <30 ml/min) while on teriflunomide treatment, and none on placebo. Please identify those patients and submit the narratives if they have not been submitted already.

9. Your IND safety report # 2011SA014363, submitted on December 9, 2011, refers to a 42 yo female in study EFC10531, diagnosed with focal nodular hyperplasia of the liver (by ultrasound), 5 months into teriflunomide 14 mg treatment. Did she have a baseline abdominal ultrasound? Was she taking concomitant medications? What medications did she take prior to entering the study? Provide any additional information you have on this patient.

Please submit your response by COB December 29, 2011. Feel free to provide your response by email and submit an identical archival submission to NDA 202992 at your convenience.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave

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/s/

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HAMET M TOURE
12/15/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, December 06, 2011 5:07 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We have the following information request:

1) Please provide translated hospital records for patient #006049-643-3201-0009, who presented toxic hepatitis with ALT 32x ULN and jaundice on day 134 of teriflunomide 14 mg/day treatment.
2) Please provide date of FDA submission for the initial 15-day report for this case

Submit the information by COB Friday 12/9/11.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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/s/

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HAMET M TOURE
12/06/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, November 28, 2011 10:26 AM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request the following information by Friday, December 16, 2011, COB.

1. For the following subjects from Study EFC6049 who were listed as discontinuing treatment for non-AE reasons, we request a full narrative and patient file, in the format requested on 11/1/11. Include in the narrative all available details on the reason(s) for discontinuation, as well as how the reason for discontinuation for each subject was categorized in ISS Table 6, 7, 8, or 9.

| **Subject Number** | **Treatment assignment (mg of teriflunomide)** | **Comment** |
|---|---|---|
| 1201/0010 | 14 mg | Subject had "foggy feeling in head", which was rated as severe. |
| 1202/0027 | 7 mg | Low neutrophil count. |
| 1204/0011 | 14 mg | Elevated GGT |
| 1207/0004 | 7 mg | Discontinuation reason: "Subject did not wish to continue (subj feels she is having symptoms that never occurred while on infb. she would like to restart Avonex" |
| 1208/0004 | 14 mg | Worsening depression at discontinuation |
| 1209/0003 | 14 mg | Leukopenia at discontinuation |
| 1209/0013 | 14 mg | Severe flu symptoms at time of discontinuation |
| 1602/0003 | 14 mg | Moderate hair loss at discontinuation |
| 1604/0004 | 14 mg | Erysipelas of right lower limb at time of discontinuation |
| 1802/0002 | 14 mg | Low neutrophil count at time of discontinuation |
| 2008/0014 | 14 mg | Psychiatric disorder, verbatim term "organic phsyoxis", categorized as severe, started 2 days prior to discontinuation |
| 2203/0009 | 7 mg | Subject had articular pains that he thought could be connected to study drug (according to narrative discontinuation reason) |
| 2408/0001 | 14 mg | **Please provide details on the protocol violation.** Subject had a low neutrophil count. |
| 2408/0004 | 14 mg | Four ongoing AEs (abdominal pain, gingival hypersensitivity, myalgia, and abdominal meteorism) , each rated as severe, at time of discontinuation. |
| 2409/0009 | 0 mg | "Discontinuation reason: Subject did not wish to continue (the patient did not wish to continue due to adverse event and lack of efficacy)" (according to narrative) |
| 2606/0004 | 7 mg | Ongoing AEs at discontinuation included low white blood cell count, low neutrophils, and anxiety. |
| 2608/0002 | 7 mg | Ongoing "mood changes" at discontinuation. |
| 3003/0003 | 7 mg | Flu-like symptoms with sequelae just prior to discontinuation. |
| 3206/0010 | 14 mg | Elevated GGT at discontinuation. |
| 3504/0002 | 14 mg | Moderate respiratory infection at discontinuation |
| 3801/0007 | 7 mg | Worsening mood disorder at time of discontinuation |

2. For all discontinuations, provide datasets which lists the subjects (include trial name, center number, subject number, treatment assignment) who contributed to each category of discontinuation in ISS Tables 6, 7, 8, and 9 (one dataset per table), as well as the text of the discontinuation reason provided in each subject's narrative.

Please provide your archival response to NDA 202992.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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/s/

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HAMET M TOURE
11/28/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, November 22, 2011 3:10 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

Please clarify whether the following patients had evaluations to rule out interstitial lung disease.

1. Patient 002001-124-0015-0008 treated with teriflunomide 7 mg/day had a serious AE of bronchitis and exacerbation of bronchial asthma during the extension study. This patient was a heavy smoker but did not have a prior history of asthma. During the study he presented other non-serious episodes of wheezing and asthma, one in April 2006, from which he had not recovered at the time of last follow up. As per the CRF, the patient withdrew from the study on May 2006 because he did not wish to continue in the study. The narrative reports that during one hospitalization chest X-ray was clear, however, it is unclear when that X-ray was done and there is no information about follow up X-ray, computerized tomography (CT) or pulmonary function tests (PFT) in the narrative and CRF.

2. Patient 006049-250-2402-0016 developed mixed ventilatory deficiency, coded as respiratory failure during teriflunomide 7 mg/day treatment, during extension study. Respiratory function improved after drug discontinuation. There is no information about chest X-ray/CT, or PFT included in the narrative and CRF.

Please provide your archival response to NDA 202992 by Friday, December 2, 2011.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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HAMET M TOURE
11/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

**PROPRIETARY NAME REQUEST**
**UNACCEPTABLE**

Sanofi-Aventis U.S., LLC
200 Crossing Boulevard
Mailstop: BX2-712C
Bridgewater, New Jersey 08807

ATTENTION: Cynthia Psaras, PhD
Director, Global Regulatory Affairs

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 for Teriflunomide Tablets, 14 mg.

We also refer to your August 19, 2011, correspondence, received August 19, 2011, requesting review of your proposed proprietary name, Aubagio. We have completed our review of your proposed proprietary name Aubagio and have concluded that it is vulnerable to name confusion that could lead to medication errors with a pending proposed proprietary name due to (b) (4). Therefore, at this time, the acceptability of the proposed proprietary name, Aubagio, is dependent upon which application is approved first. If Aubagio is approved first, we will direct the other pending product seek an alternative name. If the other pending application is approved prior to your application, then you will be requested to submit another name.

Given this determination you may wish to submit an alternative proposed proprietary name at this time. We note that you have proposed an alternate proprietary name in your submission dated August 19, 2011. In order to initiate the review of the alternate proposed proprietary name, (b) (4), submit a new complete request for proprietary name review within 14 days of this letter. The review of this alternate proposed proprietary name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager, at (301) 796-5058. For any other information regarding this application contact Hamet Toure, Regulatory Project Manager in the Office of New Drugs (OND) at (301) 796-7534.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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LAURIE A KELLEY
11/17/2011

CAROL A HOLQUIST
11/17/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, November 14, 2011 5:21 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

At the pre-NDA meeting, the Division of Neurology Products asked for analyses of the number of subjects screened, the number of subjects who failed screening, and the reasons for screening failures in Study EFC6049/TEMSO. Table 14.2.1.1.1 describes the disposition of patients in this study. However, there is no description of the reasons for "Fail to meet entrance criteria." Please provide the reason for failing entry criteria (n=155). Please respond by 11/21/11.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
11/14/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, November 14, 2011 5:12 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

Please provide exposure of patients (in patient years, by treatment group) in the TOWER study. If this information is already in the application, please direct the reviewer to the location of such information.

Please respond by 11/16/11.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
11/14/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, November 07, 2011 2:34 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** RE: NDA202992: Psaras out of office from November 7-10

Appears This Way On Original

Dear Dr. Psaras,

This is an example of the format that the reviewer would like to see for the concomitant medications taken during the study.

Patient ID# xxx
Date of first dose of study drug: 5/9/2007

| Concomitant medications | Reason | Concom med start date | Concom med start RELATIVE study day | Concom med stop date | Concom med stop RELATIVE day | Conti |
|---|---|---|---|---|---|---|
| GABAPENTIN | Epilepsy | 1/2/2006 | -492 | | | ye |
| ESCITALOPRAM | Depression | 3/3/2008 | 300 | | | ye |
| IBUPROFEN | Pain | 3/10/2008 | 307 | 3/15/2008 | 312 | no |
| PARACETAMOL | Fever | 10/21/2008 | 349 | 10/21/2008 | 349 | no |

There is no need to provide information about prior medications not taken at the time of study entry and no need to provide any additional information about adverse events.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

**From:** Cynthia.Psaras@sanofi-aventis.com [mailto:Cynthia.Psaras@sanofi-aventis.com]
**Sent:** Monday, November 07, 2011 12:18 PM
**To:** Toure, Hamet

**Subject:** RE: NDA202992: Psaras out of office from November 7-10

Dear Dr.Touré,

As per your original request, the patient listings were provided for patients who died, had an serious adverse event, or who withdrew from the study due to an adverse event. Our previous understanding was that you wanted the concomitant medication and AE data for these same patients. See attached proposals for the concomitant medications and adverse event data. Our proposal is that each patient will have an individual file linked to the original patient listing. As explained in our teleconference last week, the patient listing is linked to the narrative which is linked to the CRF. Please let me know if this is acceptable. Thank you.

Have a nice day,
Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Monday, November 07, 2011 11:44 AM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** RE: NDA202992: Psaras out of office from November 7-10

Dear Dr. Psaras,

Please submit the dates in which concomitant medications were received, in a format similar to the one submitted for laboratory data but including the relative day to the start of study medication for all patients for whom narratives were submitted. Such information will greatly facilitate the reviewer's safety evaluation of your application. Please submit the information by 11/30/11.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi-aventis.com [mailto:Cynthia.Psaras@sanofi-aventis.com]
**Sent:** Friday, November 04, 2011 5:09 PM
**To:** Toure, Hamet
**Subject:** NDA202992: Psaras out of office from November 7-10

Dear Hamet,

I will be at an off-site meeting next week. If you get feedback from your reviewer on the questions I posed today, send me an email and, if necessary, I will call you. Thank you.

Have a nice weekend,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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/s/

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HAMET M TOURE
11/07/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, November 07, 2011 11:44 AM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** RE: NDA202992: Psaras out of office from November 7-10

Dear Dr. Psaras,

Please submit the dates in which concomitant medications were received, in a format similar to the one submitted for laboratory data but including the relative day to the start of study medication for all patients for whom narratives were submitted. Such information will greatly facilitate the reviewer's safety evaluation of your application. Please submit the information by 11/30/11.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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**From:** Cynthia.Psaras@sanofi-aventis.com [mailto:Cynthia.Psaras@sanofi-aventis.com]
**Sent:** Friday, November 04, 2011 5:09 PM
**To:** Toure, Hamet
**Subject:** NDA202992: Psaras out of office from November 7-10

Dear Hamet,

I will be at an off-site meeting next week. If you get feedback from your reviewer on the questions I posed today, send me an email and, if necessary, I will call you. Thank you.

Have a nice weekend,

*Cynthia*

Cynthia Psaras, PhD
Director, Global Regulatory Affairs
sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Code: 55D-225A
Bridgewater, NJ 08807-0890
Tel: 908-981-4874

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/s/

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HAMET M TOURE
11/07/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Tuesday, November 01, 2011 11:08 AM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Psaras,

You have submitted patient profiles with information limited to laboratory and ECG data and abnormal CT or MRI findings. We acknowledge that our request was not clear. Please submit complete patient profiles including all the information recorded for that patient, including but not limited to age, gender, date of screening, randomization and starting therapy, whether the patient completed or did not complete the study, with dates and reason for withdrawal, adverse events ( reported term preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug), prior medications and concomitant medications with dates of start/end, vital signs, laboratories, Xrays, ECG, MRI and special studies with dates.

We appreciate that you created a PDF file for each patient and a table of contents with links to each assessment for each patient. However, a single PDF file per study, with a TOC indicating where data for each patient starts will suffice.

Please submit this information by 11/30/11.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi-aventis.com [mailto:Cynthia.Psaras@sanofi-aventis.com]
**Sent:** Tuesday, November 01, 2011 9:19 AM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Hamet,

The information for item 2 (see attached email) was submitted yesterday afternoon in two submissions. Amendment 0011 contains the patient listings as well as IND safety reports and autopsy reports as appropriate, for all the requested narratives in the NDA except for Study EFC10531/ TOWER. To maintain the confidentiality / blind of the TOWER study, amendment 0012 with similar information was submitted by someone outside the project team.

Have a nice day,
Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Wednesday, October 12, 2011 1:55 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Appears This Way On Original

Dear Dr. Psaras,

We refer to NDA 202992. We request the information listed below as part of the patient files requested by 10/31/11. Along with the original versions, we request English language versions of all requested documents.

See the table below for specific information requests for each subject.

| Subject | Requested Information |
|---|---|
| LTS6048<br>0030/0004<br>Placebo/7 mg | • All available ECG data for this subject<br>• Autopsy report, if an autopsy was performed<br>• Any assessments made by a cardiologist for this subject |
| LTS 6050<br>2407/0030<br>7 mg/7 mg | - Autopsy report |
| LTS6050<br>3203/0010<br>4 mg/14 mg | - Autopsy report |

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
11/01/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, October 26, 2011 4:29 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

1. As per agreement at the pre NDA meeting Sanofi-Aventis was to provide narratives of deaths, serious AE and discontinuations due to AEs. The FDA reviewer is not able to locate narratives for several serious adverse events that did not require drug discontinuation, for instance:

| |
|---|
| 006049-276-2007-0012 - Syncope |
| 006049-616-3003-0029 - Monoparesis |
| 006049-643-3205-0014 – Multiple sclerosis |
| 006049-792-5001-0001 – Multiple sclerosis |
| 006049-040-1601-0007 – Varicose vein |
| 006049-804-3510-000 - Haemothorax |

Please direct the reviewer to the location of these narratives by COB 10/28/11.

