

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204410Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>		NDA NUMBER 204410	
		NAME OF APPLICANT/NDA HOLDER Actelion Pharmaceuticals Ltd	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) OPSUMIT®			
ACTIVE INGREDIENT(S) macitentan		STRENGTH(S) 10 mg	
DOSAGE FORM tablet, oral			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 7,094,781		b. Issue Date of Patent August 22, 2006	c. Expiration Date of Patent October 12, 2022
d. Name of Patent Owner Actelion Pharmaceuticals Ltd		Address (of Patent Owner) Gewerbestrasse 16	
		City/State Allschwil	
		ZIP Code CH-4123 (SWITZERLAND)	FAX Number (if available) +41 61 565 65 00
		Telephone Number +41 61 565 65 65	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.) Actelion Clinical Research, 1820 Chapel Ave West, Suite 300	
Cheryl CZACHOROWSKI Director, Drug Regulatory Affairs		City/State Cherry Hill / New Jersey	
		ZIP Code 08002	FAX Number (if available) (856) 773-4247
		Telephone Number 856 773 4782	E-Mail Address (if available) cheryl.czachorowski@actelion.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

*E. Ruhlmann*

Date Signed

*July 27, 2012*

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Eric RUHLMANN	
Address Actelion Pharmaceuticals Ltd / Legal Department	City/State Allschwil
ZIP Code CH-4123 (SWITZERLAND)	Telephone Number +41 61 565 62 42
FAX Number (if available) +41 61 565 66 91	E-Mail Address (if available) eric.ruhlmann@actelion.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
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		NAME OF APPLICANT/NDA HOLDER Actelion Pharmaceuticals Ltd	
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<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 8,268,847		b. Issue Date of Patent September 18, 2012	c. Expiration Date of Patent April 18, 2029
d. Name of Patent Owner Actelion Pharmaceuticals Ltd		Address (of Patent Owner) Gewerbstrasse 16	
		City/State Allschwil	
		ZIP Code CH-4123 (SWITZERLAND)	FAX Number (if available) +41 61 565 65 00
		Telephone Number +41 61 565 65 65	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Cheryl CZACHOROWSKI Director, Drug Regulatory Affairs		Address (of agent or representative named in 1.e.) Actelion Clinical Research, 1820 Chapel Ave West, Suite 300	
		City/State Cherry Hill / New Jersey	
		ZIP Code 08002	FAX Number (if available) (856) 773-4247
		Telephone Number 856 773 4782	E-Mail Address (if available) cheryl.czachorowski@actelion.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

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**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
10 and 11	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) use in combination with phosphodiesterase-5 inhibitors in the treatment of pulmonary arterial hypertension (WHO group I) in adult and adolescent patients 12 years of age and older to reduce morbidity and mortality
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**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**



Date Signed

September 20, 2012

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric RUHLMANN

Address

Actelion Pharmaceuticals Ltd / Legal Department

City/State

Allschwil

ZIP Code

CH-4123 (SWITZERLAND)

Telephone Number

+41 61 565 62 42

FAX Number (if available)

+41 61 565 66 91

E-Mail Address (if available)

eric.ruhlmann@actelion.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
 Food and Drug Administration  
 Office of Chief Information Officer  
 1350 Piccard Drive, Room 400  
 Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## EXCLUSIVITY SUMMARY

NDA # 204410

SUPPL #

HFD # 110

Trade Name Opsumit

Generic Name Macitentan

Applicant Name Actelion Pharmaceuticals

Approval Date, If Known

### **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 X 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 X 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 X

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

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

YES  NO X

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 X

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 X

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 X

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



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: Edward Fromm, R.Ph., RAC  
Title: Chief, Project Management Staff, Division of Cardiovascular and Renal Products  
Date: 10/15/13

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D  
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

EDWARD J FROMM  
10/15/2013

NORMAN L STOCKBRIDGE  
10/15/2013



October 4, 2012

**DEBARMENT CERTIFICATION STATEMENT**

Actelion Pharmaceuticals Ltd. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in cursive script that reads "Cheryl Czachorowski".

Cheryl Czachorowski  
Director, Drug Regulatory Affairs  
1 856 773 4782

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 204410 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Opsumit Established/Proper Name: Macitentan Dosage Form: Tablet		Applicant: Actelion Pharmaceuticals LTD Agent for Applicant (if applicable): NA
RPM: Edward Fromm		Division: Division of Cardiovascular and Renal Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)                      Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>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.</b></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is: <b>October 19, 2013</b></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> 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.

<sup>2</sup> 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., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	Not Applicable
❖ Application Characteristics <sup>3</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)  Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)  Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input checked="" type="checkbox"/> MedGuide  <input checked="" type="checkbox"/> Communication Plan  <input checked="" type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	X Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	X Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>3</sup> 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	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: 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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: 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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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).*

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	X Included
Documentation of consent/non-consent by officers/employees	X Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Included
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	NA
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	Tracleer and Letairis

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	NA
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included (10-19-2012)
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	Included (Tracleer and Letairis)
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	July 11, 2013
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• <i>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.</i></li> </ul> </li> </ul>	Acceptable-January 2, 2013 December 27, 2012, July 7, 2013
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM December 1, 2012 <input checked="" type="checkbox"/> DMEPA June 14 and July 18, 2013 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) Sept. 24, 2013 <input checked="" type="checkbox"/> ODPD (DDMAC) Sept. 11, 2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS Not Applicable <input type="checkbox"/> Other reviews <u>Patient Labeling Team</u> -Sept 9, 2013 <u>Maternal Health Team</u> –June 25 (Oct. 17), 2013
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	RPM Filing Review- December 12, 2012, RPM Overview-Oct. 18, 2013  <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	X Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____</li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	Not Applicable-Orphan Exemption  <input type="checkbox"/> 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 ( <i>include certification</i> )	X Verified, statement is acceptable
❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	Midcycle T-con Minutes-March 28, 2013
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	X No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	X N/A
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	March 15, 2012
• EOP2 meeting ( <i>indicate date of mtg</i> )	August 17, 2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	Late Cycle Meeting Minutes-August 13, 2013
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Oct, 18, 2013
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Oct. 15, 2013
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Sept 19, 2013
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None Two (in Safety tab of Action Package).
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See Dr. Southworth's Sept 19, 2013 review
• Clinical review(s) ( <i>indicate date for each review</i> )	June 21 and July 25, 2013
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See pgs. 10-11 of Dr. Gordon's June 21, 2013 review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<u>Hepatology Review</u> - J. Senior-Sept. 9, 2013
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	X Not applicable

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	October 19, 2013  <input type="checkbox"/> July 22, September 24, October 8, 2013
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> June 3, 2013, Letters-May 14, 22, Sept 6, and 12.
<b>Clinical Microbiology</b> X None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None cosigned review below
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None June 18, 2013
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None cosigned reviews below.
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None June 29 and Sept. 6, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None P. Brown-Sept 24, 2013
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None cosigned review below
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None August 26, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	X No carc stat review
❖ ECAC/CAC report/memo of meeting	April 3, 2013
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	X None requested

<b>Product Quality</b> <input type="checkbox"/> None	
<b>❖ Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	X None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	S. Sood- August 21, 2013
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	Product Quality-May 24, 2013 Biopharmaceutics-June 18, 2013
<b>❖ Microbiology Reviews</b> <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	X Not needed
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	X None
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>	
X <b>Categorical Exclusion</b> <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	May 24, 2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	Not applicable
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	Not applicable
<b>❖ Facilities Review/Inspection</b>	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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<sup>7</sup>)</i>	Date completed: October 9, 2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation</b> <i>(check box only, do not include documents)</i>	X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> 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.

## Appendix 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.

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/s/  
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EDWARD J FROMM  
10/21/2013

**Fromm, Edward J**

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**From:** Shah, Vibhakar J  
**Sent:** Wednesday, October 09, 2013 5:07 PM  
**To:** Fromm, Edward J  
**Cc:** Southworth, Mary Ross; Wong, Thomas; Srinivasachar, Kasturi; Stockbridge, Norman L; Temple, Robert; Locicero, Colleen L; Gooen, Tara; Doleski, David; Lynn, Steven J; Sklamberg, Howard  
**Subject:** Status of Inspection for pending NDA 204410 (macitentan)-PDUFA date 10/18 - OC/OMPQ recommendation: ACCEPTABLE  
**Attachments:** Detailed EES Report N 204410.pdf  
**Importance:** High

Ed,

Please see attached EES report providing OC/OMPQ's overall "ACCEPTABLE" recommendation for all facilities supporting the NDA 204410. Please feel free to contact me if you have a question in this regard.

Thanks,

*- Vibhakar*

**Vibhakar Shah, Ph.D.**

*Senior Policy Advisor*

DGMPA/OMPQ/OC/CDER/USFDA

Phone: 301-796-1750; Fax: 301-847-8741

Email: [vibhakar.shah@fda.hhs.gov](mailto:vibhakar.shah@fda.hhs.gov)

p.s.: Please excuse any typos

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**From:** CDER EESQUESTIONS  
**Sent:** Wednesday, October 09, 2013 4:52 PM  
**To:** Philpy, Elizabeth; Gooen, Tara; Lynn, Steven J; Doleski, David; CDER EESQUESTIONS  
**Cc:** Sklamberg, Howard; Shah, Vibhakar J; Smedley, Michael; Farbman, Mary; Cruz, Concepcion; Williams, Juandria  
**Subject:** RE: Status of Inspection for pending NDA 204410 (macitentan)-PDUFA date 10/18

All,

Overall Compliance recommendation processed for NDA 204410/000. Attached you will find the detailed EES report.