If not submitted, please submit narratives of all serious adverse events that were not previously submitted, even if they did not require discontinuation, from all treatment groups and all trials by 11/15/11

2. For adverse event reports of Multiple Sclerosis, provide detailed information about studies conducted to rule out causes of neurologic deterioration other than MS relapse, treatment received and outcome. Please provide information by COB 11/15/11.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
10/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

**FILING COMMUNICATION**

Sanofi-aventis U.S. Inc.
Attention: Cynthia Psaras, Ph.D.
Director, Global Regulatory Affairs
200 Crossing Blvd
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, for Teriflunomide 14 mg tablets.

We also refer to your amendments dated August 12, 2011, August 18, 2011, August 19, 2011 (2), September 2, 2011, September 9, 2011, September 19, 2011, and September 30, 2011 (3).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. We have considered your request for priority review and have concluded that your application does not represent a major advance in treatment or provide a treatment where no adequate therapy exists. A useful oral therapy that can be used safely in a wide range of the multiple sclerosis population as a first line therapy has already been approved for marketing. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 12, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 15, 2012.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. We have a number of comments that require your attention.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. In the highlights section, the verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. The year must correspond to the current approval action.
2. In the contraindications section, list known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
3. In the Full Prescribing Information (FPI) section, a horizontal line must separate the Table of Contents and FPI.
4. For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:
   "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

We request that you resubmit labeling that addresses these issues by November 16, 2011. The resubmitted labeling will be used for further labeling discussions.

The review team commends you for the completeness of your evaluation of the drug abuse and dependence liability in your NDA.

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 acknowledge receipt of your request for a partial waiver of pediatric studies for this application for pediatric patients ages birth to 9 years. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application for pediatric patients ages 10 to 17. All deferral requests must include supporting information and documentation to support the deferral request. We note that you did not submit the supporting information and documentation. Please submit the required supporting information and documentation for your partial deferral request. The partial deferral request must contain a timeline for the completion of these studies, i.e., the dates (month/day/year) of (1) protocol submission; (2) study completion; and (3) submission of study reports. In addition, you must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time (Refer to

Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm07956.pdf).

Please submit the requested information within 30 days of this letter. Once we have reviewed the additional information, we will notify you if the partial deferral request is denied.

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

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

---

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/s/

---

RUSSELL G KATZ
10/25/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, October 21, 2011 1:20 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

1. The half life of teriflunomide is 19.4 days. Please clarify what was the cut-off for collection of adverse events (AE) after last teriflunomide dose in each of the trials included in this application and what was the cut-off for analyses of AE used in the ISS.
2. Please provide the number and percentage of patients who underwent accelerated washout (with cholestyramine or charcoal) in each of the studies included in the application.
3. Please clarify how were AE that occurred during accelerated washout handled in the analyses of AEs (were they counted into the teriflunomide-treated AEs?).

Please submit a response to question 1 by COB 10/25/11, and a response to Questions 2 and 3 by COB 11/14/11. You may provide your response by email and follow with an archival response to NDA 202992 at your convenience.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
10/21/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, October 12, 2011 1:55 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer to NDA 202992. We request the information listed below as part of the patient files requested by 10/31/11. Along with the original versions, we request English language versions of all requested documents.

See the table below for specific information requests for each subject.

| Subject | Requested Information |
|---|---|
| LTS6048<br>0030/0004<br>Placebo/7 mg | • All available ECG data for this subject<br>• Autopsy report, if an autopsy was performed<br>• Any assessments made by a cardiologist for this subject |
| LTS 6050<br>2407/0030<br>7 mg/7 mg | - Autopsy report |
| LTS6050<br>3203/0010<br>14 mg/14 mg | - Autopsy report |

Please let me know if you have any questions.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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HAMET M TOURE
10/12/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

**REQUEST FOR METHODS VALIDATION MATERIALS**

Sanofi-Aventis U.S. LLC
Attention: Cynthia Psaras
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Cynthia Psaras:

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

We will be performing methods validation studies on Aubagio (teriflunomide) Tablets, 7 mg, as described in NDA 202992

In order to perform the necessary testing, we request the following sample materials and equipments:

| | |
|---|---|
| (b) (4) | Aubagio 7 mg Tablets |
| 200 mg - | Teriflunomide Reference Standard |
| 50 mg - | A813226 |
| 50 mg - | (b) (4) Reference Standard |
| 1 - | HPLC column, (b) (4) |

Send the MSDSs and certificates of analysis for the reference standards and tablets.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

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JAMES F ALLGIRE
10/06/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, October 06, 2011 10:04 AM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Psaras,

With respect to item #1 of our 10/3/11 request, we acknowledge that at the pre-NDA meeting of March 28, 2011, we agreed with your proposal not to submit a single AE dataset for phase 1 studies. However, such submission would greatly facilitate the reviewers' work. Please submit the datasets as requested on 10/3/11 no later than 10/21/11.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi-aventis.com [mailto:Cynthia.Psaras@sanofi-aventis.com]
**Sent:** Wednesday, October 05, 2011 2:09 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request

Dear Dr. Touré,

References are made to items 1 and 2 in the email below.

With respect to item 1, as reflected in the Agency's pre-NDA minutes, we provided an adverse event dataset for the Phase 2 / 3 study pools containing unique patient identifiers, verbatim terms, and MedDRA coding with all levels of the MedDRA hierarchy (primary and alternative coding paths) in the NDA. This data set is found in 5.3.5.3, ISS, Analysis data sets, adae.xpt. In the Agency's pre-NDA meeting minutes for Question 12, page 29, the Agency agreed with the sponsor that we did not need to submit Phase 1 adverse event datasets.

We also provided blinded listings of serious adverse events, nonserious adverse events, adverse events leading to discontinuation, and deaths for the ongoing trials, EFC6260 / TOPIC and EFC10891 / TENERE, in 5.3.5.3, ISS, ISS document, 11.2 for TOPIC and 11.3 for TENERE. The full data was provided for EFC 10531 / TOWER in Amendment 1 to the NDA.

If you are in agreement, the sponsor will consider that item 1 has been completed. Please let us know at your earliest convenience.

With respect to item 2, we plan to provide the requested information for patients in Phase 2 / 3 studies.

Best regards,
Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Monday, October 03, 2011 3:37 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

Please submit below item #1 by COB 10/10/11 and item #2 by COB 10/31/11.

1. In our pre-NDA meeting discussion, we requested pooled datasets (see text below from page 26 of the FDA meeting minutes under discussion of Question 12):

> *Adverse Event Datasets*
>
> For each of the phase 1 and phase 2-3 study pools, we request that the submitted datasets contain verbatim terms and MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path, as well as all alternate MedDRA coding paths.
>
> Each SAS transport file should have a unique patient identifier.

We were able to locate datasets containing pooled adverse event data for Pool 1 (placebo-controlled monotherapy studies) and Pool 2 (active treatment monotherapy studies). Please assist us in locating or please submit adverse event datasets for the following subject pools: a) single-dose clinical pharmacology studies; b) repeated-dose clinical pharmacology studies; and c) ongoing studies.

We request that the submitted datasets contain verbatim terms and MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path, as well as all alternate MedDRA coding paths. Each SAS transport file should have a unique patient identifier. Please identify serious adverse events and discontinuations due to adverse events in the datasets.

2. Some narratives are incomplete and do not include all relevant laboratory, radiology or ECG data. Moreover, the CRFs do not include laboratory values, ECG, radiology or special tests. Please submit individual patient files containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event or discontinued from the trial due to an adverse event. For those patients who had an IND safety report, please include dates when the initial and follow up safety reports were submitted to IND 067476.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
10/06/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Monday, October 03, 2011 3:37 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

Please submit below item #1 by COB 10/10/11 and item #2 by COB 10/31/11.

1. In our pre-NDA meeting discussion, we requested pooled datasets (see text below from page 26 of the FDA meeting minutes under discussion of Question 12):

> *Adverse Event Datasets*
>
> For each of the phase 1 and phase 2-3 study pools, we request that the submitted datasets contain verbatim terms and MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path, as well as all alternate MedDRA coding paths.
>
> Each SAS transport file should have a unique patient identifier.

We were able to locate datasets containing pooled adverse event data for Pool 1 (placebo-controlled monotherapy studies) and Pool 2 (active treatment monotherapy studies). Please assist us in locating or please submit adverse event datasets for the following subject pools: a) single-dose clinical pharmacology studies; b) repeated-dose clinical pharmacology studies; and c) ongoing studies.

We request that the submitted datasets contain verbatim terms and MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path, as well as all alternate MedDRA coding paths. Each SAS transport file should have a unique patient identifier. Please identify serious adverse events and discontinuations due to adverse events in the datasets.

2. Some narratives are incomplete and do not include all relevant laboratory, radiology or ECG data. Moreover, the CRFs do not include laboratory values, ECG, radiology or special tests. Please submit individual patient files containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event or discontinued from the trial due to an adverse event. For those patients who had an IND safety report, please include dates when the initial and follow up safety reports were submitted to IND 067476.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
10/03/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, September 23, 2011 3:05 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Psaras,

We refer you to NDA 202992. Please provide the latest protocol, dated January, 2011, for study EFC10531 Tower.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
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/s/

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HAMET M TOURE
09/23/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Thursday, September 22, 2011 12:07 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** RE: 202992_Information request_091611

Dear Dr. Psaras,

For item 1, the request pertains to all ISS subject pools analyzed, including:

- Placebo-controlled Pool 1
- Active Treatment Pool 2
- Adjunct Phase 2 Studies
- Clinical pharmacology studies (pooled single-dose studies and pooled repeated-dose studies)
- Ongoing studies

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

---

**From:** Cynthia.Psaras@sanofi-aventis.com [mailto:Cynthia.Psaras@sanofi-aventis.com]
**Sent:** Wednesday, September 21, 2011 5:09 PM
**To:** Toure, Hamet
**Subject:** RE: 202992_Information request_091611

Hamet,

For item 1, we just want to be sure this pertains to Phases 2 and 3. Is that correct? Thanks.

Have a nice evening,
Cynthia

---

**From:** Toure, Hamet [mailto:Hamet.Toure@fda.hhs.gov]
**Sent:** Friday, September 16, 2011 8:24 PM
**To:** Psaras, Cynthia R&D/US
**Cc:** Toure, Hamet; Ramos, Nilda R&D/US
**Subject:** 202992_Information request_091611

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

1. We request that you provide lists of all subjects with events related to each event category, using the following table format.

Please provide a separate data tables (in sas transport format) for the following categories of adverse events analyzed:

- Nausea

- Diarrhea
- Hepatic disorders
- Pulmonary disorders/interstitial lung disease
- Peripheral neuropathy
- Malignancy
- Blood pressure increase/hypertension
- Bone marrow disorders
- Hypersensitivity/anaphylactic reaction
- Pancreatic disorders
- Infections
- Alopecia
- Pregnancies
- Cardiac arrhythmias
- Convulsions
- Hemorrhage
- Embolic and thrombotic events
- Angioedema
- Severe cutaneous reactions



Please sort by study pool, study, and subject ID.

| Study Pool | Study | Unique Subject ID | Randomized Dose | Latency* (days) | Country | Age | Sex | Preferred Term | SAE Y/N | Discontinuation Y/N |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |

- Latency = time from day of first treatment to diagnosis
- SAE = Serious Adverse Event

2. Please provide (or direct us to) a summary of adverse events found in searches using the Angioedema SMQ and the Severe Cutaneous Reaction SMQ with hyperlinks to the related narratives (see p. 30 of the FDA meeting minutes for the 3/28/2011 pre-NDA meeting).

3. We request a list of studies found in the database searches listed on page 17 of the ISS.

4. Please provide or direct us to the peripheral neuropathy datasets, which were discussed in Question 12 of the pre-NDA meeting minutes.

5. Regarding the 7-Day Safety Report, submitted to IND 067476 on August 31, 2011, which reported a myocardial infarction in Study EFC10531, Investigator 7240002, Patient 003, we request the following:

- The unique subject ID used for this subject in the datasets submitted 8/18/11
- A listing of blood pressure measurements for this subject at baseline and post-treatment
- A listing of vital sign measurements from the subject's emergency room and hospital treatment

Please provide your archival response to NDA 202992 by September 30, 2011.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
09/22/2011
Sent at request of safety TL

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, September 21, 2011 5:25 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request_092111

Dear Dr. Psaras,

We request this information by September 27, 2011.

For studies ongoing at the time of the cut-off for original NDA 202992 (EFC10531/TOWER, EFC10891/TENERE, EFC6260/TOPIC, EFC5058/TERACLES), we request a table with the following information for all investigators:

| Study ID | Investigator Name | Investigator Number | Center Number |
|---|---|---|---|
| | | | |

This information is necessary to integrate information from safety reports submitted to IND 067476, which appear to list the investigator number but not the center number, and the datasets submitted to NDA 202992, which appear to list the center number but not the investigator number.

Please include the applicable center number with future safety reports submitted to IND 067476.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
09/21/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, September 16, 2011 8:24 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet; 'Nilda.Ramos@sanofi-aventis.com'
**Subject:** 202992_Information request_091611

Dear Dr. Psaras,

We refer you to NDA 202992. We have the following information request:

1. We request that you provide lists of all subjects with events related to each event category, using the following table format.

Please provide a separate data tables (in sas transport format) for the following categories of adverse events analyzed:

- Nausea
- Diarrhea
- Hepatic disorders
- Pulmonary disorders/interstitial lung disease
- Peripheral neuropathy
- Malignancy
- Blood pressure increase/hypertension
- Bone marrow disorders
- Hypersensitivity/anaphylactic reaction
- Pancreatic disorders
- Infections
- Alopecia
- Pregnancies
- Cardiac arrhythmias
- Convulsions
- Hemorrhage
- Embolic and thrombotic events
- Angioedema
- Severe cutaneous reactions

Please sort by study pool, study, and subject ID.

| Study Pool | Study | Unique Subject ID | Randomized Dose | Latency* (days) | Country | Age | Sex | Preferred Term | SAE Y/N | Discontinuation Y/N |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |

- Latency = time from day of first treatment to diagnosis
- SAE = Serious Adverse Event

2. Please provide (or direct us to) a summary of adverse events found in searches using the Angioedema SMQ and the Severe Cutaneous Reaction SMQ with hyperlinks to the related narratives (see p. 30 of the FDA meeting minutes for the 3/28/2011 pre-NDA meeting).

3. We request a list of studies found in the database searches listed on page 17 of the ISS.

4. Please provide or direct us to the peripheral neuropathy datasets, which were discussed in Question 12 of the pre-NDA meeting minutes.

5. Regarding the 7-Day Safety Report, submitted to IND 067476 on August 31, 2011, which reported a myocardial infarction in Study EFC10531, Investigator 7240002, Patient 003, we request the following:

- The unique subject ID used for this subject in the datasets submitted 8/18/11

- A listing of blood pressure measurements for this subject at baseline and post-treatment
- A listing of vital sign measurements from the subject's emergency room and hospital treatment

Please provide your archival response to NDA 202992 by September 30, 2011.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

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/s/

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HAMET M TOURE
09/16/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, September 02, 2011 4:00 PM
**To:** 'Nilda.Ramos@sanofi-aventis.com'
**Cc:** Cynthia.Psaras@sanofi-aventis.com; Toure, Hamet
**Subject:** 202992_Information request

Dear Dr. Ramos,

We refer to NDA 202992. We have the following information request:

We do see the Site ID numbers in the demographics database, and we do see the listing of investigators, but not a listing of the Site ID numbers associated with their principal investigators, locations, contact information, and addresses as needed for choosing an inspection site.

Please send us an explanation of your site IDs or if you are already transmitted, point out to us where they are listed.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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HAMET M TOURE
09/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

**NDA ACKNOWLEDGMENT**

Sanofi-aventis U.S. Inc.
Attention: Cynthia Psaras, Ph.D.
Director, Global Regulatory Affairs
200 Crossing Blvd
Bridgewater, NJ 08807

Dear Dr. Psaras:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Teriflunomide 14 mg tablets

Date of Application: August 12, 2011

Date of Receipt: August 12, 2011

Our Reference Number: NDA 202992

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 11, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

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

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center of Drug Evaluation and Research

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/s/

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RUSSELL G KATZ
09/02/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Friday, August 26, 2011 1:49 PM
**To:** 'Nilda.Ramos@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request_26 August 2011

**Attachments:** HighlightsofClinicalPharmacology.doc

Dear Ms. Ramos,

We refer to your teriflunomide NDA, submitted and received August 12, 2011. Please submit an updated clinical pharmacology table (see attached) to us as soon as possible. Please also submit all study related ECG waveforms to the ECG warehouse at: www.ecgwarehouse.com.

HighlightsofClinicalP harmacolo...

Kindly provide your response as an archival submission to NDA 202992.

Best regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
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/s/

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HAMET M TOURE
08/26/2011

## Toure, Hamet

**From:** Toure, Hamet
**Sent:** Wednesday, August 17, 2011 12:35 PM
**To:** 'Cynthia.Psaras@sanofi-aventis.com'
**Cc:** Toure, Hamet
**Subject:** 202992_Information request_17 August 2011

Dear Dr. Psaras,

We refer to your August 12, 2011, New Drug Application for teriflunomide. Please let us know where your detailed list of eCTD documents is located. If you have not submitted a list, please submit a complete list of the locations for eCTD submitted documents and datasets at your earliest convenience.

Please provide your response to this information request as an archival submission to NDA 202992.

Kind regards,

Hamet Touré, PharmD MPH
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
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HAMET M TOURE
08/17/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

**Food and Drug Administration**
**Silver Spring MD 20993**

IND 067476

**MEETING MINUTES**

Sanofi-aventis U.S. Inc.
Attention: Dr. Qinghua Ji, MD
Associate Director
Regulatory Research and Development Portfolio
200 Crossing Blvd
Bridgewater, NJ 08807

Dear Dr. Ji,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for teriflunomide tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 28, 2011. The purpose of the meeting was to discuss your proposed New Drug Application (NDA) for the monotherapy program for teriflunomide in the treatment of relapsing multiple sclerosis.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center of Drug Evaluation and Research

# MEMORANDUM OF MEETING MINUTES

**Meeting Type:** [Type B]

**Meeting Date and Time:** [March 28, 2011, 1400 to 1500]
**Meeting Location:** [White Oak; building 22, room 1309]

**Application Number:** [IND 067476]
**Product Name:** [Teriflunomide]
**Indication:** [Multiple Sclerosis]
**Sponsor/Applicant Name:** [Sanofi-Aventis]

**Meeting Chair:** [Russell Katz, MD]
**Meeting Recorder:** [LT Hamet Touré, PharmD MPH]

## FDA ATTENDEES

Russell Katz, MD, Division of Neurology Products, Director
Eric Bastings, MD, Deputy Director
Billy Dunn, MD, Team Leader
Jody Green, MD, Clinical Reviewer
Evelyn Mentari, MD, Safety Reviewer
Lois Freed, PhD, Nonclinical Team Leader
Richard Houghtling, PhD, Nonclinical Reviewer
Kun Jin, PhD, Biostatistics Supervisor
Xiaorong Yan, PhD, Biostatistics Reviewer
Angela Men, PhD, Clinical Pharmacology Team Leader
Katherine Bonson, PhD, Controlled Substance Staff Pharmacologist
Yeruk Mulugeta, PharmD, Office of Clinical Pharmacology Reviewer
Elizabeth Durmowicz, MD, Pediatric and Maternal Health Medical Officer
Nadia Hejazi, MD, Pediatric and Maternal Health Medical Officer
Mildred Wright, RN, MSN, Pediatric and Maternal Health Regulatory Project Manager
LCDR Courtney Suggs, PharmD, Pediatric and Maternal Health Regulatory Project Manager
Allison Upalawanna, PharmD Candidate
LT Hamet Touré, PharmD, MPH, Regulatory Project Manager

## SPONSOR ATTENDEES

Philippe Truffinet, MD - Clinical Leader
Barbara Wamil, MD - Clinical Leader
Lynn Davenport, PhD - Drug Safety Evaluation Leader
Sandrine Turpault, Pharm.D - Drug Disposition (PK) Leader

Anita Burrell, MBA - Project Director
Marion McGlynn, MS - MBA, Operations Director
Hadj Benzerdjeb, MD - Global Pharmacovigilance and Epidemiology Leader
Manfred Oster, MD - Global Pharmacovigilance and Epidemiology
Deborah Dukovic, MS - Biostatistics Leader
Lin Wang, PhD - Project Biostatistician
Francoise Menguy-Vacheron, Pharm.D, PhD - Clinical and Exploratory Pharmacology
Caroline DeSurmont-Ruchaud, PhD – Global Regulatory Affairs
Odile Ernoux, MD – Global Regulatory Affairs
Qinghua (Sarah) Ji, MD - Global Regulatory Affairs

# LIST OF QUESTIONS FOR THE AGENCY

## CLINICAL

### Efficacy

***Question 1:*** *Does the agency agree with the proposed presentation of efficacy data from the placebo-controlled studies of teriflunomide (7 mg and 14 mg once daily) in the treatment of relapsing forms of multiple sclerosis?*

***FDA Preliminary Response***
We agree with the proposed presentation of data from EFC6049 (TEMSO) and HMR1726/2001. For EFC10531 (TOWER), please make clear in your interim analysis the duration of treatment (both in aggregate and in bins of various duration) of subjects with trial medication.

In addition, in your NDA submission, please include secondary and supportive analyses of the primary endpoint such as the protocol specified secondary analysis and analyses on observed cases and per-protocol population. In addition to confirmed relapses, data and analysis of all relapses, confirmed and non-confirmed, should be included in the submission.

***Sanofi-aventis Response:***
In the Phase 3 studies, the primary analysis population for efficacy is the ITT population defined as all randomized patients who have at least 1-day study medication exposure, analyzed in the treatment group assigned by randomization. For EFC6049 (TEMSO) the primary analysis of ARR in this population includes confirmed, on treatment relapses analyzed using a Poisson regression model with robust error variance (estimates of unadjusted rates will also be provided). In addition to this primary analysis of ARR, the Sponsor will also provide analysis of all on treatment relapses, both confirmed and unconfirmed, analysis of ARR in the per-protocol population, analysis of all confirmed relapses including those occurring after treatment discontinuation and analysis of time to first relapse.

Although ARR was a secondary efficacy variable in HMR1726/2001, analyses of ARR in the efficacy-evaluable and completer populations will be provided. In this study, all on treatment relapses were included, i.e. no confirmation was obtained.
Could the Agency confirm that the above analyses meet the Agency's requirements? In particular, can the Agency please provide clarification for "analyses of observed cases" if an additional analysis is required.

For EFC10531 (TOWER), primary analysis of confirmed, on treatment relapses and analysis of all on treatment relapses (confirmed and non-confirmed) will be provided

using the same methods as for EFC6049 (TEMSO), as indicated, only descriptive data will be provided.

The Sponsor would like to obtain clarification on the presentation of efficacy from TOWER that is required.

**Meeting discussion:**

**The "analysis of observed cases" refers to the cases noted in HMR 1726/2001 that were not confirmed but were observed. For the TOWER study, we agree with your plan to evaluate the treatment response by treatment duration in discrete time intervals. Pertaining to the submission of efficacy data, if a futility analysis is planned that may lead to an early termination of the trial, then you would need to submit a formal Statistical Analysis Plan in advance and present your data with statistical analysis, otherwise descriptive data will suffice.**

***Question 2:*** *Does the Agency agree that the overall integrity of the Study EFC10531/TOWER as a second Phase 3 efficacy study will be adequately maintained given the interim analysis will be performed and the report (full safety and limited efficacy as described in Question 1) written by a separate, independent group within the Sponsor's organization not involved with the teriflunomide project*?

***FDA Preliminary Response***

Yes.

**Sanofi-aventis Response:**

The sponsor appreciates the Agency response and acknowledges their agreement.

**Meeting discussion: None**

## Safety

### Integrated safety analysis – Phase 2-3 studies

***Question 3:*** *Does the Agency agree with the proposed pooling strategy for the analysis of teriflunomide safety in Phase 2-3 studies, including a placebo-controlled pool and a non-comparative active treatment pool?*

***FDA Preliminary Response***

We agree with the proposed pooling strategy for the analysis of teriflunomide safety in phase 2-3 studies, including a placebo-controlled pool and a non-comparative active treatment pool. In addition two these two pools, we request detailed reporting on the TEMSO trial results within the Integrated Summary of Safety.

***Sanofi-aventis Response:***

A detailed analysis of the placebo controlled pool 1 (TEMSO + 2001 phase 2 study) will be provided in the SCS/ICS. Based on the fact that the additional contribution of study 2001 to the pool will be of 179 patients (179/1265; 14%), the Sponsor believes that this analysis will not significantly differ from the TEMSO stand alone analysis.

Therefore, the Sponsor proposes to focus on its initial strategy to present pool 1 analysis, but is willing to perform additional analyses for TEMSO in the SCS/ICS, if required. The Sponsor intends to provide Pool 1 plus the full TEMSO CSR with all associated narratives will be included. Will this presentation of data be sufficient?

**Meeting discussion:**

**We request detailed reporting of the TEMSO Study results (including deaths, discontinuations, serious adverse events, and common adverse events) as part of the Integrated Summary of Safety. You note you will include these data in the study report and commit to providing links to these data from the Integrated Summary of Safety. This is an acceptable way of providing this information. We request that you include links to specific tables, figures, or pages of the TEMSO study report, as opposed to simply providing a link to the report itself.**

***Question 4:*** *Does the Agency agree with the inclusion of the Phase 2 adjunct studies under "Other Patient Populations" in the Summary of Clinical Safety?*

***FDA Preliminary Response***

The NDA safety assessment should be based on all worldwide knowledge regarding this product. We request that safety results of the three completed phase 2 adjunct therapy studies (PDY6045, PDY6046, and LTS6047) be reported in the Integrated Summary of Safety. We request reporting and discussion of deaths, all discontinuations, and serious adverse events that occurred in these studies; narratives should be provided for these categories of events. Summaries of adverse events should either be included in the Integrated Summary of Safety or should be easy to obtain through a linked document.

***Sanofi-aventis Response:***

The Sponsor understands that the NDA safety assessment must be based on all available data and knowledge and intends to include PDY6045, PDY6046 and LTS6047 safety assessment in the Summary of Clinical Safety/Integrated Summary of Safety. Since adjunct therapy is an indication different from monotherapy, i.e. background therapy results in a different patient population than patients without background therapy, adjunct therapy studies will not be pooled with monotherapy studies. Consequently, the sponsor proposes that the data/discussion for these adjunct studies follow the pooled safety assessment in each section of the Summary of Clinical Safety/ Integrated Summary of Safety, and be located under a separate heading of "Other Patient Populations". Selected adverse event summaries will be included in the Summary of Clinical Safety/Integrated Summary of Safety and others will be referenced and linked to the respective clinical study report which has been prepared for these studies and will be included in the NDA submission. Discussion of adverse events of special interest will be included in the related section. Narratives, including for deaths, discontinuations and serious adverse events will be included in the submission.

**Meeting discussion:**

**You confirm you intend to submit all safety data available worldwide and make narratives available through hyperlinks in the ISS. For additional clarity, we request that the heading "Adjunct Phase 2 Studies" be used for adjunct studies, instead of the heading "Other Patient Populations" proposed in your response above.**

**You note your SCS, located in section 2.7.4, will cover all the elements of the ISS with the exception of large tables and narratives, which will be located in section 5.3.5.3. You commit to providing specific links from section 2.7.4 to section 5.3.5.3.**

***Question 5:*** *Does the Agency agree with the inclusion of blinded safety data (AEs, SAEs, AEs leading to discontinuation, and AEs leading to death) for the ongoing Phase 3 studies, EFC10891/TENERE and EFC6260 (TOPIC), under "Ongoing Studies at Cut-Off"?*

***FDA Preliminary Response***

We request reporting and evaluation of blinded safety data under "Ongoing Phase 2 and Phase 3 Monotherapy Studies at Cut-Off" for LTS 6048, LTS6050, EFC10891 (TENERE) and EFC6260 (TOPIC), and EFC10531 (TOWER). We also request discussion of safety data from EFC6058 (TERACLES) under "Ongoing Adjunct Therapy Studies at Cut-off." Please include narratives for deaths, all discontinuations, and SAEs.