Regards,  
Rokhsana

Executive CAC

Date of Meeting: April 2, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Karen Davis Bruno, Ph.D., Ph.D., DMEP, Alternate Member  
Albert DeFelice, Ph.D., DCRP, Team Leader  
William T. Link, Ph.D., DCRP, Presenting Reviewer

Author of Draft: William Link

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

NDA #204410

Drug Name: macitentan

Sponsor: Actelion

Background:

Mouse Carcinogenicity Study

The study employed 60 mice/sex/group (strain B6C3F1 (SPF)), dosed for 104 weeks, at doses of 0 (control, 0.5% methylcellulose), 5, 30, 100 and 400 mg/kg/day, orally by gavage. Excessive mortality in female mice at the 400 mg/kg/day dose demonstrated that a Maximally Tolerated Dose (MTD) was achieved in the study. There were no statistically significant increases in neoplastic findings in the study.

Rat Carcinogenicity Study

The study employed 51 rats/sex/group (strain HanRcc: WIST(SPF)), at doses of 0 (control, 2 groups, both received 0.5% methylcellulose), 10, 50, and 250 mg/kg/day. Excessive mortality in the High Dose group females established an MTD was achieved and necessitated reduction of the mid and high dose from 50 to 25 mg/kg and from 250 to 50 mg/kg, respectively, at approximately 1 year into the study. There were no statistically significant increases in neoplastic findings in the study.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\

- /Division File, DCRP
- /Albert DeFelice, Ph.D., Team leader, DCRP
- /William T. Link, Ph.D., Reviewer, DCRP
- /Russell Fortney/CSO/PM, DCRP
- /ASeifried, OND IO

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/s/  
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ADELE S SEIFRIED  
04/03/2013

DAVID JACOBSON KRAM  
04/03/2013



NDA 204410

**MID-CYCLE COMMUNICATION**

Actelion Pharmaceuticals, LTD.  
c/o Actelion Clinical Research, Inc.  
Attention: Cheryl Czachorowski  
Director, Drug Regulatory Affairs  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08002

Dear Ms. Czachorowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for OPSUMIT (macitentan) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 21, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please call:

Edward Fromm, R.Ph., RAC  
Regulatory Health Project Manager  
(301) 796-1072

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication

**MID-CYCLE COMMUNICATION**

**Telecon Date and Time:** March 21, 2013-11:00A-12 Noon

**Application Number:** 204410  
**Product Name:** OPSUMIT (macitentan) Tablets  
**Indication:** PAH (Pulmonary Arterial Hypertension)  
**Applicant Name:** Actelion Pharmaceuticals, LTD

**Meeting Chair:** Norman Stockbridge, M.D., Ph.D.  
**Meeting Recorder:** Edward Fromm, R.Ph., RAC

**FDA ATTENDEES**

*Office of Drug Evaluation 1, Division of Cardiovascular and Renal Products*  
Norman Stockbridge, M.D., Ph.D., Director  
Stephen Grant, M.D., Deputy Director  
Maryann Gordon, M.D., Medical Officer  
Edward Fromm, R.Ph., RAC, Chief, Project Management Staff

*Office of Biostatistics, Division of Biometrics I*  
Jialu Zhang, Ph.D., Statistician

*Office of Clinical Pharmacology, Division of Clinical Pharmacology I*  
Sreedharan Sabarinath, Ph.D., Clinical Pharmacologist

*Office of New Quality Drug Assessment*  
John Duan, Ph.D., Biopharmaceuticist,

*Office of Planning & Informatics*  
Kimberly Taylor, Operation Research Analyst

**ACTELION ATTENDEES**

Martine Clozel, Chief Scientific Officer  
Guy Braunstein, Head of Global Clinical Development  
Per Nilsson, Head of Strategic Development  
Alberto Gimona, Head of Global Clinical Science & Epidemiology  
Loic Perchenet, Senior Clinical Project Scientist  
Sebastien Roux, Clinical Area Head  
Jasper Dingemans, Head of Clinical Pharmacology  
Patricia Sidharta, Senior Clinical Pharmacologist  
Cecile Valette, Head of Medical Safety Surveillance  
Hani Mickail, Head of Drug Safety  
Paul Lagarenne, Head of Drug Safety US

Ulrich Mentzel, Head of Preclinical Development  
Alexander Treiber, Senior Group Leader, Preclinical PK and Metabolism  
Marisa Bacchi, Head of Biostatistics  
Robin Mukherjee, Senior Expert Statistician  
Cheryl Czachorowski, Director, Drug Regulatory Affairs  
Joyce Acbay, Senior Director, Drug Regulatory affairs  
Frances Duffy-Warren, Head of Drug Regulatory US  
Sonja Pumpluen, Head of Global DRA  
Frederic Naud, Senior Technical Project Leader  
Rudi Frank, Head of Global Quality Management  
Manaud de Raspide, Senior Technical Project Leader

#### **OTHER ATTENDEES**

(b) (4) Independent Assessor, Eastern Research Group, Inc.  
(b) (4) Independent Assessor, Eastern Research Group, Inc.

### **1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of your NDA in order to inform you of issues that we currently believe to be important. In conformance with the prescription drug user fee reauthorization agreements, these comments are not our final assessments of the information reviewed and should not be construed to be so. The issues identified are preliminary and may change as we complete our review of your application. In addition, we may later identify additional information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

### **2.0 REVIEW ISSUES (to date)**

#### **Biopharmaceutics**

Dr. Duan noted that the dissolution data provided in the application appear to support tightening of the dissolution acceptance criterion to  $Q = (b) (4)$  at 30 minutes. Actelion agreed and said they would tighten the specification to the FDA request.

Dr. Duan mentioned that there appeared to be to an exposure difference by particle size when using the GastroPlus simulation and he asked for clarification for the particle size distributions used in the simulation. Actelion acknowledged the request and said they hoped to send a response to the agency by March 26, 2013.

#### **Clinical Pharmacology**

Dr. Sabarinath asked for information regarding the active metabolite of macitentan for the PBPK analyses used for absolute bioavailability estimation. Specifically, the request was for the

SimCYP compound files for the active metabolite so that the full PBPK model for macitentan complete with its active metabolite can be used for drug-drug interaction simulations. The firm said they would send the compound files for the PBPK model to the agency as soon as possible.

### **NonClinical Phamacology**

The Division noted that macitentan appeared to be pharmacologically similar to bosentan. Actelion said that macitentan was different from bosentan in two important aspects: (1) Greater persistence of binding at the ET (endothelin) receptor. (2) Fewer drug-dug interactions because macitentan and its active metabolite did not interact with proteins involved in hepatic bile salt transport.

### **Clinical**



Dr. Gordon noted that another issue that needed further review was whether the drug is effective in the USA. She noted that there were few subjects enrolled in the USA and few events were observed in the placebo group. The review issue is whether ex-North American data are applicable to patients in the USA. Actelion noted that 11% of the patients in the SERAPHIN trial were from North America and they accounted for 7% of the primary endpoint events. They emphasized that the point estimate for the primary endpoint in the 10 mg subjects in North America was similar to that in the rest of the world.

A further review issue, Dr Gordon noted, was whether macitentan as monotherapy was acceptable or does it have to show efficacy when added to other PAH therapy. The applicant replied that most of the subjects in SERAPHIN were taking sildenafil and they believed that the 10-mg dose was effective as add-on therapy.

### **3.0 INFORMATION REQUESTS**

Please note Dr. Duan's and Sabaranith's requests during the telecon.

### **4.0 SAFETY CONCERNS/RISK MANAGEMENT**

Dr. Gordon noted that some subjects administered doses above 10 mg in study 102 developed increased serum transaminase levels. She was uncertain about the significance of this finding and how it might be described in labeling. Dr. Grant noted that elevations of serum

aminotransferases and liver failure have been reported with bosentan, another endothelin receptor antagonist. He inquired whether Actelion submitted a REMS in their application. Actelion replied that one had been submitted for teratogenicity, but not liver injury.

Dr. Grant asked how many subjects were exposed to the 10-mg dose in the confirmatory trial. Actelion responded that 250 patients were exposed to the 10-mg dose. Dr. Grant said that 250 patients were not enough to rule out the possibility that macitentan at a dose of 10 mg causes a clinically significant rate of liver injury. Actelion noted that PAH is an orphan disease with a limited number of patients available for study. Dr. Grant replied the Division understood the limitations inherent in developing drugs for orphan diseases but that the Agency has stated that review of drugs for orphan diseases was not different. A pharmacologically similar drug is associated with liver injury and adequate data to determine if macitentan also causes liver injury do not appear to be available. Actelion noted that an open label study in idiopathic pulmonary fibrosis could also provide additional safety data with the 10-mg dose.

The Division noted that physicians sometimes prescribe higher doses than the dose(s) recommended in labels. For example, although the maximum recommended dose for sildenafil is 20 mg tid, prescriptions for 80 mg tid are not uncommon. Whether the concern about liver injury can be adequately mitigated by labeling or whether a REMS or Post-Marketing Requirement (PMR) is needed remains a review issue.

The Division of Risk Management (DRISK) is reviewing the application and will provide comments to the applicant. Mr. Fromm will check with them for an update on any comments they will be providing to the applicant.

## **5.0 ADVISORY COMMITTEE MEETING**

The Division stated that there were no plans at this time to discuss macitentan at an Advisory Committee meeting because its actions appeared to be consistent with other members of its pharmacologic class and there appeared to be no novel issues raised by this application. The Division noted that this view was based on the review of the application to date and could change if reviews warranted it.

## **6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

The internal Late-Cycle meeting is scheduled for July 8, 2013 and the Late-Cycle face-to-face meeting with Actelion is scheduled for July 17, 2013. The Division expects draft labeling to be available by the beginning of July 2013.

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/s/  
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EDWARD J FROMM  
03/28/2013

NORMAN L STOCKBRIDGE  
03/28/2013



NDA 204410

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Actelion Pharmaceuticals, Ltd.  
c/o Actelion Clinical Research, Inc.  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08002

ATTENTION: Cheryl Czachorowski  
Director, Global Drug Regulatory Affairs

Dear Ms. Czachorowski:

Please refer to your New Drug Application (NDA) dated and received October 19, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Macitentan Tablets, 10 mg.

We also refer to your correspondence dated and received October 19, 2012, requesting review of your proposed proprietary name, Opsumit. We have completed our review of Opsumit and have concluded that it is acceptable.

The proposed proprietary name, Opsumit, 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 October 19, 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, Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Daniel Brum at (301) 796-0578.

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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CAROL A HOLQUIST  
01/02/2013



NDA 204410

**FILING COMMUNICATION**

Actelion Pharmaceuticals Ltd.  
Attention: Ms. Cheryl Czachorowski  
Director, Drug Regulatory Affairs  
1820 Chapel Avenue West  
Suite 300  
Cherry Hill, NJ 08002

Dear Ms. Czachorowski:

Please refer to your New Drug Application (NDA) dated October 19, 2012, received October 19, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Opsumit (macitentan) 10 mg tablets.

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. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is October 19, 2013.

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, mid-cycle, 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 July 1, 2013. In addition, the planned date for our internal mid-cycle review meeting is March 14, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. We do not see the rationale of selecting a rotation speed of 75 rpm for the dissolution testing, and we recommend that you obtain dissolution data at (b) (4).

2. The dissolution data provided (including the stability data) appear to support tightening of the dissolution acceptance criterion to Q (b) (4) at 30 minutes. We recommend that you implement this criterion and provide the revised specification table for your drug product.
3. We do not understand how your parameter sensitivity analysis (including the model chosen, the parameter selected and the parameter ranges) using GastroPlus supports your conclusion regarding the effect of particle size on the bioavailability.
4. We do not see photostability testing results on a primary batch of the drug product as per ICH Guidance, Q1A(R2). Refer to ICH Guidance, Q1B, Photostability Testing of New Drug Substance and Products for recommended testing conditions.
5. Can you confirm that the same Master Batch Record for the macitentan 10 mg film-coated tablets pre-validation batch will also be used for commercial product? If it is, please provide an English translation of this MBR. If not, please provide an English translation copy of the MBR to be used for commercial production.
6. We do not see a Validation Package for the drug substance.
7. We note the NDA number on your REMS materials appears as “204401” instead of “204410”.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Please provide the SimCYP® workspaces, compound and output files from the PBPK analyses used for absolute bioavailability estimation.\

(b) (4)  
What was the algorithm used to treat the patients randomized to the 10 mg dose who had adverse events? Were they discontinued from macitentan or were they treated with the lower dose? We assume that the dose of macitentan was limited by toxicity. There are populations whose concentration of macitentan and active metabolites are nearly doubled. As such, the 3 mg formulation may be appropriate for this population.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

#### **Indications and Usage**

If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Please revise as follows: “OPSUMIT is an endothelin receptor antagonist indicated for...”.

We request that you resubmit labeling that addresses these issues by January 15, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions or concerns, please contact Dan Brum, PharmD, RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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NORMAN L STOCKBRIDGE  
12/12/2012



NDA 204410

**NDA ACKNOWLEDGMENT**

Actelion Clinical Research, Inc.  
Attention: Ms. Cheryl Czachorowski  
Director, Drug Regulatory Affairs  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08002

Dear Ms. Czachorowski:

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: OPSUMIT (macitentan) Tablets, 10 mg

Date of Application: October 19, 2012

Date of Receipt: October 19, 2012

Our Reference Number: NDA 204410

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 December 18, 2012, 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 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 Cardiovascular and Renal 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>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Dan Brum, Pharm.D., RAC  
Regulatory Health Project Manager  
(301) 796-0578

Sincerely,

*{See appended electronic signature page}*

Edward Fromm, R.Ph., RAC  
Chief, Project Management Staff  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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EDWARD J FROMM  
11/02/2012

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG USER FEE  
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website:  
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>ACTELION PHARMACEUTICALS LTD Cheryl Czachorowski 1820 Chapel Avenue West Suite 300 Cherry Hill NJ 08002 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>204-410</p>
<p>2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE</p> <p>856-773-4782</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>OPSUMIT ( macitentan )</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3012719</p>
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7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES?  YES  NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

**OMB Statement:**  
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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<p>PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE <i>CHERYL CZACHOROWSKI</i></p> <p><i>Cheryl Czachorowski</i></p>	<p>TITLE <i>DIRECTOR,</i></p> <p><i>DRUG REGULATORY AFFAIRS</i></p>	<p>DATE</p> <p><i>03 OCT 2012</i></p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$0.00

Form FDA 3397 (01/10)



IND 77258

**MEETING MINUTES**

Actelion Pharmaceuticals Ltd.  
Attention: Ms. Cheryl Czachorowski  
Director, Drug Regulatory Affairs  
1820 Chapel Avenue West  
Suite 300  
Cherry Hill, NJ 08002

Dear Ms. Czachorowski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for macitentan (b) (4) 10 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 15, 2012.

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, please call Dan Brum, Pharm.D., BCPS, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosures:

- meeting minutes
- sponsor's slides and sponsor's responses to preliminary comments (emailed to Dan Brum on 3/12/12)

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** March 15, 2012 @ 12 p.m.  
**Meeting Location:** White Oak Bldg 22 Room 1309

**Application Number:** 77258  
**Product Name:** macitentan tablets  
**Indication:** PAH  
**Sponsor/Applicant Name:** Actelion

**Meeting Chair:** Norman Stockbridge  
**Meeting Recorder:** Dan Brum

### FDA ATTENDEES

DCRP: Norman Stockbridge (director), Steve Grant (deputy director), Tom Marciniak (clinical team leader), Maryann Gordon (clinical), Nhi Beasley (data standards lead), Dan Brum (regulatory project manager)

Office of Biometrics I: Jialu Zhang (reviewer)

Office of Clinical Pharmacology: Raj Madabushi (clinical pharmacology team leader), Sudharshan Hariharan (clinical pharmacology reviewer), Satjit Brar (pharmacometrics reviewer)

### SPONSOR ATTENDEES

Sébastien Roux, MD	Clinical Area Head
Loïc Perchenet, PhD	Clinical Project Leader
Marisa Bacchi, PhD	Head of Biostatistics
Adele Morganti, MSc	Senior Project Statistician
Patricia Sidharta, PharmD	Senior Clinical Pharmacologist
Jan Richter, PhD	Global Project Leader Drug Regulatory Affairs
Cheryl Czachorowski	US Project Leader Drug Regulatory Affairs
Douglas Smith	Medical Writing Group Leader

### BACKGROUND

Actelion is developing macitentan, a dual endothelin (ET<sub>A</sub> and ET<sub>B</sub>) receptor antagonist, for the treatment of pulmonary arterial hypertension in adults. The development program to support macitentan for the proposed indication of PAH is based on Protocol AC-055-302/SERAPHIN, entitled "A multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, Phase III study to assess the effects of ACT-064992 on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension".

The primary objective of the study is to demonstrate that macitentan delays the time to the first morbidity/mortality event in patients with PAH. The event-driven Phase 3 study, SERAPHIN, completed enrollment in December 2009 with 742 patients randomized in a 1:1:1 ratio (macitentan 3 mg QD, macitentan 10 mg QD, placebo QD). As of January 2012, approximately 90% of the target number of events (285) had been collected and the study is planned to be completed in Q2 2012.

The purpose of this meeting was to discuss to the adequacy of the nonclinical and clinical data package for the expected 4<sup>th</sup> quarter 2012 NDA submission. The sponsor requested responses to the following questions listed in the meeting briefing package. The questions are repeated below; preliminary responses are in **bold, black font**, and **bold, green font** reflects the main discussion points during the meeting. Note the sponsor submitted responses to the preliminary responses via email on March 12, 2012 (attached).

### **Nonclinical**

#### **Question 1: Inactive metabolite**

The pharmacologically inactive metabolite ACT-373898, which was present in different toxicology species, was found in subjects with severe renal impairment (SRI) at a higher exposure than in the absence of SRI. Actelion is of the opinion that, after completing its characterization by an Ames test, the contribution of the metabolite ACT-373898 to the overall toxicity assessment will have been established and that the overall toxicity evaluation of the metabolite will be adequate for the submission and review of the NDA. Does the Agency agree?

#### **Preliminary response**

**Yes**

**No discussion**

#### **Question 2: Nonclinical data package**

Actelion considers the nonclinical data package sufficient to support the submission and review of an NDA for macitentan. Does the Agency agree?

#### **Preliminary response**

**Yes**

**No discussion**

#### **Question 3: Carcinogenicity datasets**

Actelion considers the proposal for the submission of carcinogenicity datasets adequate to enable review of the data by the Agency. Does the Agency agree?

#### **Preliminary response**

**Yes**

**No discussion**

## **Clinical pharmacology**

### **Question 4: Clinical pharmacology data package**

Actelion considers the clinical pharmacology program adequate and sufficient to support the submission and review of an NDA for macitentan. Does the Agency agree?