Please discuss the anticipated cut-off date for analyses of ongoing studies with the Division.

***Sanofi-aventis Response:***

The ongoing Phase 3 studies at the time of the submission are EFC10531/TOWER, LTS6048 (2001 extension), LTS6050 (TEMSO extension), EFC10891/TENERE, EFC6260/TOPIC, and EFC6058/TERACLES.

An unblinded interim analysis is proposed for EFC10531/TOWER, and a safety evaluation will be included in the study report, including narratives for any deaths, SAEs, discontinuations, and selected AESIs (with same selection criteria as for CTD including those additionally requested in Agency comments), plus individual patient CRFs associated with the narratives and datasets. The Sponsor noticed in the comments from the Agency that TOWER blinded data were requested. Would this be required in addition to the unblinded data provided in the TOWER interim analysis?

Unblinded interim analyses are planned for the LTS6048 and LTS6050 studies. Similar to EFC10531/TOWER, a safety evaluation will be included in each of the study reports, including narratives for any deaths, SAEs, and discontinuations, individual patient CRFs associated with the narratives and datasets.

For the EFC10891/TENERE (active comparator) and EFC6260/TOPIC (CIS) studies, the sponsor proposes to only include blinded summaries of AE data similar to what would be provided to the Agency for an IND annual report, plus narratives for any deaths, SAEs and discontinuations.

The EFC6058/TERACLES (adjunct therapy) study initiated recruitment in mid-February 2011 so was outside the cut-off date for ongoing studies of January 11, 2011 and so will not be included in ongoing studies for the NDA. To date, only 2 patients have been enrolled.

For ongoing studies, individual summaries for any deaths or SAEs that occur up to June 1, 2011 will be included from the pharmacovigilance database.

The cut-off dates presented in the table below were selected to support an NDA submission in 3Q 2011.

| Study | Randomization cut-off | Data cut-off[1] | Interim "lock" |
|---|---|---|---|
| LTS6048 | Randomization complete | 11 January 2011 | 24 February 2011 |
| LTS6050 | Randomization complete | 11 January 2011 | 23 February 2011 |
| EFC10531/TOWER | 30 November 2010 | 28 February 2011 | 06 April 2011[2] |
| EFC6260/TOPIC | Ongoing/no cut-off applied | 11 January 2011 | 08 March 2011 |
| EFC10891/TENERE | Randomization complete | 11 January 2011 | 11 March 2011 |

[1] The primary data presented is up to the data cut-off date, however, data up to the interim "lock" date is not excluded except for EFC10531/TOWER.
[2] Planned lock date.

**Meeting discussion:**

**We agree with your proposal and will accept unblinded data for your TOWER study. You mention that the EFC6058/TERACLES (adjunct therapy) study initiated recruitment in mid-February 2011 and to date only 2 patients have been enrolled. You also mention that the initiation of recruitment for EFC6058/TERACLES was outside the cut-off date for ongoing studies, so this study will not be included in ongoing studies for the NDA. We request that you include this information in the NDA.**

**Integrated safety analysis – Phase 1 studies**

***Question 6:*** *Does the Agency agree with the pooling strategy of Phase 1 studies for the summary of clinical safety?*

***FDA Preliminary Response***

Yes.

***Sanofi-aventis Response:***

The sponsor appreciates the Agency response and acknowledges their agreement.

**Meeting discussion: None**

***Question 7:*** *Does the Agency agree with the planned analyses and the presentation of adverse events, laboratory parameters, vital signs, and electrocardiogram (ECG) parameters from Phase 1 studies?*

***FDA Preliminary Response***

In addition to what you have proposed, we have the following comments regarding your planned analyses for Phase 1 studies:

- We request that you summarize the protocols for collecting ECG data in Phase 1 studies. For both the single dose and repeated dose study pools, we request that you report on the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

- We request analyses and narratives for deaths, all discontinuations, and SAEs.

- We request a table of treatment-emergent adverse events and a table of treatment-emergent SAEs reported in ≥1% of all teriflunomide-treated subjects in phase 1 studies, sorted by SOC and then MEDRA Preferred Term. These should include

separate columns for teriflunomide and for placebo. Vital signs analyses for the phase 1 pools should include the following:

**Table 1 Incidence of Treatment-Emergent Abnormal Vital Signs at Any Visit During Phase 1 Studies**

| **Abnormal Vital Sign (VS) Parameters Relative to Baseline/Pre-treatment VS** | Teriflunomide | Placebo |
|---|---|---|
| **Supine** | | |
| SBP increment ≥ 20 mm Hg | | |
| SBP increment ≥ 40 mm Hg | | |
| SBP decrement ≥ 20 mm Hg | | |
| SBP decrement ≥ 40 mm Hg | | |
| DBP increment ≥ 10 mm Hg | | |
| DBP increment ≥ 20 mm Hg | | |
| DBP decrement ≥ 10 mm Hg | | |
| DBP decrement ≥ 20 mm Hg | | |
| Pulse increment ≥ 15 bpm | | |
| Pulse increment ≥ 30 bpm | | |
| Pulse decrement ≥ 15 bpm | | |
| Pulse decrement ≥ 30 bpm | | |
| **Standing** | | |
| SBP increment ≥ 20 mm Hg | | |
| SBP increment ≥ 40 mm Hg | | |
| SBP decrement ≥ 20 mm Hg | | |
| SBP decrement ≥ 40 mm Hg | | |
| DBP increment ≥ 10 mm Hg | | |
| DBP increment ≥ 20 mm Hg | | |
| DBP decrement ≥ 10 mm Hg | | |
| DBP decrement ≥ 20 mm Hg | | |
| Pulse increment ≥ 15 bpm | | |
| Pulse increment ≥ 30 bpm | | |
| Pulse decrement ≥ 15 bpm | | |
| Pulse decrement ≥ 30 bpm | | |
| **Change from Supine to Standing** | | |
| SBP increment ≥ 20 mm Hg | | |
| SBP increment ≥ 40 mm Hg | | |
| SBP decrement ≥ 20 mm Hg | | |
| SBP decrement ≥ 40 mm Hg | | |
| DBP increment ≥ 10 mm Hg | | |
| DBP increment ≥ 20 mm Hg | | |
| DBP decrement ≥ 10 mm Hg | | |
| DBP decrement ≥ 20 mm Hg | | |
| Pulse increment ≥ 15 bpm | | |

| | | |
|---|---|---|
| Pulse increment ≥ 30 bpm | | |
| Pulse decrement ≥ 15 bpm | | |
| Pulse decrement ≥ 30 bpm | | |

SBP = systolic blood pressure

DBP = diastolic blood pressure

Patients are counted once during treatment regardless of number of times achieving the threshold change.

We also request the following outlier analyses of phase 1 study vital sign data. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mm Hg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Pulse Rate: <60 bpm, >100 bpm
- Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
- Temperature: >38.0 °C, <36.0 °C

***Sanofi-aventis Response:***

The sponsor appreciates the Agency response and intends to summarize all the different protocols for collecting ECG data in Phase 1 studies, and propose to pool all the automatic ECG readings data for phase 1 studies, except for TES10852 (thorough ECG) study for which ECGs consisted of semi-automatic readings by a cardiologist and therefore would be provided separately.
The analyses proposed by the Sponsor, based on the company standard, and the analyses proposed by the Agency are described in the table below. Given the similarity between both, is it acceptable the Sponsor uses its standard?

| Sanofi-Aventis Potentially Clinically Significant Abnormalities | FDA proposal |
|---|---|
| *Males* *Females*<br>Borderline 431-450 ms 451-470 ms<br>Prolonged> 450 ms > 470 ms<br>QTc ≥ 500 ms ≥ 500 ms | QTc >450 ms, >480 ms, and >500 ms |

The sponsor acknowledges the Agency requests for additional adverse event and vital sign analyses. Concerning the additional analysis requests, the sponsor would like to get clarification on some of the items described above. These are listed below:

A. As outlined in the pre-NDA briefing package, planned integrated vital sign analyses for phase 1 studies will be done for the repeated dose pool only. For the additional vital sign analyses, does the Agency request that such analyses be prepared for both single and repeated dose studies?

**Meeting discussion:**

**Yes, we request that such analyses be prepared for both single and repeated dose studies.**

B. For the additional adverse event analyses, is it sufficient for the sponsor to provide separate summaries for the single and repeated dose pools?

**Meeting discussion:**

**Your proposal is acceptable.**

C. For the additional adverse event and vital sign analyses, the Agency requests that these summaries "include separate columns for teriflunomide and placebo." Is it sufficient for the sponsor to provide summaries by the pooled teriflunomide dose groups agreed upon in Question 6?

**Meeting discussion:**

**We agree.**

Analysis of vital signs including supine blood pressure analysis as well as pulse rate, body weight decrease and temperature following predefined FDA threshold will be provided.

**Safety Database**

***Question 8:*** *Does the agency consider that the safety database provided at the time of initial NDA submission along with the additional data provided in the 120-day safety update would allow the Agency to perform a benefit /risk evaluation of teriflunomide?*

***FDA Preliminary Response***

On face, the numbers of subjects appear to be adequate. However, more detailed evaluation will be necessary to determine whether there is adequate subject exposure to evaluate specific safety issues.

***Sanofi-aventis Response:***

*The sponsor acknowledges the Agency response.*

**Meeting discussion: None**

**Presentation of safety data**

***Question 9:*** *Does the Agency agree with the proposed analyses for the assessment of safety data including adverse events, adverse events of special interest, laboratory data, vital signs data and ECG data?*

***FDA Preliminary Response***

In addition to what you have proposed, we have the following comments regarding your planned analyses for phase 2 and 3 studies:

- We request analyses and narratives for deaths, all discontinuations, and SAEs.

- We request a table of treatment-emergent adverse events and a table of treatment-emergent SAEs reported in ≥1% of all teriflunomide-treated subjects in phase 2 and 3 studies, sorted by SOC and then MEDRA Preferred Term. These should include separate columns for each dose of teriflunomide and placebo.

- We request that you summarize the protocols for collecting ECG data in phase 2 and 3 studies. For each phase 2-3 study pool, we request that you report on the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

*Vital Signs*

Vital signs analyses for the Phase 2 and 3 pools should include the following for each pool:

**Table 1 Incidence of Treatment-Emergent Abnormal Vital Signs at Any Visit During Phase 2 and 3 Studies**

| **Abnormal Vital Sign (VS) Parameters Relative to Baseline/Pre-treatment VS** | Teriflunomide 7 mg | Teriflunomide 14 mg | Placebo |
|---|---|---|---|
| **Supine** | | | |
| SBP increment ≥ 20 mm Hg | | | |
| SBP increment ≥ 40 mm Hg | | | |
| SBP decrement ≥ 20 mm Hg | | | |

| | | | |
|---|---|---|---|
| SBP decrement ≥ 40 mm Hg | | | |
| DBP increment ≥ 10 mm Hg | | | |
| DBP increment ≥ 20 mm Hg | | | |
| DBP decrement ≥ 10 mm Hg | | | |
| DBP decrement ≥ 20 mm Hg | | | |
| Pulse increment ≥ 15 bpm | | | |
| Pulse increment ≥ 30 bpm | | | |
| Pulse decrement ≥ 15 bpm | | | |
| Pulse decrement ≥ 30 bpm | | | |
| **Standing** | | | |
| SBP increment ≥ 20 mm Hg | | | |
| SBP increment ≥ 40 mm Hg | | | |
| SBP decrement ≥ 20 mm Hg | | | |
| SBP decrement ≥ 40 mm Hg | | | |
| DBP increment ≥ 10 mm Hg | | | |
| DBP increment ≥ 20 mm Hg | | | |
| DBP decrement ≥ 10 mm Hg | | | |
| DBP decrement ≥ 20 mm Hg | | | |
| Pulse increment ≥ 15 bpm | | | |
| Pulse increment ≥ 30 bpm | | | |
| Pulse decrement ≥ 15 bpm | | | |
| Pulse decrement ≥ 30 bpm | | | |
| **Change from Supine to Standing** | | | |
| SBP increment ≥ 20 mm Hg | | | |
| SBP increment ≥ 40 mm Hg | | | |
| SBP decrement ≥ 20 mm Hg | | | |
| SBP decrement ≥ 40 mm Hg | | | |
| DBP increment ≥ 10 mm Hg | | | |
| DBP increment ≥ 20 mm Hg | | | |
| DBP decrement ≥ 10 mm Hg | | | |
| DBP decrement ≥ 20 mm Hg | | | |
| Pulse increment ≥ 15 bpm | | | |
| Pulse increment ≥ 30 bpm | | | |
| Pulse decrement ≥ 15 bpm | | | |
| Pulse decrement ≥ 30 bpm | | | |

SBP = systolic blood pressure

DBP = diastolic blood pressure

Patients are counted once during treatment regardless of number of times achieving the threshold change.

We also request the following outlier analyses of vital sign data. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Pulse Rate: <60 bpm, >100 bpm
- Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
- Temperature: >38.0 °C, <36.0 °C

*Laboratory measurements*

When available, we request that you use the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for shift tables documenting changes in laboratory values from baseline.[1] We request that you clearly list the laboratory criteria used for each toxicity grade within the analysis tables.

*Drug-Demographic Interactions*

We request that your analyses for potential drug-demographic interactions include analyses stratified by age, sex, location (U.S. vs. non-U.S., as well as by geographic region), and history of taking so-called "disease-modifying drugs" for multiple sclerosis[2] prior to study entry. We also request information on the numbers of subjects who have taken "disease-modifying drugs" for multiple sclerosis prior to study entry stratified by location (U.S. vs. non-U.S., as well as by geographic region).

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[1]Accessed on 3/15/11 at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[2] "Disease-modifying drugs" for multiple sclerosis that should be analyzed include: interferon beta-1a, interferon beta-1b, glatiramer acetate, mitoxantrone, natalizumab, and fingolimod.

*General requests for safety analyses*

- Please ensure that all adverse events are presented, and not only events deemed "drug-related."

- Outlier analyses should have the laboratory values used as thresholds for analysis clearly listed with each analysis.

- Please provide the normal laboratory values used in data analysis.

- Please make sure that a coding dictionary with a list of investigator verbatim terms and the preferred terms to which they were matched is submitted as an SAS transport file.

- Every SAS file should have unique patient identifiers.

- Given that the majority of subjects in EFC6049 (TEMSO) are from non-U.S. locations, we request that you provide justification for the applicability of your data to U.S. patients.

- If you think that a REMS will be necessary, we recommend that you submit it with the NDA.

***Sanofi-aventis Response:***

The Sponsor acknowledges the FDA comments and intends to provide narratives for deaths, all discontinuations and SAEs.

The sponsor will provide the additional summaries of treatment-emergent adverse events and treatment-emergent SAEs requested; however, we would like to clarify the 1% criterion. Can the Agency confirm the request is for summaries of all preferred terms that occur at a frequency of 1% or greater in either teriflunomide treatment arm (7 mg or 14 mg), separately for TEAEs and treatment-emergent SAEs and for each pool as described below:

- Pool 1: TEAEs with PT ≥1% in either teriflunomide treatment group (in pool 1)
- Pool 1: TE SAEs with PT ≥1% in either teriflunomide treatment group (in pool 1)
- Pool 2: TEAEs with PT ≥1% in either teriflunomide treatment group (in pool 2)
- Pool 2: TE SAEs with PT ≥1% in either teriflunomide treatment group (in pool 2)

In all cases presented by primary SOC and PT with internationally agreed order for SOC and decreasing frequency of PT in the teriflunomide 14 mg group.

The sponsor proposes the same comments for the presentation of ECG data as in Question 7. As indicated in the Briefing Document, no ECGs were collected in the TEMSO study, nor in its extension LTS6050. A thorough ECG study has been completed, and results will be provided.

The sponsor agrees with the proposed thresholds for analysis of vital signs, but would like to underline that blood pressure was taken only in supine (TEMSO and its LTS6050 extension) or sitting position (2001 and LTS6048 extension) and therefore no change from supine to standing will be presented.

The analyses of laboratory data as per statistical analyses defined in the study reports are based on company standard criteria, supported by literature, association guidelines, and

published guidance documents which for most part are comparable to CTCAE criteria with some exceptions. A comparative table is attached as Appendix 1 at the end of this document. All completed study reports were generated using the company standard criteria. For the clinical summary of safety, the sponsor proposes to use the company's standards and to perform additional analyses based on the CTCAE definition when thresholds are different or do not exist in the company standards, such as decreased numbers of lymphocytes.

Drug-Demographic Interactions - We accept Agency's recommendation and it will be addressed in NDA. In terms of the US patients in the NDA, there will be 8 patients from the TEMSO study, and 204 from the EFC10531/TOWER interim analysis.

Regarding the request for a coding dictionary, the sponsor's datasets contain both verbatim terms and preferred terms based on MedDRA 13.1. The sponsor would like to ask for clarification if there is something beyond this that is required.

**Meeting discussion:**

**Your proposal is acceptable. You note you will not change the CSR as written but will provide them as such.**

**Regarding analyses of laboratory data, you offered to provide tables comparing company standard criteria and CTCAE criteria for clinically significant abnormalities. These tables would specify which criteria you plan to use for each laboratory parameter. You should provide these tables.**

**Regarding your request for clarification, we request that the datasets contain verbatim terms and terms for all levels in the MedDRA hierarchy, including terms for the primary paths and all secondary paths for a given Preferred Term.**

**Evaluation of specific safety aspects**

***Question 10:*** *Does the agency agree with the proposed list of adverse events of special interest to be evaluated: nausea, diarrhea, hepatic disorders, pulmonary disorders/ interstitial lung disease, peripheral neuropathy, malignancy, blood pressure increase/ hypertension, bone marrow disorders, hypersensitivity/ anaphylactic reaction, pancreatic disorders, infections and alopecia?*

***FDA Preliminary Response***

In addition to the topics you have listed in Question 10, we request that you also evaluate the following categories of events: Pregnancies, Cardiac arrhythmias (MedDRA SMQ),

Convulsions (MedDRA SMQ), Hemorrhage (MedDRA SMQ), and Embolic and Thrombotic Events (SMQ). We request that your discussion of infections specifically address opportunistic infections.

The list of specific safety aspects should be inclusive of all categories of adverse events with evidence of increased frequency with teriflunomide. If there are others that are not mentioned in Question 10 or in the list above, we request discussion of these safety aspects as well.

*Pancreatic Disorders*

Regarding pancreatic disorders, we request that narratives for each case include the following information (if available; if not available, this should be noted): amylase levels, lipase levels, blood triglyceride measurements, blood lactate measurements, and results of any imaging tests.

*Malignancy*

We request that discussion of malignancy cases with teriflunomide include the following information:

- We request a table of all known cases of malignancy (or pre-malignant conditions) that have occurred in subjects who participated in studies of teriflunomide. The table should include the study, subject number, event Preferred Term, cumulative dose of teriflunomide received at the time of the event, latency from first dose of teriflunomide to malignancy diagnosis, subject's age at the time of diagnosis, subject's country of origin, subject's sex, duration of follow-up for that subject, and a link to the narrative.

- We request tables with the number of reported malignancies, number of subjects, incidence proportions, subject-years of exposure, and incidence rates for cases of malignancy in completed and ongoing trials for placebo-treated and teriflunomide-treated subjects. We also request presentation of these analyses stratified by duration of subject follow-up (less than 1 year, 1 to less than 2 years, 2 to less than 3 years, and more than 3 years). For each subject group, we request the median cumulative dose, the cumulative dose range, and the median duration of treatment exposure.

*Additional request:*

To assist in our evaluation of the teriflunomide study data, we request that you provide a list of the inclusion and exclusion criteria for each of the teriflunomide studies, including those introduced as part of protocol amendments.

***Sanofi-aventis Response:***

The Sponsor acknowledges the request and plans to provide the data requested.

Regarding adverse events with increased frequency with teriflunomide, common and potentially related TEAEs defined as TEAEs with HLTs >2% in either teriflunomide group and >1.5 times the incidence rate in either teriflunomide group compared to placebo presented by SOC, HLT and PT with decreasing frequency of HLT (and PT within HLT) in the teriflunomide 14 mg group will be provided for pool 1.

**Meeting discussion:**

**You should provide adverse events that are numerically larger in percentage in the drug group compared to the placebo group.**

**Assessment of drug abuse and dependence liabilities**

***Question 11:*** *A drug abuse liability assessment (DALA) of teriflunomide has been performed by the Sponsor based on currently available nonclinical and clinical data, and suggests that acute or chronic use of teriflunomide (7 or 14 mg once daily in subjects) does not show a signal of potential for abuse and dependency. Based on these data, the Sponsor does not plan to conduct any additional clinical or nonclinical studies for abuse liability assessment. Does the Agency agree with the Sponsor's conclusion? If yes, does the Agency agree with Sponsor's proposal not to include the DALA integrated document in the NDA?*

***FDA preliminary response:***

We do not recommend that additional preclinical or clinical abuse related studies be conducted. Assessment of the abuse potential of teriflunomide is a review issue and will be evaluated when the NDA is filed. Thus, the NDA should include all primary data described in the "Drug Abuse Liability Assessment" document.

***Sanofi-aventis Response:***

*The sponsor appreciates the Agency's comments, and agrees to include all primary data described in the "Drug Abuse Liability Assessment" document in the NDA.*

**Meeting discussion:**

**You note you will update the DALA document as a standard document in section 5.3.5.3. Your proposal is acceptable. We request you update all clinical data with ongoing studies.**

**Patient narratives, Case report forms, and Analysis datasets**

***Question 12:*** *Does the Agency agree with the Sponsor's proposal for inclusion of narratives, CRFs and datasets, including the content and format?*

***FDA Preliminary Response***

It is unclear why the criteria for submitting narratives should be different for Study 2001. We request that you use the following criteria for submitting narratives for all studies, including Study 2001:

- Death
- SAE
- All treatment discontinuations (including SAE, lost to follow-up, other, physician decision, patient decision)[3]
- ALT or AST > 3x ULN
- ALT or AST > 3x ULN and total bilirubin > 2x ULN
- Any treatment-emergent hepatic disorder
- Absolute Neutrophil Count < 1 GIGA/L
- Pancytopenia
- Interstitial lung disease

[3] Please define terms related to discontinuations, such as "premature termination," "treatment discontinuation," or "study discontinuation" if they are used in the context of your NDA.

- Peripheral neuropathy
- Malignancy
- Pancreatic disorder
- Hypersensitivity/anaphylactic reaction
- Seizures
- AEs in the HLGT Embolism and Thrombosis
- Cardiac arrhythmias
- Increase in serum creatinine > 2x baseline measurement
- Pregnancy: please include discussion of the outcome of the pregnancy, including reasons for termination if this occurred.

For narratives, please use a common template that is easy to review. Narrative summaries should provide a common synthesis of all available clinical data and an informed discussion of the case. Narrative summaries should allow a better understanding of what the patient experienced. The following items should be included:

- Patient age and gender
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event

- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by the available clinical data
- For events without a definitive diagnosis, a list of differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

If more than one event is contained in a single narrative, then there should be a line listing at minimum for each event. It is preferable, however, to have separate narratives, especially if events in an individual are separated by 6 months or more.

*Adverse Event Datasets*

For each of the phase 1 and phase 2-3 study pools, we request that the submitted datasets contain verbatim terms and MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path, as well as all alternate MedDRA coding paths.

Each SAS transport file should have a unique patient identifier.

***Sanofi-aventis Response***:

Regarding the additional narrative criteria, the sponsor agrees to provide the additional narratives, but would like to obtain specific clarification on particular events for inclusion.

- All treatment discontinuations (including AE, lost to follow-up, other, physician decision, patient decision). The Sponsor would like to understand the level of information needed for discontinuations. For any patients who, in the investigator's opinion, discontinued for reasons other than adverse events, the sponsor proposes to include a listing of AEs for these patients along with the timing and reason for discontinuation as opposed to providing full patient narratives.

- Any treatment-emergent hepatic disorder. The Sponsor considers that relevant cases have been captured under other categories such as SAEs, ALT > 3ULN, etc. so does not propose to produce additional narratives.

- Interstitial lung disease. The Sponsor proposes to provide narratives for AEs, identified by interstitial lung disease narrow standardized MedDRA query search.

- Peripheral neuropathy. The Sponsor proposes to provide narratives for confirmed cases of peripheral neuropathy (from CRF Page: confirmed by other studies or overall assessment, or confirmed by electrophysiological nerve conduction studies)

- Pancreatic disorder. The Sponsor proposes to provide narratives for Abnormal Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) findings for pancreas.

- Hypersensitivity/anaphylactic reaction. The Sponsor proposes to provide narratives for severe cases.

- Convulsions. The Sponsor proposes to provide for serious events.

- Cardiac arrhythmias – The Sponsor proposes to provide for cardiac arrhythmia (SMQ narrow)

Does the Agency agree with these criteria?

Narratives will include the information requested by the Agency with some clarifications provided below. An example has been provided in the Briefing Package. The Sponsor does not routinely include a discussion of differential diagnosis.

Adverse Event Datasets - The Sponsor did not plan to provide individual Phase 1 datasets in the original NDA as outlined in the eData submission planning template as in Appendix 11.11. Is this acceptable to the Agency?

**Meeting discussion:**

**You intend to provide summary tables with specific reasons for withdrawal as documented in the CRF. You intend to list adverse events occurring four weeks before and after withdrawal. We do not agree with your proposal. We request you list all adverse events, as well as all abnormal laboratory results. Also, patients who withdraw consent should be listed as such and not classified as "other". You should make every effort to fully describe reasons for a subject's discontinuation from a study. We note you do not intend to send the CRF for patients who withdraw for reasons other than adverse events. You should submit CRFs for all discontinuations. If there is a question of whether an item should be submitted to the NDA, it generally is better to err on the side of submitting the item.**

**Regarding the request for narratives for any treatment-emergent hepatic disorder, we request that you use the Drug-Related Hepatic Disorders SMQ, in addition to other categories, including ALT or AST >3x ULN. We agree with your interstitial lung disease proposal.**

**We committed to providing comments regarding peripheral neuropathy in the meeting minutes, which are as follows:**

> **We request that you provide narratives for cases of peripheral neuropathy using the Peripheral neuropathy SMQ. We realize that this search may capture some subjects with MS symptoms, but we think an assessment of all symptomatic subjects is important, including subjects whose symptoms may not have been recognized as peripheral neuropathy by investigators. We also**

**request the following information in your discussion of peripheral neuropathy.**

**1. We request a summary of peripheral neuropathy testing as described in each study protocol. Include when each testing protocol was instituted. If a testing protocol was instituted after the start of the trial (and therefore some subjects were not subject to the testing protocol), you should specify that this was the case.**

**2a. We request tables that summarize the frequency of all terms and of each term from the Peripheral neuropathy SMQ by treatment arm for each study.**

**2b. We request a dataset with a line for each subject with at least one adverse event categorized within the Peripheral Neuropathy SMQ. We request that the dataset include the following information:**

1. Unique Subject ID
2. Days from first dose to AE onset
3. MedDRA Primary Preferred Term
4. Adverse Event Reported Term[4]
5. Serious Adverse Event
6. Study number
7. Subject number
8. Randomized treatment group
9. Days from most recent study dose prior to AE onset to date of AE onset
10. Whether this subject had peripheral neuropathy confirmed by electrophysiological nerve conduction studies, biopsy, other studies, or overall assessment (Yes/No)
11. If item 10 above was coded as yes, list the basis for confirmation of peripheral neuropathy in this subject

[4] For subjects with more than one qualifying Preferred Term, it would be acceptable to have 2 additional character variable listing all other Preferred terms and verbatim terms.