### **Preliminary response**

**The clinical pharmacology program is adequate to support the submission and review of an NDA. However, we have the following comments/clarification questions:**

- 1. Conflicting statements are made in the briefing package with regard to the number of patients in which sparse PK sampling was performed. On page 17 of the briefing package, the first paragraph states PK sampling for macitentan and ACT-132577 was performed “at the End-of-Treatment (EOT) for all randomized patients”, yet the PK/PD assessments will be performed in a subpopulation of approximately 120 macitentan-treated PAH patients”. Please clarify the amount of data available for exposure-response analysis.**

**Discussion: The sponsor said there will be 500 samples from approximately 500 subjects available for the exposure-response analysis.**

- 2. Please supply information regarding the formulations that were used in all stages of the clinical development and the to-be-marketed formulation of macitentan. A pivotal bioequivalence trial will be required if there is a change in the formulation used in the Phase 3 trial and the to-be-marketed formulation.**

**No discussion**

- 3. Based on the receptor binding and functional assays, the active metabolite, ACT-132577 has approximately 3- to 5-fold less potency for the ET<sub>A</sub> and ET<sub>B</sub> receptors compared to the parent compound. As observed in repeated dosing studies, approximately an 8-fold accumulation of ACT-132577 was observed. Therefore, the PK/PD analysis of the Phase 3 study should attempt to determine the relative contribution of ACT-132577 to the overall activity on efficacy and safety measures.**

**No discussion**

- 4. Please supply details of how the prior pre-clinical and clinical information informed dose selection for the Phase 3 trial.**

**Discussion points: The sponsor confirmed that dose selection was influenced by hemodynamic observations made in patients with *hypertension*, not PAH.**

5. With regard to the popPK and exposure-response analysis, please explore the influence of concomitant PAH medications (including prostacyclins) on the PK and PK/PD of efficacy and safety endpoints.

**Discussion points:** Dr. Brar explained that prostacyclins may influence exposure of macitentan, and therefore recommended the sponsor explore this issue when conducting the popPK analysis.

6. Given that macitentan might be prescribed to HIV+ patients who have PAH, how do you plan to address potential drug interactions between macitentan and protease inhibitors?

**Discussion points:** The sponsor said macitentan and its active metabolite do not induce 3A4 and neither are substrates for OATP; however, because macitentan is a substrate of 3A4, a DDI study with ketoconazole (a strong CYP3A inhibitor) was performed which resulted in a 2-fold increase in the AUC of macitentan. Because the sponsor had previously studied doses of macitentan that produced a greater than 2-fold increase in exposure without sequela, the sponsor commented that the DDI with ketoconazole was not a safety concern. This was the rationale for not to conduct clinical DDI studies with protease inhibitors which are either moderate or strong inhibitors of CYP3A. However, Dr. Hariharan mentioned that labeling recommendations for ketoconazole and protease inhibitors will be made based on the exposure-response relationship for safety following NDA submission.

7. Please address the questions in the Clinical Pharmacology Summary Aid (emailed separately) and include your responses with the NDA submission.

**No discussion**

#### **Question 5: Population PK and PK/PD**

Actelion is of the opinion that the current PK/PD and population PK strategy is sufficient to support the submission and review of an NDA for macitentan. Does the Agency agree?

**Please see response to Question 4.**

**No discussion**

#### **Clinical**

#### **Question 6: AC-055-302/SERAPHIN Statistical Analysis Plan**

Actelion considers the proposed SAP for the efficacy assessment of the AC-055-302/SERAPHIN study conducted under an SPA, adequate to support the submission and review of an NDA for macitentan. Does the Agency agree?

### **Preliminary response**

**Yes. Please also submit your randomization codes to the Division now. Submit them as an encrypted file (e.g., with WinZip) and submit the encryption key at the time of NDA submission.**

**No discussion (see sponsor's attached response dated March 7, 2012)**

### **Question 7: Subgroup analysis for efficacy and safety**

Does the Agency agree that the selection of baseline subgroup factors for efficacy analysis is appropriate for providing information relevant for this indication?

### **Preliminary response**

**In addition to the factors you have proposed [i.e., PAH therapy(ies) at baseline (patients not receiving vs patients receiving specific concomitant PAH therapy(ies) at baseline), sex (male vs female), and race (White vs Asian vs other)], include the following additional factors:**

- **etiology**
- **country**

(b) (4)

**Discussion points: The Division voiced no concerns related to the sponsor's proposed choice of variables and grouping (see sponsor's slide 1). The Division acknowledged that the third bullet in the preliminary response above can be ignored because it was duplicative (see strikethrough text).**

### ***Efficacy***

**With regard to the sponsor's slide 2 (Subgroup Analyses: Each Individual Dose Vs. Placebo) and slide 3 (Subgroup Analyses: Pooled Doses (At Group Level) Vs. Placebo), the Division suggested that the sponsor perform analyses on each individual dose versus placebo rather than pooling the doses (at the group level) versus placebo (i.e., the Division preferred the approach used in slide 2 instead of slide 3).**

**In addition to providing a graphic displaying each subgroup variable independent of the other subgroup variables, Dr. Stockbridge suggested providing a graphical display (e.g., forest plot) that takes into account the influence of subgroup variables on each other. After some discussion pertaining to the complexity and potential pitfalls of such an analysis, the sponsor said they would try to provide both.**

### ***Safety***

**In addition to text and tables, the sponsor agreed to use figures to present the safety outcomes of interest (e.g., aminotransferase elevations, edema, hypotension, decreases in hemoglobin).**

**Question 8: Clinical safety database**

Does the Agency agree that the macitentan safety database is adequate to characterize the safety profile and support the submission and review of the macitentan NDA for PAH?

**Preliminary response**

Yes

**No discussion**

**Question 9: Integrated Summary of Safety**

Actelion considers the proposed content, data cut-off date, and pooling strategy defined for the Integrated Summary of Safety (ISS) adequate to allow for the review and evaluation of the safety profile of macitentan in PAH. Does the Agency agree?

**Preliminary response**

**Yes, but also include the patient profiles (which you suggested that we waive) as well as the CRFs for *all* subjects who discontinued in SERAPHIN when you submit the NDA. Note that CRFs include all documents with clinical information regarding the patients regardless of whether you have labelled them as CRFs, e.g., SAE worksheets, event worksheets or fax coversheets, data queries, site-prepared narratives, adjudications packages, etc., are all CRFs.**

**No discussion**

**Question 10: Day 120 safety update**

Does the FDA agree with the content and data cut-off dates proposed for the Day 120 safety update to the NDA?

**Preliminary response**

**Yes, but if the NDA is delayed then the data cut-off dates may need to be modified to ensure you provide up-to-date information.**

**No discussion**

**Question 11: Proposed datasets**

Does the FDA agree with the proposed approach to the datasets planned for submission within the application?

**Preliminary response**

**Yes, but include all CRF data available in electronic form in the SAS datasets, e.g., if an electronic CRF (eCRF) system was used, the datasets should include all data in the CRFs. In addition submit the following datasets:**

- **A dataset providing the original and final investigator verbatim terms for any AEs or event descriptions that the investigators changed or deleted.**
- **If an eCRF system was used, submit the audit trail of changes to the eCRFs.**

- **A dataset documenting the CEC actions, e.g., dates of adjudication package submissions and adjudicator actions, original adjudications by adjudicator, final adjudication.**

**Because the requested datasets may not fit cleanly into the SDTM format, you may wish to discuss with the Division the submission of some non-SDTM format datasets.**

**Discussion points: The Division clarified that the preliminary response is aimed at only the Phase 3 trial (and not Phase 2).**

**The sponsor clarified that all CRFs are in paper format, not electronic format. In response to the Division's request, the sponsor agreed to provide a change log explaining how the information from the CRFs was converted to electronic datasets.**

### **Question 12: Risk Evaluation and Mitigation Strategy proposal**

All approved ERAs have a Risk Evaluation and Mitigation Strategy (REMS). As macitentan is teratogenic, Actelion is proposing that there will be a REMS to minimize the risk of fetal exposure. Following availability and evaluation of the pivotal clinical study data, the need for other safe-use conditions will be proposed after the safety profile has been established. See Section 10.3.5 for more detailed information on the REMS proposal.

Does the Agency agree with the proposed REMS elements (by provision of a macitentan medication guide and assessment timetable) related to the teratogenicity of macitentan?

#### **Preliminary response**

**We acknowledge your proposal to submit a risk evaluation and mitigation strategy (REMS) to minimize the risk of fetal exposure.**

**A complete review of the proposed REMS in conjunction with the full clinical review of the NDA will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.**

**Since you plan to submit a REMS with the original NDA submission, please submit all planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement your proposal.**

**In addition, we have the following high-level comments on your proposal. These comments should be considered as general advice only and cannot be considered final until a complete REMS review has been performed.**

- **Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.**
- **Product marketing materials generally are not appropriate to educate about product risks.**

**We remind you that a proposed REMS will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria.**

**No discussion**

### **Regulatory**

#### **Question 13: ISS and ISE location**

Does the Agency agree with the proposed Common Technical Document (CTD) location of the ISS and Integrated Summary of Effectiveness (ISE) within the application?

#### **Preliminary response**

**Yes**

**No discussion**

### **Additional requests/comments**

- 1. The greatest challenge in recent CV outcome trials has been complete follow-up on all patients. We urge you to have all living patients return for a face-to-face follow-up visit at the end of the trial. If some last follow-up is done by phone for patients who discontinued treatment early, we recommend using a structured protocol and form capturing the details of who participated in the phone follow-up and explicit documentation on the questions asked and responded to. For patients who withdrew consent the details of withdrawal of consent should be documented, i.e., to treatment, to continuing visits, to continuing phone contacts, to provider contacts, and to all contacts. For patients who withdrew consent to treatment but who allow follow-up, the follow-up should be documented well as described for all living patients.**

**Discussion points: According to the sponsor, only 11 patients were lost to follow-up; the sponsor plans to do a sensitivity analysis imputing values for those patients assuming the worst case scenario. Dr. Marciniak urged the sponsor to have complete follow-up on all patients to the end of the study for components of the primary endpoint in order to be able to do an intention-to-treat (ITT) analysis.**

- 2. At your earliest convenience, please send samples of the investigational medicinal products used in the SERAPHIN trial to me at the following address:**

**Daniel Brum  
10903 New Hampshire Ave.  
White Oak 22/Room 4160  
Silver Spring, MD 20993-0002**

**No discussion**

- 3. Liver datasets request**

**Please submit a dataset that contains multiple records per randomized subject and the following information:**

- the unique subject id
- treatment arm
- indicator flag for treated subjects
- randomization date
- study termination date
- first medication date
- last medication date
- the following liver test results, ratios, and date of collection: ALT, AST, total bilirubin, and alkaline phosphatase, and an indicator for central or local lab.

All liver test results should be in consistent units. There should be a date for each lab test, e.g., ALT\_date, AST\_date.

**A dataset that contains multiple records per subject and the following information: the unique subject id, treatment arm, the date and results of all laboratory tests done to rule out other causes of drug-induced liver injury.**

**Discussion points: The sponsor will provide the above in a dataset.**

If expert hepatologists review the liver cases, please submit a data set containing one record per event and the following information: the unique subject ID, treatment arm, date of event, a column named for each hepatologist with his/her causality assessment, and a column for the final assessment of causality.

Please submit MedDRA coding dictionaries for the Preferred Terms used to identify hepatic-related AEs as SAS transport files.

**Discussion points: The sponsor did not have a systematic way of selecting cases for expert hepatologists review. Given the small number of potential Hy's Law cases that expert hepatologists reviewed, Dr. Beasley said that it was acceptable not to submit a dataset with their causality assessments.**

4. Please submit a table listing all of the tables and figures featured in the main Clinical Study Report of the phase 3 trial. The table should contain the following:
  - title of the table or figure in NDA
  - a page number hyperlink to the location of table or figure
  - a name hyperlink to the SAS code (and/or macros) used to create the table or figure
  - names of the datasets used to create the table or figure (a hyperlink is useful, but not necessary)

**No discussion**

- 5. Please submit copies of the original protocol, statistical analysis plan, DSMB charter, CEC charter, and CEC directions and all amendments to them. Please submit copies of all DSMB, CEC, and executive committee minutes and all presentations, letters, newsletters, or site manuals sent to investigators.**

**No discussion**

- 6. We encourage you to submit a formal meeting request for a “top-line” results meeting at least 2 months prior to the planned NDA submission date.**

**No discussion**

### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
-----------	--------------	--	---	---

- 1.
- 2.

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
-----------	--------------	--------------------------------	----------------------	---------------

- 1.
- 2.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There are no issues requiring further discussion.

### **4.0 ACTION ITEMS**

There are no action items from the meeting.

## **5.0 ATTACHMENTS AND HANDOUTS**

There were two handouts.

Additional information requests that were emailed to the sponsor on March 7, 2012:

1. Clinical Pharmacology Summary Aid
2. Office of Scientific Investigations Pre-NDA site selection information request
3. eDISH data request (liver)



**IND 77,258 Macitentan for PAH  
Response to March 7, 2012 FDA Communication  
for March 15, 2012 Pre-NDA Meeting  
(emailed March 12, 2012)**

Reference is made to a January 17, 2012 (SN 0093) meeting request (Pre-NDA), briefing information dated February 13, 2012 (SN 0095), and FDA meeting preliminary comments dated March 7, 2012. The following includes a summary of items to address, along with supporting information, to help facilitate the Pre-NDA Meeting scheduled for March 15<sup>th</sup> between 12-1 PM. An [updated list of attendees](#) is also provided.

**Nonclinical**

Question 1: Inactive metabolite - No further discussion

Question 2: Nonclinical Data package - No further discussion

Question 3: Carcinogenicity datasets – No further discussion

**Clinical Pharmacology**

Question 4: Clinical pharmacology data package

- FDA response #1 – a clarification is provided [see [Response 4.1](#)], no further discussion, unless FDA has further comment on the information provided.
- FDA response #2 – the clinical and to-be-marketed formulation information requested is provided [see [Response 4.2](#)]; no further discussion unless FDA has further comment on the information provided.
- FDA response #3 – This information will be included in the NDA, no further discussion.
- FDA response #4 – To be discussed at the meeting. Information regarding dose selection was submitted in the July 16, 2007 Pre-IND briefing document (Question 7 rationale on page 27), whereby FDA responded that the doses seemed reasonably well-justified (August 29, 2007 FDA correspondence). The initial IND (SN 0000 dated June 5, 2008) also included a summary of the justification for dose selection (2.5 Clinical Overview, Section 5). It is planned to include all details associated with dose selection within the NDA submission.
- FDA response #5 – To be discussed at the meeting.
- FDA response #6 – To be discussed at the meeting, please see [[Bruderer S, 2012](#)] as background to aid in the discussion.
- FDA response #7 – No further discussion.

Question 5: Population PK and PK/PD – No further discussion.

**Clinical**

Question 6: AC-055-302 SERAPHIN Statistical Analysis Plan – The randomization codes were submitted to IND 77,258 previously (serial number 0001 dated June 18, 2008), and the encryption key will be submitted at the time of NDA submission. No further discussion.

Question 7: Subgroup analysis for efficacy and safety – To be discussed at the meeting, refer to slides [see [Response 7](#)] for display at the meeting.

Question 8: Clinical Safety Database – No further discussion.

Question 9: Integrated Summary of Safety – We agree to provide all requested information, but may address the format and content of a patient profile with the future submission of the datasets for review/comment.

Question 10: Day 120 safety update – No further discussion.

Question 11: Proposed datasets – To be discussed at the meeting

Question 12: Risk Evaluation and Mitigation Strategy proposal – No further discussion.

**Regulatory**

Question 13: ISS and ISE location – No further discussion.

**Additional requests/comments:**

- #1: To be discussed at the meeting.
- #2: Product will be shipped, Mr. Brum will be contacted for details.
- #3: To be discussed at the meeting.
- #4: This will be provided in the NDA. No further discussion.
- #5: This will be provided in the NDA. No further discussion.
- #6: A top-line results meeting will be requested. No further discussion.

**OSI Pre-NDA site selection information request:** This will be provided in the NDA. No further discussion.

**Updated list of Actelion participants**

(strikethrough indicates those not attending):

Sébastien Roux, MD*	Clinical Area Head
Loïc Perchenet, PhD*	Clinical Project Leader
(b) (4)	(b) (4)
Marisa Bacchi, PhD*	Head of Biostatistics
Adele Morganti, MSc*	Senior Project Statistician
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Patricia Sidharta, PharmD*	Senior Clinical Pharmacologist
(b) (4)	(b) (4)
Jan Richter, PhD*	Global Project Leader Drug Regulatory Affairs
Cheryl Czachorowski	US Project Leader Drug Regulatory Affairs
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Douglas Smith*	Medical Writing Group Leader

\*: individuals who completed a foreign visitor form.

## Response 4.1

### **Question 4: Clinical pharmacology data package**

Actelion considers the clinical pharmacology program adequate and sufficient to support the submission and review of an NDA for macitentan. Does the Agency agree?

**FDA Preliminary Comment #1: Conflicting statements are made in the briefing package with regard to the number of patients in which sparse PK sampling was performed. On page 17 of the briefing package, the first paragraph states PK sampling for macitentan and ACT-132577 was performed “at the End-of-Treatment (EOT) for all randomized patients”, yet the PK/PD assessments will be performed in a subpopulation of approximately 120 macitentan-treated PAH patients”. Please clarify the amount of data available for exposure-response analysis.**

**Actelion Response: Approximately 120 patients are available for PK/PD analysis. In this subpopulation of the SERAPHIN study, at Month 6, a trough PK sample was collected and hemodynamic assessment were performed. In addition, in all randomized patients in the SERAPHIN study, it is planned to collect a PK sample at the End of Treatment visit. It is estimated that approximately 500 samples will be available for further exposure-response analysis.**

## Response 4.2

### Question 4: Clinical pharmacology data package

Actelion considers the clinical pharmacology program adequate and sufficient to support the submission and review of an NDA for macitentan. Does the Agency agree?

**FDA Preliminary Comment #2:** Please supply information regarding the formulations that were used in all stages of the clinical development and the to-be-marketed formulation of macitentan. A pivotal bioequivalence trial will be required if there is a change in the formulation used in the Phase 3 trial and the to-be-marketed formulation.

### Actelion Response

(b) (4) (0.3 mg, 1 mg, 3 mg, 10 mg, and 100 mg) were manufactured for early Phase 1 and 2 clinical trials [see Table 1 below].

(b) (4)  
 The formulation developed for use in Phase 3 clinical trials are white, round, biconvex, film-coated tablets (placebo, (b) (4) 3 mg and 10 mg). Results of a biocomparison study (study AC-055-108) show that the pharmacokinetic profile of the film-coated tablet formulation, used in Phase 3, is comparable to the (b) (4) formulation used in the Phase 1 and Phase 2 programs.

The to-be-marketed formulation is the same as the film-coated tablet formulation used in Phase 3 clinical trials; (b) (4)  
 [see Table 2 below].

**Table 1 Dosage forms used during clinical development of macitentan**

Dosage form	Study Number
(b) (4)	AC 055 101, 102, 103, 104, 105, 106, 107, 201
Tablet	AC 055 108
Tablet	AC 055 109, 110, 111, 112, 113, 114, 115, 116, 117, B201, 302, 303, C302, C303

**Table 2 Composition of macitentan film-coated tablets**

Ingredient	Actual mass/tablet	Actual mass/tablet	Actual mass/tablet	Actual mass/tablet
	Clinical	Commercial	Clinical	Commercial
Appearance of the tablet	(b) (4)			
<b>Core</b>				
Macitentan				
Polysorbate 80				
Lactose monohydrate				
Microcrystalline cellulose				
Povidone				
Sodium starch glycolate type A				
Magnesium stearate				
<b>Mass of the core</b>				
<b>Film Coat</b>				
(b) (4)				
<b>Mass of the coat</b>				
<b>Mass of the film coated tablets</b>	72.80 mg	72.80 mg	72.80 mg	72.80 mg

**Bruderer S, 2012**

The attached publication is background information for the following question and response:

**Question 4: Clinical pharmacology data package**

Actelion considers the clinical pharmacology program adequate and sufficient to support the submission and review of an NDA for macitentan. Does the Agency agree?