**Your definition of pancreatic disorder is too narrow. In addition to the criteria that you proposed, we request narratives for all adverse events with a three-fold or greater pancreatic enzyme (amylase or lipase) elevation.**

**We request all cases of anaphylaxis. We committed to providing additional comments regarding hypersensitivity in the meeting minutes, which are as follows:**

> **In addition to narratives for all cases of anaphylaxis (using the MedDRA Anaphylactic reaction SMQ), we also request narratives for all adverse events using the Angioedema SMQ and the Severe Cutaneous Reactions SMQ.**

**We request narratives for all convulsion adverse events (using the Convulsions SMQ).**

**We agree with your proposal regarding cardiac arrhythmias.**

**We agree you do not need to submit phase 1 datasets.**

**120-Day Safety Update Report**

***Question 13:*** *Does the Agency agree with the proposed content and format of the 120-Day Safety Update Report?*

***FDA Preliminary Response***

The format that you have described is acceptable.

***Sanofi-aventis response:***

*The sponsor appreciates the Agency response and acknowledges their agreement.*

**Meeting discussion: None**

**SAS Analysis Programs**

***Question 14:*** *Does the Agency agree with the Sponsor's proposal to submit the SAS programs for the following key efficacy analyses: EFC6049/TEMSO primary analysis of primary (ARR) and key secondary (12 week sustained disability progression) endpoints; EFC10531/TOWER primary analysis of primary endpoint (ARR)?*

***FDA Preliminary Response***

Yes. In addition, please confirm that SAS programs will be available for other efficacy analyses as well, such as the secondary endpoints in the EFC 6049/TEMSO trial and the endpoints in the HMR1726/2001 study.

***Sanofi-aventis Response:***

The sponsor appreciates the Agency's comments, and proposes to submit the SAS programs for the following key efficacy analyses: EFC6049/TEMSO primary analysis of primary (ARR) and key secondary (12 week sustained disability progression) endpoints; EFC10531/TOWER primary analysis of primary endpoint (ARR) at the time of NDA submission and submit the SAS programs for secondary endpoints in the EFC6049/TEMSO and the endpoints in the HMR1726/ 2001 during the review period. Does the agency agree with the proposal?

**Meeting discussion:**

**Your proposal is acceptable. We also request that you submit the FC6049/TEMSO primary analysis adverse event datasets.**

**Clinical Pharmacology**

***Question 15:*** *The Sponsor plans to provide the Key Result Summaries (including PK and safety data) for the 3 below-mentioned clinical pharmacology studies at the time of the NDA submission. Does the agency agree?*

- *INT11720: effect of teriflunomide on the PK of metoprolol (substrate of CYP2D6), caffeine (substrate of CYP1A2) and omeprazole (substrate of CYP2C19)*
- *INT11697: effect of teriflunomide on the PK of repaglinide (substrate of CYP2C8)*

- *INT11932: effect of teriflunomide on the PK of bupropion (substrate of CYP2B6)*

***FDA Preliminary Response***

Yes.

***Sanofi-aventis response:***

*The sponsor appreciates the Agency response and acknowledges their agreement.*

**Meeting discussion: None**

## NON-CLINICAL

***Question 16:*** *Does the Agency agree that the totality of the nonclinical data to be presented in the NDA is sufficient to support the application for the proposed indication?*

***FDA Preliminary Response***

On face, the nonclinical development program appears sufficient to support an NDA; however, the adequacy of these data will be a matter of review.

***Sanofi-aventis Response:***

*The sponsor appreciates the Agency's input.*

**Meeting discussion: None**

## REGULATORY

### Overall Content of the NDA

***Question 17:*** *Does the Agency agree that the totality of the current data to be presented in the initial NDA and the proposed Amendment 1 (interim analysis of the EFC10531/TOWER) will support a thorough review of the application for the proposed indication?*

***FDA Preliminary Response***

In the context of our answers to your various questions above and below, yes. Also, see answer to question 1.

**Sanofi-aventis Response:**

The sponsor appreciates the Agency's input.

**Meeting discussion: None**

***Question 18:*** *The Sponsor proposes to submit the final results from Study EFC10531/TOWER and Study EFC10891/TENERE (Phase 3, active-comparator, non-IND study) upon completion as an efficacy supplement to the original NDA; does the Agency find this plan acceptable?*

***FDA Preliminary Response***

Yes.

**Sanofi-aventis Response:**

The sponsor appreciates the Agency response and acknowledges their agreement.

**Meeting discussion: None**

**Overall Table of Contents**

***Question 19:*** *Does the Agency agree with the proposed overall Table of Contents for the e-CTD?*

***FDA Preliminary Response***

Yes.

***Sanofi-aventis Response:***

*The sponsor appreciates the Agency response and acknowledges their agreement.*

**Meeting discussion: None**

**Pediatric Program**

***Question 20:*** *The Sponsor proposes to conduct a pediatric clinical study in children 10-17 years of age with relapsing MS (as monotherapy) and seeks full waiver for children ages birth (0) to 9 years. Does the Agency agree?*

***FDA Preliminary Response***

A "full waiver" is a request to waive the requirement under PREA to submit a pediatric assessment in the entire pediatric population (birth to 16 years). In contrast, a "partial waiver" is a request to waive submission of a pediatric assessment in a specific pediatric age group.
A partial waiver in pediatric patients less than 10 years of age may be reasonable; however, a final decision regarding a partial waiver for this age group is dependent on review of the NDA and review of the request by the Pediatric Review Committee. Given the currently available information, a partial waiver in pediatric patients less than 10 years due to "too few patients with the disease to study" is likely to be acceptable. Regarding those ages 10-17, a deferral is likely, but is also dependent on findings upon review (see response to question 21). Please note that data to support your partial waiver and deferral requests must be provided in your NDA submission. In addition, all deferral requests must include a pediatric plan. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) sufficient to demonstrate dose, safety, and efficacy. The pediatric plan must contain a timeline for the completion of pediatric studies, i.e. the dates, specifically day, month and year, of (1) protocol submission, (2) study completion and (3) submission of study reports. In addition, you must submit evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. See Draft Guidance for Industry, How to Comply with Pediatric Research Equity Act: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf.

***Sanofi-aventis Response:***

***The sponsor appreciates the Agency response and acknowledges their comments.***

**Meeting discussion: None**

***Question 21:*** *In anticipation of the Agency issuing a Written Request in response to Sponsor's recently submitted Proposed Pediatric Study Request and based on the positive results in adults in Study EFC6049 / TEMSO, the Sponsor plans to initiate the proposed pediatric clinical trial prior to the approval of the relapsing MS monotherapy indication in adults. Does the Agency agree?*

***FDA Preliminary Response***

Pediatric studies should not be initiated until the nonclinical data are adequate to support clinical studies in the pediatric population, FDA has determined that the adult trials provide adequate safety and efficacy data to support initiation of clinical studies in the pediatric population, and FDA has agreed with your proposed pediatric clinical development program. We encourage you to initiate the nonclinical studies required to support initiation of the pediatric clinical studies. We have identified a number of deficiencies in the development program outlined in your proposed pediatric study request (PPSR) and additional input on your PPSR will be provided in a future communication.

***Sanofi-aventis Response:***
The sponsor intends to meet the requirements leading to the issuance of a Written Request from the Agency. For planning purposes, the sponsor would like to confirm with the Agency that the pediatric efficacy and safety study (EFC11759) can not be initiated until the approval for RMS monotherapy indication in adults.

(b) (4)

**Meeting discussion:**

(b) (4)

**We will provide our comments regarding your PPSR as soon as is feasible. It is possible that we would issue a WR prior to an approval of your product for RMS monotherapy, but sometime after the NDA is submitted. This will be determined during our review.**

**Juvenile animal toxicology studies are not needed to support clinical trials in patients ≥ 12 years of age.**

**Proposed Labeling**

***Question 22:*** *Does the Agency agree that demonstration of the efficacy and safety of the drug with the available data to be provid**ed in the NDA will be sufficient to support the proposed indication for the 14 mg dose: "TM" is indicated for the treatment of patients with relapsing forms of multiple sclerosis*** (b) (4) *and the proposed dosage and administration recommendation: "**The recommended dose of "TM" is 14 mg orally once daily. "TM" can be taken with or without food.**"?*

***FDA Preliminary Response***
This question is premature. Labeling content (including indication and dosage) is a review issue.

***Sanofi-aventis Response:***

*The sponsor acknowledges the Agency response.*

**Meeting discussion: None**

## Additional Discussion:

**You should submit analyses in addition to descriptive data for your presentation of the efficacy from TOWER.**

**You may submit sample data in advance or call us for assistance with regard to the relapse dataset to make sure all necessary information is included.**

## Additional Requests:

**1. We request that you submit a summary of the known adverse effects of leflunomide, including references to the published literature. Please provide copies of the references.**

**2. We request analyses of the number of subjects screened, the number of subjects who failed screening, and the reasons for screening failures for the TEMSO study.**

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/s/

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RUSSELL G KATZ
04/15/2011

**From:** Wheelous, Teresa A
**Sent:** Saturday, May 28, 2005 3:28 PM
**To:** eric.phillips@us.sanofi.com
**Subject:** IND 67,476 Teriflunomide End of Phase 2 - Preclinical meeting minutes

Eric,

The following are the preclinical portions of the End of Phase 2 meeting minutes:

IND 67,476
Page 1

# MEMORANDUM OF MEETING MINUTES
# (addendum covering the discussions for Questions 1 & 2)

MEETING DATE: November 12, 2004
TIME: 10 – 11:30 AM
LOCATION: WOC 2, conference room E
APPLICATION: 67,476 Teriflunomide
TYPE OF MEETING: End of Phase 2
MEETING CHAIR: Dr. Russell Katz

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

Dr. Russell Katz – Division Director, HFD-120
Dr. Eric Bastings – Group Leader
Dr. Susan McDermott – Medical Reviewer
Dr. Lois Freed – Supervisory Pharmacologist
Dr. Andrea Powell – Pharmacology / Toxicology Reviewer
Dr. Ramana Uppoor - Clinical Pharmacology & Biopharmaceutics Team Leader
Dr. Ta-Chen Wu – Clinical Pharmacology & Biopharmaceutics Reviewer
Dr. Kun Jin – Biometrics Team Leader
CDR Teresa Wheelous – Sr. Regulatory Management Officer

**AVENTIS ATTENDEES AND TITLES:**

Dr. Ross Rocklin – Global Clinical Director
Dr. Hester Visser – Global Project Team Leader
(b) (4)
Dr. Linda Scarzzini – Pharmacovigilance
Dr. Kai Jiang – Statistician
Dr. Bradford Jensen – Drug Metabolism and Pharmacokinetics
Dr. Bharti Shat – Drug Metabolism and Pharmacokinetics
Dr. Lynn Davenport – Toxicologist
Dr. Steve Caffe – Drug Regulatory Affairs
Dr. Eric Floyd – Drug Regulatory Affairs
Dr. Kevin Hibbert – Drug Regulatory Affairs
Ting Chen – Drug Regulatory Affairs
Dr. Debra Gayda – Drug Regulatory Affairs
Anita Burrell – Health Economist

**BACKGROUND:**

The September 14, 2004 meeting request was received on September 15, 2004 and granted on
September 29, 2004. The meeting package was received on October 12, 2004.

**MEETING OBJECTIVES:**

Discuss and review the proposed Phase 3 clinical development program for monotherapy treatment of patients with relapsing form of multiple sclerosis (b) (4)

**This addendum to the meeting minutes covers the discussion of the Sponsor's Questions 1 and 2 only. The meeting minutes for the discussion of Questions 3-11 and 14-16 have been sent to the Sponsor (issue date: April 29, 2005).**

**Preclinical Toxicology**

**Question 1:**

**Aventis considers that the current pre-clinical toxicological assessments (i.e., existing teriflunomide pre-clinical studies, together with the leflunomide chronic toxicity and reproductive toxicity studies) are sufficient to support the initiation of Study HMR1726D/3001 as a pivotal study. Does the Agency concur?**

The Division does not concur. The major points of discussion are listed below.

1. The major nonclinical issue is the bone marrow toxicity in dogs, demonstrated in oral toxicity studies of teriflunomide and leflunomide.

In the 3-month terifunomide study, all ten animals treated with 8 mg/kg/day were noted with marked to massive decreases in granulopoiesis within 16-24 days of treatment.

In the 6-month leflunomide study, none of ten animals treated with 8 mg/kg/day were noted with a decrease in granulopoiesis, even though nine of these animals were treated for at least 140 days.

The plasma concentrations of teriflunomide achieved in these studies were similar (at 8 mg/kg/day) and were clinically relevant.

The Division acknowledged the previous human experience with teriflunomide and leflunomide, but remains concerned because (1) the bone marrow toxicity is a serious toxicity with sudden onset, (2) the mechanism of this toxicity in dogs is not understood, (3) reversibility has not been demonstrated, and (4) the latency period for a similar toxicity in humans (if relevant) is unknown.

The Division noted that the Sponsor had not addressed this issue in the original IND package or in the end-of-phase 2 meeting package.

The Division asked the Sponsor if the bone marrow toxicity in dogs could be due to an impurity. The Sponsor replied that they would investigate this possibility.

The Sponsor stated that it was important to note that the dog is eight-fold more sensitive to the anti-proliferative effects of teriflunomide than human; however, the Division noted that this would not explain the fact that the bone marrow effects seen in dogs after

administration of teriflunomide and leflunomide were different.

The Division stated that the Sponsor should provide detailed *in vivo* metabolic profiles for leflunomide and teriflunomide in animals and humans.

The Division stated that the mechanism for this toxicity needs to be understood before further human experience is allowed. However, the Sponsor was told that they may submit an argument that provides adequate justification for proceeding with clinical development prior to completing the requested mechanistic and PK/ADME studies. It was the Sponsor's opinion that the clinical monitoring program is sufficiently intensive to detect early bone marrow toxicity in humans. They were told to submit their arguments to the IND.

2. The Sponsor stated that in the on-going 12-month oral teriflunomide toxicity study in dogs,
the high dose was originally set at 2 mg/kg/day, but was subsequently increased to 4 mg/kg/day due to lack of demonstrable toxicity. The Division noted that the adequacy of this
study will be a matter of review.

3. The high dose employed in the 3-month oral teriflunomide toxicity study in rats was not a
maximally tolerated dose.

There was some discussion about the fact that the interpretation of the toxicity studies in
rats conducted with leflunomide was complicated by the incidence of Tyzzer's disease.

The Sponsor stated that the high dose (9 mg/kg) tested in the recently completed 6-month oral teriflunomide toxicity study in rats is a maximum tolerated dose.

4. The Sponsor was told that the on-going *in vitro* mouse lymphoma tk assay on the impurity/degradant (b) (4) needs to include colony sizing.

5. The Sponsor was told that they should conduct an *in vitro* cytogenetic evaluation of chromosomal damage in mammalian cells or an *in vitro* mouse lymphoma tk assay with colony sizing for teriflunomide.

**Preclinical General / Safety Pharmacology**

**Question 2:**

**The ICH Guideline S7A (Safety Pharmacology Studies for Human Pharmaceuticals, November 2000) recommends that safety pharmacology be conducted in compliance with**
**GLP guidelines. At the time that the teriflunomide safety pharmacology studies were**
**conducted (1999), Aventis was not routinely performing safety pharmacology studies under**
**good laboratory practice (GLP) standards (see Table 1, Section 10.2.4). The studies were**
**conducted in Aventis facilities under the supervision of qualified scientists and with appropriate quality control procedures in place. In light of the fact that (1) there were**
**minimal adverse effects observed in these studies, and (2) substantial clinical data are**

**available for teriflunomide at this time, Aventis considers that the safety pharmacology**
**package for teriflunomide is sufficient. Does the Agency concur?**
The Division stated that the non-GLP safety pharmacology studies are acceptable because of the
extent of previous human experience.

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/s/
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Russell Katz
5/26/05 10:25:51 AM

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/s/

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Teresa Wheelous
5/28/05 03:33:25 PM

**From:** Wheelous, Teresa A
**Sent:** Monday, May 02, 2005 9:30 AM
**To:** 'eric.phillips@us.sanofi.com'
**Subject:** IND 67476 Teriflunomide End of Phase 2 Meeting Minutes

Eric,

The following are the End of Phase 2 meeting minutes for all of the disciplines except the preclinical discipline:

IND 67,476
Page 1

# MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 12, 2004
TIME: 10 – 11:30 AM
LOCATION: WOC 2, conference room E
APPLICATION: 67,476 Teriflunomide
TYPE OF MEETING: End of Phase 2
MEETING CHAIR: Dr. Russell Katz

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

Dr. Russell Katz – Division Director, HFD-120
Dr. Eric Bastings – Group Leader
Dr. Susan McDermott – Medical Reviewer
Dr. Lois Freed – Pharmacology / Toxicology Team Leader
Dr. Andrea Powell – Pharmacology / Toxicology Reviewer
Dr. Ramana Uppoor - Clinical Pharmacology & Biopharmaceutics Team Leader
Dr. Ta-Chen Wu – Clinical Pharmacology & Biopharmaceutics Reviewer
Dr. Kun Jin – Biometrics Team Leader
CDR Teresa Wheelous – Sr. Regulatory Management Officer

**AVENTIS ATTENDEES AND TITLES:**

Dr. Ross Rocklin – Global Clinical Director
Dr. Hester Visser – Global Project Team Leader
(b) (4)
Dr. Linda Scarzzini – Pharmacovigilance
Dr. Kai Jiang – Statistician
Dr. Bradford Jensen – Drug Metabolism and Pharmacokinetics
Dr. Bharti Shat – Drug Metabolism and Pharmacokinetics
Dr. Lynn Davenport – Toxicologist
Dr. Steve Caffe – Drug Regulatory Affairs
Dr. Eric Floyd – Drug Regulatory Affairs
Dr. Kevin Hibbert – Drug Regulatory Affairs
Ting Chen – Drug Regulatory Affairs
Dr. Debra Gayda – Drug Regulatory Affairs
Anita Burrell – Health Economist

IND 67,476
Page 2

**BACKGROUND:**

The September 14, 2004 meeting request was received on September 15, 2004 and

granted on
September 29. 2004. The September 20, 2004 meeting package was received on October 12, 2004

**MEETING OBJECTIVES:**

Discuss and review the proposed Phase 3 clinical development program for monotherapy treatment of patients with relapsing form of multiple Sclerosis (b) (4).

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**DISCUSSION POINTS:**

**Preclinical**

**Questions #1, #2, #12, & #13 will be provided separately.**

**Drug Metabolism & Pharmacokinetics**

**Question 3:**

**Aventis considers that the existing data on the dispositional profile and properties of teriflunomide, together with the proposed additional drug metabolism, non-clinical and clinical pharmacokinetic studies, are appropriate to support the Phase III monotherapy clinical development program. Does the Agency concur?**

Though not a prerequisite at this point before initiating the proposed Phase III study, we suggest that the Sponsor conduct the mass balance study in humans at the earliest possible time. The Sponsor should continue to characterize the metabolic pathways (and their contributions) of teriflunomide in humans. Together with the outcome from the population PK-PD analyses of teriflunomide for the Phase II study (HMR1726D/2001), results will be helpful for confirming the dose selection and for better designing the study.

**Question 4:**

**Does the Agency concur with the proposed drug-drug interaction (DDI) studies, and that no additional DDI studies will be needed if the results from the planned studies do not indicate additional risk?**

OCPB comment: Effects of teriflunomide on potential co-medications that are substrates of CYP1A2 or UDPGT should be explored in view of its induction potential on these two metabolic enzymes in fresh human hepatocytes. The Sponsor should clarify the "positive controls" used in these in vitro induction studies. Additional studies may be needed based on the results of the mass balance study and the complete identification of metabolic pathways.

**Question 5:**

**Does the Agency concur with the approach that no special population study will be needed if**

**the results from the planned in vitro, animal and human teriflunomide studies support the**
**lack of pharmacokinetic difference in special populations?**

OCPB comment: There is no sufficient evidence or data to support the lack of PK difference after oral teriflunomide in patients with hepatic impairment or chronic renal insufficiency.
We note that the leflunomide label cautions against use of the drug in severe hepatic impairment. We recommend that a PK study in hepatic impaired subjects be conducted. Also, based on the results of mass balance, renal impairment study may be necessary.



**Phase 3 Clinical Program**
**Question 6:**
**Given the serious and severely debilitating nature of MS, Aventis proposes that Study HMR1726D/3001, supported by Study HMR1726D/2001, is adequate to demonstrate sufficient clinical efficacy, safety, and tolerability of teriflunomide. Does the Agency concur?**

The Agency informed the sponsor that they will need two independent positive studies to support an application. Further, they noted that previous Phase II trial (2001) was not adequate to prove the clinical benefit of the drug such that the company would be able to forego a second pivotal trial. The sponsor noted that other MS drugs had been approved on the basis of one trial. The Agency told the sponsor that they discussed this with colleagues from what was previously CBER, because they had been responsible for approving the interferon drugs for MS. The Agency said that their colleagues had noted that the basis for the approval for most of these drugs was their ability to compare the new product to other drugs in the same class. Furthermore, they said that in some cases the drugs appeared to be essentially identical from a structural basis. The Agency also told the sponsor that this was not the case for teriflunomide, and so they would be required to meet the usual standard of two, positive, independent trials.

The sponsor asked if the Agency would accept the combination trials (drug-drug interaction studies with Copaxone and teriflunomide and with interferon-beta and teriflunomide) as supportive studies. The Agency said that they probably would, depending on the protocol, but would need to review the protocols first. The sponsor's statistician asked if it would be acceptable to show non-inferiority in the combination trials. The Agency said that this is

problematic and in general is not recommended as it is very difficult to prove noninferiority.

**Question 7:**

**Aventis proposes that annual relapse rates in Multiple Sclerosis patients with relapses is an appropriate primary endpoint for the pivotal Study HMR1726D/3001; and that the primary endpoint of Study HMR1726D/2001 (reduction in disease activity as measured by a reduction in the number of MRI lesions) is adequate to support registration. Does the Agency concur?**

The Agency told the sponsor that the planned primary endpoint, annualized relapse rate in Study 3001, was acceptable as a primary efficacy endpoint. The sponsor asked if there was a preferred way of counting relapses. The Agency noted that they usually look at group relapse rates, but this was not an absolute requirement. They would be willing to consider other methods (e.g. percentage relapse free) for counting relapses.

**Question 8:**

**Clinical safety exposure with teriflunomide was gained from short-term Phase I studies (HMR1726C/1001, HMR1726C/1002 and HWA 486/1024) in healthy volunteers and a longterm Phase II study (HMR1726D/2001) in subjects with Multiple Sclerosis. Aventis considers the current safety package sufficient for supporting the initiation of Study HMR1726D/3001.**

**Does the Agency concur?**



No, the Agency discussed in detail their safety concerns with teriflunomide. They concluded that before any other protocols are approved, the company must address the issue of bone marrow toxicity seen in the 3-month dog studies with teriflunomide. Further, the Agency told the sponsor that their proposed phase III trial (3001) and two combination phase II trials (teriflunomide and interferon-beta, and teriflunomide and glatiramer acetate) are on clinical hold. However, in order to avoid being placed on clinical hold, the sponsor announced that it will officially withdraw these three protocols from the IND. The Agency verbally accepted these withdrawals, noting that the reviewers had not yet received the two combination study protocols.

The sponsor asked if they could perform an interim analysis at one year so that they could potentially submit their NDA at this point if the study was positive, as in the case of

natalizumab. The Agency told the sponsor that they would not rule this out as a possibility
up front, but it was a very difficult case to prove and that replication of findings would be critical.

The Agency also told the sponsor that they will send specific clinical comments about concerns about the protocols. However, they also told the sponsor that they should require
double contraception in their phase II and phase III trials, as well as HIV testing for all subjects.

The Agency's requirement for HIV testing was discussed at length. The sponsor opposes it
because they deem it unnecessary and overly burdensome to the investigators and patients.
Specifically, they state that MS patients do not want to be tested for HIV, and that this requirement would hinder enrollment. The Agency asked if there were any studies to support this, but the sponsor could not provide such citations. The sponsor also said that there were no documented cases of HIV in a patient with MS, and that the two diseases appear to be mutually exclusive. The Agency asked what this was based on, and the sponsor
noted that there were no case reports in the literature of the two diseases occurring simultaneously. The Agency noted that the lack of case reports did not prove that these diseases could not co-exist in the same person, and asked what was known about concurrence of the diseases in other countries, particularly in areas of high HIV prevalence.
The sponsor noted again that there were no case reports to support that the two diseases may
occur simultaneously in the same person. They went on to indicate that in vitro studies would suggest that the drug has a protective effect against HIV infection. The Agency stated that that the company should put together an argument for not performing HIV testing
in patients, and that this would be reviewed.

**Question 9:**

**The proposed indication for teriflunomide is: for the treatment of relapsing forms of Multiple**
**Sclerosis** (b) (4) **. Aventis proposes that the secondary endpoint of accumulation of disability, as measured by Expanded Disability Status Scale (Appendix 1)**
**(treated with the same statistical rigor as the primary endpoint)** (b) (4) **Does the Agency concur?**

The Agency told the sponsor that the general policy for secondary outcomes for labeling
contained the following basic requirements:

The secondary outcomes must be prospectively designated.

They must be replicated.

The statistical analysis plan must include an a priori method for dealing with multiplicity if multiple outcomes are to be analyzed.

The Agency must agree with the sponsor up front that the secondary outcomes are appropriate. Specifically, they must assess a domain other than the primary outcome. The Agency went on to say that in this case, EDSS would likely be seen as an acceptable secondary outcome if relapse rate is the primary outcome.

The sponsor asked if MRI findings could be used as a secondary outcome, and the Agency said that it is possible depending on the proposal. The sponsor asked if there was a limit to the number of secondary outcomes, and the Agency said that there was no limit per se, but typically sponsors will have one or two secondary outcomes because of repetition with the primary outcome.

The Agency asked the sponsor about their statistical analysis plan for dealing with primary and secondary outcomes in light of the multiple dosing. Specifically, they asked the order of statistical testing in relationship to the dosing. They gave the following example: if a patient wins on the primary outcome at the high dose, the Agency asked if the sponsor planned to test secondary outcomes at the high dose next, or if they would proceed to testing the primary outcome at the lower dose next. The sponsor was told that they should include these details in their statistical analysis plan, and were also asked to provide a justification for using the Poisson analysis. Further, the Agency's statistician recommended that the sponsor also clearly state how drop-outs will be handled statistically in their proposed trials.

The Agency also told the sponsor that in the case of an MS trial when the primary outcome is relapse rate, the Agency does not typically accept language for labeling that suggests the drug shows an effect on the underlying disease itself.

**Question 10:**

**In April 2001, an international panel in association with the National Multiple Sclerosis Society of America recommended revised diagnostic criteria for MS. These new criteria have become known as the McDonald's criteria (Appendix 2). These criteria make use of advances in magnetic resonance imaging (MRI) techniques and are intended to replace the**

**Poser**
**criteria and the older Schumacher criteria. Aventis has concluded that the McDonald criteria**
**are more applicable to the current and future practice of medicine and proposes to utilize**
**these criteria in the patient selection of Study HMR1726D/3001. Does the Agency concur with**
**this approach?**

The Agency said that the McDonald criteria are acceptable for Study HMR1726D/3001.

**Clinical Fatigue Impact Scale**
**Question 11:**
**Aventis will implement the Fatigue Impact Scale (FIS) (Appendix 3) in Study HMR1726D/3001 to demonstrate that teriflunomide significantly reduces fatigue versus**
**placebo. Does the Agency concur that the FIS is a validated and appropriate instrument for**
**the evaluation of fatigue in patients with relapsing forms of MS?**



The Agency told the sponsor that they may be able to use the FIS as a secondary outcome in
the trial.