**FDA Preliminary Comment #6: Given that macitentan might be prescribed to HIV+ patients who have PAH, how do you plan to address potential drug interactions between macitentan and protease inhibitors?**

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## Response 7

See slides for display and discussion to support the following Questions and preliminary response (the slides are also located in file: [IND77258 Macitentan Biostat 12March2012.ppt](#))

### Question 7: Subgroup analysis for efficacy and safety

Does the Agency agree that the selection of baseline subgroup factors for efficacy analysis is appropriate for providing information relevant for this indication?

#### FDA Preliminary response

In addition to the factors you have proposed [i.e., PAH therapy(ies) at baseline (patients not receiving vs patients receiving specific concomitant PAH therapy(ies) at baseline), sex (male vs female), and race (White vs Asian vs other)], include the following additional factors:

- etiology
- country
-  (b) (4)

## QUESTIONS FOR THE SUBGROUP ANALYSES

- DOES THE FDA AGREE ON THE CHOICE OF VARIABLES AND GROUPING:



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/s/  
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DANIEL BRUM  
03/26/2012

NORMAN L STOCKBRIDGE  
03/26/2012



Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

SEP 3 2009

Actelion Clinical Research, Inc.  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, New Jersey 08002

Attention : Brian D. Schlag, M.A. M.S.  
Associate Director, Drug Regulatory Affairs

Re: Designation request # 09-2822

Dear Mr. Schlag:

Reference is made to your request for orphan-drug designation submitted on behalf of Actelion Ltd. dated April 16, 2009, of macitentan for "treatment of pulmonary arterial hypertension." We also refer to our letters dated April 23 and May 29, 2009, and to your submission dated July 14, 2009.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of macitentan is granted for *treatment of pulmonary arterial hypertension*. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Peter L. Vaccari, R.Ph., RAC, at (301) 827-3666. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Timothy R. Coté', with a large, sweeping flourish above the name.

Timothy R. Coté, M.D., M.P.H.

Director, Office of Orphan Products Development

## Meeting Minutes

**Date:** August 17, 2007  
**Application:** P-IND 77,258  
**Drug:** ACT-064992  
**Sponsor:** Actelion  
**Meeting Purpose:** Pre-IND Meeting  
**Meeting Type:** B

### FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader
Peter Hinderling, M.D.	Clinical Pharmacology
Cherry Liu, Ph.D.	Statistician
James Hung, Ph.D.	Director, Division of Biometrics I
Russell Fortney	Regulatory Project Manager

### Actelion Attendees:

Frances Duffy-Warren, Ph.D.	Head US Regulatory Affairs
Jan Richter, Ph.D.	Global DRA Project Manager
Ulrich Mentzel, Ph.D.	Head of Toxicology
Per Nilsson, M.D., Ph.D.	Head of Strategic Clinical Development
Loic Perchenet, Ph.D.	Clinical Leader
(b) (4)	Clinical Consultant to Actelion
Patricia Sidharta, Pharm.D.	Clinical Pharmacologist
Ngoc Nguyen, Ph.D.	Life Cycle Leader
Maurizio Rainisio, Ph.D.	Head of Biometry

### Actelion Participants by phone:

Martine Clozel, M.D.	Head Drug Discovery
Sonja Pumpluen	Head Global Drug Regulatory Affairs
Isaac Kobrin	Head Clinical Development
Yasper Dingemanse	Head Clinical Pharmacology
Sebastien Roux	Therapeutic Area Head
Jennifer Dohanish	US Drug Regulatory Affairs

### Background:

ACT-064992 is an orally active dual endothelin receptor antagonist (ERA) being developed for the treatment of symptomatic pulmonary hypertension. The sponsor has completed three phase 1 trials along with a phase 2 trial to date. This meeting was scheduled to discuss the development program for ACT-064992. Preliminary responses to the submitted questions were provided to the sponsor, and are copied below, followed by any additional discussion that took place during the meeting.

**Meeting:**

1. Based on the nonclinical safety program, Actelion considers the target organ toxicity sufficiently characterized and the resulting safety margins appropriate to support the start of the planned Phase 3 program. Does the Agency agree?

**Preliminary FDA response:** Yes

**Additional discussion during meeting:** No additional discussion.

2. In dog toxicity studies, vascular lesions were observed mainly in the right coronary artery and the right atrium. Actelion considers these findings to be dog-specific lesions observed with the endothelin receptor antagonists due to exaggerated pharmacodynamic effects. The findings are considered to have a limited relevance to man. Does the Agency agree?

**Preliminary FDA response:** Yes, we consider the dog to be most sensitive species, although the monkey is also expected to be vulnerable to such toxicologic pathology, and that such is provoked by a variety of vasoactive compounds. Although of unknown clinical relevance, they are considered – and can be a basis of – a projected safety margin.

**Additional discussion during meeting:** No additional discussion.

3. Teratogenic effects were observed in pilot embryo-fetal toxicity studies in rats and rabbits. The studies were performed under GLP. Actelion considers teratogenicity in animals as a class-effect of endothelin receptor antagonists. It is considered that the effects were sufficiently characterized in the above-mentioned studies, and that additional studies are not necessary to further characterize the effects. Does the Agency agree?

**Preliminary FDA response:** Segment III studies, i.e., peri-postnatal up to weaning, will also be required at the time of NDA filing.

**Additional discussion during meeting:** No additional discussion.

4. Actelion considers the proposed clinical pharmacology program adequate to start the pivotal Phase 3 trial, as well as to support future registration. Does the Agency agree?

**Preliminary FDA response:** The proposed program is adequate to start the Phase 3 trial. However, the proposed program is not adequate to support future registration. Your program should include interaction studies with rifampicin and cyclosporine, and a population PK-PD sub-study in the Phase 3 clinical trial.

**Additional discussion during meeting:** The sponsor agreed to perform the rifampicin and cyclosporine interaction studies as well as a PK-PD sub-study in the Phase 3 trial. Dr. Hinderling asked which PD parameters would be measured. The sponsor said that is still under consideration, but that they will likely include some hemodynamic measures.

5. The sponsor believes that a single, large, multi-center, randomized, double-blind, placebo-controlled, event-driven, Phase 3 study (AC-055-302) with the composite primary endpoint ‘Time from baseline to first morbidity/mortality event’ and powered to detect a highly significant treatment effect ( $p < (b) (4)$ ) at

either dose of ACT-064992 tested (3 mg and 10 mg q.d.) is sufficient and adequate to demonstrate efficacy and safety to support the approval of ACT-064992 for the indication:

(b) (4)

Does the Agency agree?

**Preliminary FDA response:**

**A.** We do not agree with your proposed definition for worsening PAH because several of its components are subjective (b) (4) and others are dependent upon some test being performed (b) (4). We do not believe that an endpoint committee can compensate for differences in investigator behavior. We prefer a simpler endpoint based on event occurrence: death, atrial septostomy, lung transplantation, or hospitalization for worsening PAH with the initiation of changed therapy for PAH or HF. While rates of hospitalization may vary by region, we believe that PAH hospitalizations will be easier to adjudicate (b) (4). We will be happy to discuss our views with you at the meeting.

**Additional discussion during meeting:** The sponsor agreed that death, septostomy and transplantation are hard endpoints, but noted that they are quite uncommon. While they also agreed that symptom based indices of worsening are subjective, they argued that hospitalization is also subjective. They presented a revised definition of clinical worsening based on a 15% reduction in 6MWT *and* worsening of symptoms requiring additional therapy (see attachment). Dr. Stockbridge agreed that a 15% reduction in 6MWT is meaningful. In addition, he noted that in some studies, about half of the treatment effect is attributable to a mean reduction from baseline in the placebo group. However, the Division expressed continued concern that altering therapy (e.g., adding sildenafil or increasing the dose of epoprostenol) is still a subjective measure. Dr. Karkowsky noted that if the baseline 6MWT is low, a 15% reduction is a small absolute decrease. He also noted that an increase in an already used prostanoid infusion has a low threshold and would not necessarily imply any worsening of clinical status. The sponsor noted that it might be appropriate to exclude patients already on prostanoids.

There was a discussion of the relative importance of the sponsor's revised clinical worsening endpoint vs. endpoints that Dr. Stockbridge considered more meaningful (i.e., death, hospitalization, invasive procedures). The sponsor argued that their endpoint is more important than 6MWT. Dr. Stockbridge agreed, but was unsure how much of a discount on two trials at  $p < (b) (4)$  it would be worth. The sponsor offered a single trial at  $p < 0.01$ . Dr. Stockbridge said that seemed reasonable. He asked the sponsor to submit a detailed description of the protocol and the proposed endpoints so that he can review it with Dr. Temple. The sponsor agreed to provide the information.

**B.** While all-cause mortality is acceptable, you may consider using "death due to worsening PAH" as the primary endpoint component. We have observed a fair number of deaths in other PAH trials that were not clearly related to worsening PAH (e.g., particularly in patients with PAH secondary to connective tissue disorders, deaths from the primary disease are not uncommon).

**Additional discussion during meeting:** The sponsor noted that they prefer to use all-cause mortality as the endpoint. Dr. Stockbridge agreed that is acceptable. He also said that the sponsor could consider defining a subset of deaths that are disease-related.

**C.** While a primary endpoint of death/hospitalization due to PAH is good, we believe that you are more likely to win with an endpoint of change in 6MWD. You may consider using this EP in two trials at the

alpha 0.05 significance (done in different regions) or in one trial at alpha 0.00125 (*the original preliminary response indicated 0.000125 in error*) as the PEP, using death/hospitalization as the first secondary EP.

**Additional discussion during meeting:** See 5A discussion.

**D.** The postulated treatment effect of 40% reduction in hazard rate seems optimistic and is rarely seen according to the Agency's experience. We recommend that the number of events needed be calculated to detect a more conservatively postulated treatment effect, e.g., 20%.

**Additional discussion during meeting:** The sponsor said they would prefer using a 40% reduction. Dr. Stockbridge agreed that is acceptable. Dr. Stockbridge confirmed with the sponsor that this is an event-driven trial and there would not be an interim analysis planned. However, if the event rate is low, the sample size will be increased in a blinded way and the 40% hazard rate will remain unchanged. Dr. Stockbridge advised that the sponsor should continue to enroll patients until the specific event threshold has been reached. He also advised the sponsor to pre-specify an algorithm for the decision-making process, such as when the interim look will be taken, and the event rate level at which the sample size will be increased.

**E.** We recommend that the secondary endpoints be tested at the total alpha of no larger than 0.005 for the dose that the primary endpoint achieves statistical significance at  $p \leq 0.005$ . If the sponsor elects to test the multiple secondary endpoints sequentially according to a hierarchical order, then the order of testing must be pre-specified. For instance, if the primary endpoint achieves statistical significance at  $p \leq 0.005$  for the high dose, then test the secondary endpoints sequentially according to the pre-specified order at  $p \leq 0.005$  for that dose. The same strategy can be applied to the low dose.

**Additional discussion during meeting:** No additional discussion.

6. Actelion intends to develop and register ACT064992 for the indication (b) (4). Does the Agency agree that the selected patient population in the proposed Phase 3 trial (AC-055-302) is appropriate to support registration in this proposed indication?

**Preliminary FDA response:** We recommend that the patient population be WHO Group I PAH. We will examine the baseline characteristics of the patients actually studied and may restrict the indication to the types of patients with sufficient numbers to have some confidence that study results are applicable. If the numbers of patients with specific characteristics are small, we will not label the drug for use in such patients. For example, if the study enrolls only a limited number of patients with mild obstructive or mild restrictive lung disease, the drug will not be labeled for use in such patients.

**Additional discussion during meeting:** No additional discussion.

7. Based on the data from the present clinical program, Actelion proposes doses of ACT-064992 of 3 and 10 mg once daily for study AC-055-302 and considers that the selected doses are sufficiently justified. Does the Agency agree?

**Preliminary FDA response:** It is your decision regarding the final doses to study. The doses you have selected seem reasonably well-justified and we are pleased that you are proposing to study two dosages in your outcome study.

**Additional discussion during meeting:** No additional discussion.

8. Does the Agency have any comment on the proposed overall clinical development program for ACT-064992 to support the indication of [REDACTED] (b) (4), [REDACTED],

**Preliminary FDA response:** Please see our response to question 5.

**Additional discussion during meeting:** No additional discussion.

9. Actelion believes that a thorough QTc study with ACT-064992 is not warranted for the proposed indication. Does the Agency agree?

**Preliminary FDA response:** We do not agree. We believe that a thorough QTc study is necessary as at least one other ERA as shown evidence of prolonging QTc.

**Additional discussion during meeting:** The sponsor agreed to conduct a thorough QTc study.

10. Actelion intends to submit the Investigational New Drug (IND) Application in the electronic common technical document (eCTD) format. Does the Agency have any comments on this approach?

**Preliminary FDA response:** The eCTD format is welcome and appreciated. We remind you that all future submissions must also be in the eCTD format.

**Additional discussion during meeting:** No additional discussion.

Minutes preparation: *{See appended electronic signature page}*  
Russell Fortney

Concurrence, Chair: *{See appended electronic signature page}*  
Norman Stockbridge, M.D., Ph.D.

Drafted-8/28/07; Final-8/29/07

Reviewed: C.Liu-8/29/07  
J.Hung-8/29/07  
P.Hinderling-8/29/07  
A.Karkowsky-8/29/07  
N.Stockbridge-8/29/07

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Norman Stockbridge  
8/29/2007 03:16:29 PM

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 204410

**LATE-CYCLE MEETING MINUTES**

Actelion Pharmaceuticals, LTD.  
c/o Actelion Clinical Research, Inc.  
Attention: Cheryl Czachorowski  
Director, Drug Regulatory Affairs  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08002

Dear Ms. Czachorowski,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for OPSUMIT (macitentan) Tablets.

We also refer to the late cycle meeting (LCM) between representatives of your firm and the FDA on July 17, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Edward Fromm, RPh, RAC, Regulatory Project Manager at (301) 796-1072.

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, Pharm.D.  
Deputy Director for Safety  
Division for Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** July 17, 2013, 10 A – 12 Noon  
**Meeting Location:** FDA White Oak, Building 22, Rm. 1311

**Application Number:** NDA 204410  
**Product Name:** Opsumit (macitentan) Tablets  
**Indication:** **PAH (pulmonary arterial hypertension)**  
**Sponsor/Applicant Name:** Actelion Pharmaceuticals,LTD

**Meeting Chair:** Mary Ross Southworth, Pharm.D.  
**Meeting Recorder:** Edward Fromm, R.Ph., RAC

**FDA ATTENDEES**

*Office of Drug Evaluation 1*

Ellis Unger, M.D., Director  
Robert Temple, M.D., Deputy Director

*Office of Drug Evaluation 1, Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D., Director  
Mary Ross Southworth, Pharm.D., Deputy Director for Safety & Cross Discipline Team Leader for the NDA  
Maryann Gordon, M.D., Medical Officer  
Albert Defelice, Ph.D., Supervisory Pharmacologist  
William T. Link, Ph.D., Pharmacologist  
Lori Wachter, RN, BSN, Safety Regulatory Project Manager  
Michael Monteleone, MS, RAC, Senior Regulatory Project Manager  
Meghan Delmastro-Greenwood, Ph.D., FDA Summer Fellow  
Kelley Quesnelle, Ph.D., FDA Summer Fellow  
Edward Fromm, R.Ph., RAC, Chief, Project Management Staff

*Office of Biostatistics, Division of Biometrics I*

James Hung, Team Leader  
Jialu Zhang, Ph.D., Statistician

*Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

Raj Madabushi, PhD, Team Leader  
Sreedharan Sabarinath, Ph.D., Clinical Pharmacologist

*Office of Clinical Pharmacology, Division of Pharmacometrics*

Dhananjay D. Marathe, Ph.D., Visiting Associate

*Office of Surveillance and Epidemiology, Division of Pharmacovigilance I*

Susan Lu, Pharm.D., Lead Pharmacist  
Amy Chen, Pharm.D., Pharmacist

*Office of Surveillance and Epidemiology, Division of Epidemiology II*

Jie Li, Ph.D., Epidemiologist

*Office of Surveillance and Epidemiology, Division of Risk Management*

Jason Bunting, Pharm.D., Pharmacist  
Kim Lehrfeld, Pharm.D., Pharmacist

*Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis*

Kim Defronzo, Pharm.D., Pharmacist

*Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology*

John Senior, M.D., Medical Officer (Hepatologist)  
Carolyn Taback, M.D., Medical Officer

*Office of Medical Policy, Office of Medical Policy Initiatives*

Sharon R. Mills, RN, BSN, CCRP, Senior Patient Labeling Reviewer

*Office of New Drugs, Pediatric and Maternal Health*

Tammie Brent-Howard, M.D., Medical Officer

*Office of Planning & Informatics*

Kimberly Taylor, Operation Research Analyst

**EASTERN RESEARCH GROUP ATTENDEES**

 (b) (4), Independent Assessor

**ACTELION ATTENDEES**

Guy Braunstein, Head of Global Clinical Development  
Martine Clozel, Chief Scientific Officer  
Per Nilsson, Head of Strategic Development  
Alberto Gimona, Head of Global Clinical Science & Epidemiology  
Loic Perchenet, Director, Global Post Approval Studies  
Marisa Bacchi, Head of Biostatistics  
Patricia Sidharta, Senior Clinical Pharmacologist  
Ulrich Mentzel, Head of Clinical Development  
Frances Duffy-Warren, Head of US Regulatory Affairs  
Joyce Acbay, Senior Director, Regulatory Affairs  
Cheryl Czachorowski, Director, Drug Regulatory Affairs  
Rajiv Patni, Senior VP Medical

**Actelion (by phone):**

Sebastien Roux, Clinical Area Head  
Alex Treiber, Head of DMPK  
Manaud de Raspide, Senior Technical Project Leader  
Paul Lagarenne, Head of Drug Safety US  
Hani Mickail, Head of Drug Safety  
Ernie Ross, VP Market Access  
Sonja Pumpluen, Global Head of DRA  
Brian Hennessy, Senior Statistician

*External Consultants*

(b) (4)

**1.0 BACKGROUND**

Opsumit (macitentan) is an orally active dual endothelin (ET) ETA and ETB receptor antagonist proposed for the treatment of pulmonary arterial hypertension (PAH).

The development program to support macitentan for PAH is based on a single, pivotal trial: Protocol AC-055-302, entitled “SERAPHIN: Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome: A multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, Phase 3 study to assess the effects of macitentan on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension.” Approximately 742 patients were randomized in a 1:1:1 ratio (macitentan 3 mg QD, macitentan 10 mg QD, placebo QD).

The primary endpoint was the time from start of treatment to the first mortality or morbidity (MM) event, defined as death, atrial septostomy, lung transplant, initiation of intravenous or subcutaneous prostanoids, or other worsening PAH.

The IND (77258) for macitentan for PAH was submitted on June 3, 2008. An End-of-Phase 2 meeting was held on August 17, 2007; a pre-NDA meeting took place on March 15, 2012.