**Adjunctive Therapy – Preclinical and Clinical Safety Studies**
**Question 14:**
**The Aventis position is that combination toxicity studies in animals would not yield any**
**meaningful data over that which has been previously reported for each compound alone**
**because:**

**There is sufficient existing pre-clinical and clinical data; on the individual compounds**

**The toxicity seen in animals with the interferons, as human-specific products is minimal, due to the formation of neutralizing antibodies;**

**The toxicity of glatiramer acetate in animals is limited as a result of its antigenicity.**

**Therefore, Aventis does not propose to conduct combination toxicity studies in animals in**
**support of an adjunct treatment clinical development program. Does the Agency concur?**

The Agency told the sponsor that they could not concur with them at this time because of the
3-month dog study showing significant bone marrow toxicity. The Agency also told the sponsor that there is a statement in the CIB that states that the toxicities of teriflunomide and
leflunomide are qualitatively and quantitatively the same. The Agency said that this

statement was misleading and would need to be removed. Furthermore, additional comments on the CIB would be forthcoming.

**Question 15:**

**Aventis considers that the proposed Phase II safety studies (HMR1726D/2003 and HMR1726D/2004) are adequately designed for the preliminary evaluation of safety and tolerability of the adjunctive use of teriflunomide with either ®-interferon or glatiramer acetate. Does the Agency concur?**

The Agency indicated that they had not yet received the official protocols, and the sponsor said that they were sent on October 24, 2004. The Agency noted that they would have to review the protocols before determining the adequacy of the trial designs. However, as mentioned above (see question 8 response), the sponsor indicated that they are withdrawing these two protocols, as well as the phase III protocol to avoid being put on clinical hold.

**In addition, Aventis proposes that no formal drug-drug interaction study in healthy volunteers between teriflunomide and ®-interferon or glatiramer acetate is warranted. Does the Agency concur?**

OCPB comment: In addition to evaluating the effects on concomitant teriflunomide, the Sponsor should consider characterizing both INF-â and GA as appropriate to address the concerns for the potential PK and/or PD interactions in proposed adjunct therapies. At the meeting, the Sponsor stated their plans to conduct Phase I studies to evaluate these drug interactions.



**Pediatric Waiver**

**Question 16:**

**Aventis does not plan to pursue a pediatric indication for MS. Aventis will be requesting an official waiver for pediatric development program for teriflunomide. Does the Agency concur?**

The Agency and sponsor agreed that this could be addressed at a later date.

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/s/
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Russell Katz
4/29/05 04:36:24 PM

*CDR Teresa Wheelous, R. Ph.*
*Senior Regulatory Management Officer*
*Office of Drug Evaluation I*
*Division of Neuropharmacological Drug Products*
*HFD-120*
*1451 Rockville Pike*
*Rockville, MD 20852*
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/s/

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Teresa Wheelous
5/2/05 09:59:31 AM

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION[1]

| | | |
|---|---|---|
| NDA # 202992<br>BLA # | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type: |
| Proprietary Name: Aubagio<br>Established/Proper Name: Teriflunomide<br>Dosage Form: Tablets | | Applicant: Sanofi-aventis<br>Agent for Applicant (if applicable): |
| RPM: LCDR Hamet Touré | | Division: D. of Neurology Products |

**NDAs and NDA Efficacy Supplements:**

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

**505(b)(2) Original NDAs and 505(b)(2) NDA supplements:**

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

**For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.**

**On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

☐ No changes ☐ Updated Date of check:

**If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.**

| ❖ Actions | |
|---|---|
| • Proposed action<br>• User Fee Goal Date is September 12, 2012 | ☒ AP ☐ TA ☐ CR |
| • Previous actions *(specify type and date for each action taken)* | ☒ None |

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

| | |
|---|---|
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | ☐ Received |
| ❖ Application Characteristics [3] | |

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 1S

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

| | |
|---|---|
| ❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter) | ☐ Yes, dates |
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* | ☐ Yes ☐ No |
| ❖ Public communications *(approvals only)* | |
| • Office of Executive Programs (OEP) liaison has been notified of action | ☒ Yes ☐ No |
| • Press Office notified of action (by OEP) | ☒ Yes ☐ No |
| • Indicate what types (if any) of information dissemination are anticipated | ☐ None<br>☐ HHS Press Release<br>☐ FDA Talk Paper<br>☐ CDER Q&As<br>☒ Other FDA Press Release |

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

| Exclusivity | |
|---|---|
| • Is approval of this application blocked by any type of exclusivity? | ☒ No ☐ Yes |
| • NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.* | ☒ No ☐ Yes<br>If, yes, NDA/BLA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)* | ☒ No ☐ Yes<br>If yes, NDA # and date 10-year limitation expires: |
| ❖ Patent Information (NDAs only) | |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | ☒ Verified<br>☐ Not applicable because drug is an old antibiotic. |
| • Patent Certification [505(b)(2) applications]:<br>Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(*i*)(A)<br>☐ Verified<br><br>21 CFR 314.50(i)(1)<br>☐ (ii) ☐ (iii) |
| • [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | ☐ No paragraph III certification<br>Date patent will expire |
| • [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).* | ☐ N/A (no paragraph IV certification)<br>☐ Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes,**" skip to question (4) below. If "**No,**" continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No,**" continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No,**" the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No,**" continue with question (5).*

| | |
|---|---|
| (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).<br><br>*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*<br><br>*If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.* | ☐ Yes ☐ No |

## CONTENTS OF ACTION PACKAGE

| | |
|---|---|
| ❖ Copy of this Action Package Checklist[4] | 09/25/12 |
| **Officer/Employee List** | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* | ☒ Included |
| Documentation of consent/non-consent by officers/employees | ☒ Included |
| **Action Letters** | |
| ❖ Copies of all action letters *(including approval letter with final labeling)* | Action(s) and date(s) September 12, 2012 |
| **Labeling** | |
| ❖ Package Insert *(write submission/communication date at upper right of first page of PI)* | |
| • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | September 12, 2012 |
| • Original applicant-proposed labeling | August 12, 2011 |
| • Example of class labeling, if applicable | |

[4] Fill in blanks with dates of reviews, letters, etc.

| | |
|---|---|
| Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* | ☒ Medication Guide<br>☐ Patient Package Insert<br>☐ Instructions for Use<br>☐ Device Labeling<br>☐ None |
| • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | September 12, 2012 |
| • Original applicant-proposed labeling | August 12, 2011 |
| • Example of class labeling, if applicable | |
| ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)* | |
| • Most-recent draft labeling | September 6, 2012 |
| ❖ Proprietary Name<br>• Acceptability/non-acceptability letter(s) *(indicate date(s))*<br>• Review(s) *(indicate date(s)*<br>• *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.* | Name granted 09/07/12<br>Name review 09/07/12<br>Acknowledge name withdrawal 06/18/12<br>Acknowledge name withdrawal 05/01/12<br>Name granted 02/29/12<br>Name review 02/29/12<br>Name denied 11/17/11<br>Name review 11/09/11 |
| ❖ Labeling reviews *(indicate dates of reviews and meetings)* | ☐ RPM<br>☒ DMEPA 06/05/12<br>☒ DMPP/PLT (DRISK) 08/29/12<br>☒ ODPD (DDMAC) 09/04/12, 08/31/12<br>☒ SEALD 08/30/12<br>☐ CSS<br>☒ Other reviews DMEPA proprietary name review 11/9/11, 2/23/12, 9/7/12<br>Pediatric 9/5/12<br>Maternal Health 8/8/12<br>Patient labeling team 8/29/12 |
| **Administrative / Regulatory Documents** | |
| ❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*<br>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte<br>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)* | 04/25/12<br>☐ Not a (b)(2)<br>☐ Not a (b)(2) |
| ❖ NDAs only: Exclusivity Summary *(signed by Division Director)* | ☒ Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| • Applicant is on the AIP | ☐ Yes ☒ No |

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

| | |
|---|---|
| • This application is on the AIP<br>○ If yes, Center Director's Exception for Review memo *(indicate date)*<br>○ If yes, OC clearance for approval *(indicate date of clearance communication)* | ☐ Yes ☐ No<br>☐ Not an AP action |
| ❖ Pediatrics *(approvals only)*<br>• Date reviewed by PeRC 5/2/2012<br>If PeRC review not necessary, explain: _____<br>• Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)* | ☒ Included |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)* | ☒ Verified, statement is acceptable |
| ❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)* | Advice/Information requests: 8/17/11, 8/26/11, 9/2/11, 9/8/11, 9/16/11, 9/21/11, 9/22/11, 9/23/11, 10/3/11, 10/6/11 (2), 10/12/11, 10/21/11, 10/26/11, 11/1/11, 11/7/11, (2), 11/14/11 (2), 11/22/11, 11/28/11, 12/6/11, 12/15/11 (2), 12/19/11, 12/20/11, 12/22/11 (2), 1/3/12, 1/7/12 (2), 1/9/12, 1/12/12, 2/1/12, 2/3/12, 2/10/12, 2/16/12, 2/27/12, 2/29/12, 3/1/12, 3/2/12 (2), 3/5/12, 3/9/12, 3/16/12, 3/19/12, 3/27/12, 3/28/12 (3), 3/30/12, 4/2/12, 4/4/12, 4/6/12, 4/9/12 (2), 4/18/12, 4/20/12 (2), 4/25/12 (2), 4/26/12, 5/1/12 (2), 5/29/ 12, 7/2/12, 7/3/12, 7/25/12, 8/2/12, 8/3/12, 8/24/12, 8/29/12, 8/31/12, 9/5/12, 9/6/12 (2), 9/10/12 (2), 9/11/12 (2), 9/12/12 (2)<br><br>Acknowledgement letter: 09/02/11<br>Filing communication: 10/25/11<br>Acknowledge major amendment: 4/18/12<br><br>Name granted 09/07/12<br>Acknowledge name withdrawal 06/18/12<br>Acknowledge name withdrawal 05/01/12<br>Name granted 02/29/12<br>Name denied 11/17/11 |
| ❖ Internal memoranda, telecons, etc. | |
| ❖ Minutes of Meetings | |
| • Regulatory Briefing *(indicate date of mtg)* | ☐ No mtg |
| • If not the first review cycle, any end-of-review meeting *(indicate date of mtg)* | ☐ N/A or no mtg |
| • Pre-NDA/BLA meeting *(indicate date of mtg)* | ☐ No mtg 3/28/2011 |
| • EOP2 meeting *(indicate date of mtg)* | ☐ No mtg 11/12/2004 |

| | |
|---|---|
| • Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)* | |
| Advisory Committee Meeting(s) | ☒ No AC meeting |
| • Date(s) of Meeting(s) | |
| • 48-hour alert or minutes, if available *(do not include transcript)* | |
| **Decisional and Summary Memos** | |
| ❖ Office Director Decisional Memo *(indicate date for each review)* | ☐ None 9/12/12 |
| Division Director Summary Review *(indicate date for each review)* | ☐ None 9/5/12 |
| Cross-Discipline Team Leader Review *(indicate date for each review)* | ☐ None 9/11/12 |
| PMR/PMC Development Templates *(indicate total number)* | ☐ None 9/12/12 |
| **Clinical Information**[6] | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) *(indicate date for each review)* | 9/11/12, 7/23/12 |
| • Clinical review(s) *(indicate date for each review)* | 10/18/11, 7/12/12<br>QT review 10/27/11 |
| • Social scientist review(s) (if OTC drug) *(indicate date for each review)* | ☐ None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)* | Clinical review dated 9/11/12 |
| Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)* | ☒ None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | ☐ Not applicable 3/28/12 |
| ❖ Risk Management<br>• REMS Documents and Supporting Statement *(indicate date(s) of submission(s))*<br>• REMS Memo(s) and letter(s) *(indicate date(s))*<br>• Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* | No REMS<br>8/28/12<br>☐ None<br>12/14/11 |
| ❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)* | ☐ None requested 3/2/12, 7/9/12, 8/8/12, 8/10/12 |
| **Clinical Microbiology** ☒ None | |
| ❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | ☐ None |
| Clinical Microbiology Review(s) *(indicate date for each review)* | ☐ None |
| **Biostatistics** ☐ None | |
| ❖ Statistical Division Director Review(s) *(indicate date for each review)* | ☐ None Combined review |
| Statistical Team Leader Review(s) *(indicate date for each review)* | ☐ None Combined review |
| Statistical Review(s) *(indicate date for each review)* | ☐ None 9/28/11, 5/9/12 |

[6] Filing reviews should be filed with the discipline reviews.

| **Clinical Pharmacology** ☐ None | |
|---|---|
| ✓ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | ☐ None Combined review |
| Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | ☐ None Combined review |
| Clinical Pharmacology review(s) *(indicate date for each review)* | ☐ None 9/28/11, 7/3/12 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)* | ☒ None |
| **Nonclinical** ☐ None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) *(indicate date for each review)* | ☐ None 9/11/12 |
| • Supervisory Review(s) *(indicate date for each review)* | ☐ None 7/20/12, 9/12/12 |
| • Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | ☐ None 7/13/12 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)* | ☒ None |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | ☐ No carc 7/13/12 |
| ❖ ECAC/CAC report/memo of meeting | ☐ None 2/23/12<br>Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)* | ☒ None requested |
| **Product Quality** ☐ None | |
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) *(indicate date for each review)* | ☐ None 6/5/12 |
| • Branch Chief/Team Leader Review(s) *(indicate date for each review)* | ☐ None Combined review |
| • Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)* | ☐ None 8/24/11, 4/11/12, 4/13/12 |
| ❖ Microbiology Reviews<br>☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)*<br>☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)* | ☒ Not needed |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)* | ☒ None |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)* | Page 229 of 4/13/12 review |
| ☐ Review & FONSI *(indicate date of review)* | |
| ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |

| Facilities Review/Inspection | |
|---|---|
| ☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])* | Date completed:<br>☒ Acceptable<br>☐ Withhold recommendation<br>☐ Not applicable |
| ☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)* | Date completed:<br>☐ Acceptable<br>☐ Withhold recommendation |
| ❖ NDAs: Methods Validation *(check box only, do not include documents)* | ☒ Completed<br>☐ Requested<br>☐ Not yet requested<br>☐ Not needed (per review) |

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## ^ppendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.