A Special Protocol Assessment (SPA) was finalized with the Agency on December 1, 2007.

This 505(b)(1) application was submitted on October 19, 2012, and has a PDUFA goal date of October 19, 2013.

**2.0 LCM**

Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

## Hepatic Profile of Macitentan

Actelion said that they believe macitentan is safer than bosentan with regard to hepatic effects because macitentan has no direct toxicity on liver cells, fewer drug-drug interactions (because macitentan and its active metabolite do not interact with proteins involved in hepatic bile salt transport), and greater persistence of binding at the ET (endothelin) receptor because of the chemical structure of the drug.

Actelion said the International Liver Safety Board analyzed 59 cases of potential liver effects of macitentan. Forty-four of the 59 cases involved patients being treated for PAH. Most of the cases were confounded by biliary tract obstruction, heart failure, or concomitant medications. Dr. <sup>(b) (4)</sup> a consultant for Actelion and chair of the Safety Board, voiced his opinion that there is not a definite hepatic signal associated with macitentan.

Dr. Gordon asked if any of the potential cases noted above were rechallenged with macitentan. Dr. <sup>(b) (4)</sup> replied that one patient was rechallenged with macitentan and there seemed to be a relation between re-starting the drug and the hepatic effects, but it was difficult, given the patient's other medical factors, to say unequivocally that macitentan was causative.

Dr. Gordon asked why 10 mg was chosen as the dose for the SERAPHIN study. The applicant replied that in the phase 2 dose-ranging trials, the dose-response plateaued at 10 mg. They noted that 117 patients (many in trials not involving PAH) were studied at doses greater than 10 mg with very few adverse hepatic effects. Dr. Gordon expressed concern that were the drug to be approved, clinicians would push the dose above the recommended range and thus increase the likelihood of adverse hepatic effects.

Actelion presented a slide showing that increases in ALT or AST were very gradual over time, and were similar or even less than those observed with placebo. Dr. Southworth noted that compared with the clinical trial data available for bosentan at the time of its approval, there appeared to be fewer adverse hepatic events and lab values associated with macitentan based on the SERAPHIN data. It is unlikely that we would require a REMS for hepatic issues, but if the drug were to be approved, we would be likely to require a registry of macitentan patients with active reporting to the FDA.

Dr. Senior cautioned that serious liver effects were not usually detected in several hundred patients; rather at an incidence level of around 1 in 10000 patients. He recounted the experience of sitaxsentan, an ERA approved in Europe but withdrawn after serious hepatic events. Dr. Senior supported a registry with active reporting to FDA if the drug is approved.

## Clinical Pharmacology

### *Rifampin (strong CYP3A4 inducers)*

Actelion requested clarification on the recommendation from FDA to avoid co-administration of macitentan and strong CYP3A4 inducers (i.e., rifampin). The Division explained that the reduction in exposure to parent drug (~ 80% reduction) with strong CYP3A4 inducers would be expected to significantly reduce clinical efficacy, as such drugs would be expected to decrease exposures after a macitentan 10 mg dose to exposures similar to those observed with the 3 mg dose. The applicant asked if we had taken the total active moiety change into account. The reviewer acknowledged that the recommendation accounted for the total moiety. The Division also reminded the applicant that they are seeking approval for only the 10 mg dose (b) (4)

### *Ketoconazole/Ritonavir (strong CYP3A4 inhibitors)*

Actelion said that their analyses of ritonavir and other HIV drugs like lopinavir and macitentan show 2- to 3-fold the exposure with multiple doses, not 4-fold as predicted by FDA. They noted that macitentan has a good safety profile, even at doses up to 150 mg. Actelion noted that in the SERAPHIN trial, a comparison of the PK/PD relationship with adverse effects for macitentan showed little correlation, other than some minor hemoglobin changes.

The Division noted that the clinical experience with macitentan doses above 10 mg is very limited in the target population. Furthermore, the lack of any observed PK/PD relationships from the SERAPHIN trial may be because of the limitations caused by the timing of PK sample collection at the end of treatment. Hence co-administration of macitentan with strong CYP3A inhibitors like ketoconazole and ritonavir would not be recommended. (b) (4)

Of note, the Division explained that the PBPK (physiology based pharmacokinetic) modeling performed by the Agency did not consider any CYP3A4 induction properties of ritonavir, if any, and so provided a conservative estimate of about 4-fold the exposure to macitentan on repeat dosing with ritonavir 100 mg twice daily. There is limited information available on the CYP3A4 induction properties of ritonavir, especially at dose levels where it is used as a booster dose.

## Testicular Toxicity

(b) (4)  
Dr.

Southworth said that without reliable human data with macitentan, the labeling for macitentan will be similar to bosentan with respect to testicular toxicity.

## Subpart H Approval

Actelion asked if macitentan would be approved under Subpart H. Dr. Southworth said that we would provide an answer to the applicant's question after the meeting. (Post-Meeting

**Note:** in an email dated July 23, 2013, FDA conveyed that were the application to be approved, it would not be under Subpart H).

**Labeling**

Dr. Southworth said we hope to send draft labeling to the applicant in the next 2 or 3 weeks.

**Resubmission/Major Amendment**

Actelion said that they were willing to send the analyses that the Agency were requesting (b) (4) but questioned whether the submission of these new data would constitute a major amendment. (b) (4)

Dr. Southworth said the submission of the new data would be a major amendment to the NDA, (b) (4)

**LCM Regulatory Note**

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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MARY R SOUTHWORTH  
08/13/2013



NDA 204410

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Actelion Pharmaceuticals, LTD.  
c/o Actelion Clinical Research, Inc.  
Attention: Cheryl Czachorowski  
Director, Drug Regulatory Affairs  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08002

Dear Ms. Czachorowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for OPSUMIT (macitentan) Tablets.

We also refer to the Late-Cycle meeting (LCM) meeting scheduled for July 17, 2013. Attached is our background package, including our agenda for this meeting.

If you have any questions, please call:

Edward Fromm, RPh, RAC  
Regulatory Project Manager  
(301) 796-1072

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** July 17, 2013, 10 AM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1311  
Silver Spring, Maryland 20903

**Application Number:** NDA 204410  
**Product Name:** OPSUMIT (macitentan) Tablets  
**Indication:** Pulmonary Arterial Hypertension  
**Sponsor/Applicant Name:** Actelion Pharmaceuticals

### INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in response to the issues identified in this background package prior to this LCM or the Advisory Committee meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### OVERVIEW OF ISSUES IDENTIFIED TO DATE

#### CLINICAL

- 1)  (b) (4)
- 2) The results of the testicular safety study (AC-055-113) do not substantially change our belief (based on previously conducted preclinical and clinical studies with other endothelin receptor blockers) that testicular toxicity is a class effect.

- 3) [REDACTED] (b) (4). The age range of patients studied will be described in the clinical trials section.
- 4) The hepatic safety profile remains under review.

### **CLINICAL PHARMACOLOGY**

- 1.) The reduction in exposure to macitentan when given concomitantly with strong CYP3A4 inducers (i.e., rifampin) will likely result in a recommendation to avoid co-administration.
- 2.) Using PBPK modeling, exposure to macitentan would be projected to increase by 300% with repeated dosing of ketoconazole likely leading to a recommendation to avoid co-administration with ketoconazole (and other CYP3A4 inhibitors, such as ritonavir).

A single dose (10 mg) of macitentan when given with ketoconazole, administered as 400 mg once daily, increased the exposure ( $AUC_{\infty}$ ) and  $C_{max}$  to macitentan by about 2.3X and 1.3X respectively. The elimination half life of macitentan increased from about 14.1 hours to 28.5 hours, while that of the active metabolite ACT-132577 showed a modest increase (46.7 hours versus 58.6 hours). The observed DDI effects with ketoconazole could therefore be attributed to the effects on the elimination phase of macitentan. The applicant has developed a PBPK model that predicts the above described interaction. Using this model, the projected increase in exposure to macitentan on repeat dosing in presence of ketoconazole at steady state is ~ 3X. The long term safety information on macitentan on doses higher than 10 mg is limited.

#### *HIV drugs*

SERAPHIN study included only very few (~ 1 %) patients with HIV. Macitentan was not studied with lopinavir/ritonavir or other ritonavir containing HIV regimens. Ritonavir is a strong CYP3A4 inhibitor. PBPK simulations with the applicant's model were used to predict the potential impact of ritonavir (100 mg twice daily) on macitentan exposure. Since the CYP3A4 induction properties of ritonavir are not well characterized only its inhibitory effects were considered for PBPK simulations. Multiple dosing with 100 mg twice daily ritonavir and a single dose of 10 mg macitentan resulted in ~ 3X increase in macitentan exposure. Concurrent dosing of both drugs for 15 days showed ~ 4X increase in macitentan exposure at steady state. This observation is in agreement with the *in vivo* DDI observation with ketoconazole. Since ritonavir treatment for HIV will be for long term and there is no long term safety information on macitentan at doses above 10 mg, the predicted 3 to 4X increase in exposure with strong CYP3A4 inhibitors like ritonavir could be clinically significant

### **MEDICATION ERROR PREVENTION AND ANALYSIS**

DMEPA Information Request letter dated 06/14/2013.

**ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

Your proposed REMS is still under review.

## LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issue(s) – 60 minutes

Each issue will be introduced by FDA and followed by a discussion.

1. (b) (4)
2. Testicular toxicity
3. Age range of patients studied
4. Concomitant use of CYP3A4 inducers
5. Concomitant use of CYP3A4 inhibitors
6. Issues remaining under review:
  - Hepatic Safety Profile
  - REMS

3. Wrap up and Action Items –5 minutes

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
07/02/2013

NORMAN L STOCKBRIDGE  
07/02/2013