

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202813Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PARAGRAPH I CERTIFICATION

Beclomethasone Dipropionate Nasal Aerosol

In accordance with Section 505(b)(2)(A)(i) of the Federal Food, Drug and Cosmetic Act , as amended, the undersigned hereby certifies that to the best of our knowledge, and in Teva Branded Pharmaceutical Products R&D, Inc.'s opinion, there are no listed patents which claim the reference drug **Beconase AQ® (beclomethasone dipropionate monohydrate) Nasal Spray, 42 mcg.**

In accordance with Section 505(b)(2)(A)(i) of the Federal Food, Drug and Cosmetic Act , as amended, the undersigned hereby certifies that to the best of our knowledge, and in Teva Branded Pharmaceutical Products R&D, Inc.'s opinion, there are no listed patents which claim the reference drug **Vanceril DS (beclomethasone dipropionate) Inhalation Aerosol, 84 mcg.**

1.3.5.1 PATENT INFORMATION

Beclomethasone Dipropionate Nasal Aerosol is comprised of the same formulation as our currently marketed QVAR® (beclomethasone dipropionate) Inhalation Aerosol (NDA 20-911) and thus claims the same patents.

QVAR Inhalation Aerosol 40 and 80 mcg drug product has the following unexpired patent information for which patent certification forms FDA 3542a for each patent are being submitted:

- U.S. Patent No. **5,605,674** – Expiry Date: February 25, 2014
- U.S. Patent No. **5,683,677** – Expiry Date: November 04, 2014
- U.S. Patent No. **5,776,432** – Expiry Date: July 07, 2015

Patent Nos. 5,605,674, 5,683,677, 5,776,432 cover the formulation that is the subject of this new drug application for which approval is being sought. Applicant is a licensee of the respective listed patents.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 202813	
		NAME OF APPLICANT/NDA HOLDER Teva Branded Pharmaceutical Products R&D, Inc.	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME)			
ACTIVE INGREDIENT(S) Beclomethasone Dipropionate		STRENGTH(S) 80 mcg	
DOSAGE FORM Nasal Aerosol			
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.			
For hand-written or typewriter versions (only) of this report: 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.			
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.			
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.			
I. GENERAL			
a. United States Patent Number 5,605,674		b. Issue Date of Patent 02/25/1997	c. Expiration Date of Patent 02/25/2014
d. Name of Patent Owner Riker Laboratories, Inc.		Address (of Patent Owner) 3M Center #220	
		City/State St. Paul, MN	
		ZIP Code 55144	FAX Number (if available)
		Telephone Number	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.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
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 checked="" 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? 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) **5,605,674** 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? Yes 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.) For the treatment (b) (4) of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

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	
<p>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.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <p style="text-align: center; font-size: 1.2em;"><i>William Kiddell</i></p>	<p>Date Signed</p> <p style="text-align: center; font-size: 1.2em;">02/25/11</p>
<p>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).</p>	
<p>Check applicable box and provide information below.</p>	
<p><input checked="" type="checkbox"/> NDA Applicant/Holder</p>	<p><input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official</p>
<p><input type="checkbox"/> Patent Owner</p>	<p><input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official</p>
<p>Name William Kiddell</p>	
<p>Address Teva Branded Pharmaceutical Products R&D, Inc. 74 NW 176th St</p>	<p>City/State Miami, FL</p>
<p>ZIP Code 33169</p>	<p>Telephone Number (305) 575-6284</p>
<p>FAX Number (if available) (305) 575-6339</p>	<p>E-Mail Address (if available) william.kiddell@tevausa.com</p>
<p>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:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer (HFA-710) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>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.</i></p>	

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT			
<i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>			
		NDA NUMBER 202813	
		NAME OF APPLICANT/NDA HOLDER Teva Branded Pharmaceutical Products R&D, Inc.	
<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)			
ACTIVE INGREDIENT(S) Beclomethasone Dipropionate		STRENGTH(S) 80 mcg	
DOSAGE FORM Nasal Aerosol			
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.			
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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.			
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.			
1. GENERAL			
a. United States Patent Number 5,683,677		b. Issue Date of Patent 11/04/1997	c. Expiration Date of Patent 11/04/2014
d. Name of Patent Owner Riker Laboratories, Inc.		Address (of Patent Owner) 3M Center #220	
		City/State St. Paul, MN	
		ZIP Code 55144	FAX Number (if available)
		Telephone Number	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.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
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 checked="" 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? 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)
 5,683,677
 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? Yes 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.)
 For the treatment (b) (4); of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

5. No Relevant Patents

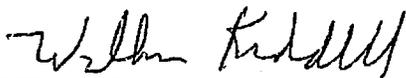
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably 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

02/25/11

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

William Kiddell

Address

Teva Branded Pharmaceutical Products R&D, Inc.
74 NW 176th St

City/State

Miami, FL

ZIP Code

33169

Telephone Number

(305) 575-6284

FAX Number (if available)

(305) 575-6339

E-Mail Address (if available)

william.kiddell@tevausa.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 (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

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: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 202813	
		NAME OF APPLICANT/NDA HOLDER Teva Branded Pharmaceutical Products R&D, Inc.	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME)			
ACTIVE INGREDIENT(S) Beclomethasone Dipropionate		STRENGTH(S) 80 mcg	
DOSAGE FORM Nasal Aerosol			
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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.			
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.			
1. GENERAL			
a. United States Patent Number 5,776,432		b. Issue Date of Patent 07/07/1998	c. Expiration Date of Patent 07/07/2015
d. Name of Patent Owner Minnesota Mining and Manufacturing Company		Address (of Patent Owner) 3M Corporate Headquarters	
		City/State St. Paul, MN	
		ZIP Code 55144	FAX Number (if available)
		Telephone Number (651) 733-1110	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.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
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 checked="" 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 type="checkbox"/> Yes	<input checked="" 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.		
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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 checked="" type="checkbox"/> Yes	<input 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

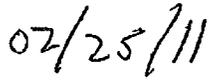
4. Method of Use

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) 5,776,432	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 checked="" 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.) For the treatment (b) (4) of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.	

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	
<p>6.1 <i>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.</i></p> <p>Warning: <i>A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</i></p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)</p> <div style="text-align: center; font-size: 1.2em;">  </div>	<p>Date Signed</p> <div style="text-align: center; font-size: 1.2em;">  </div>
<p>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).</p>	
<p>Check applicable box and provide information below.</p>	
<p><input checked="" type="checkbox"/> NDA Applicant/Holder</p> <p><input type="checkbox"/> Patent Owner</p>	<p><input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official</p> <p><input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official</p>
<p>Name William Kiddell</p>	
<p>Address Teva Branded Pharmaceutical Products R&D, Inc. 74 NW 176th St</p>	<p>City/State Miami, FL</p>
<p>ZIP Code 33169</p>	<p>Telephone Number (305) 575-6284</p>
<p>FAX Number (if available) (305) 575-6339</p>	<p>E-Mail Address (if available) william.kiddell@tevausa.com</p>
<p>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:</p> <p style="text-align: center;"> Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer (HFA-710) 5600 Fishers Lane Rockville, MD 20857 </p> <p style="text-align: center;"><i>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.</i></p>	

1.3.5.2 PATENT CERTIFICATION

PARAGRAPH I CERTIFICATION

Beclomethasone Dipropionate Nasal Aerosol

In accordance with Section 505(b)(2)(A)(i) of the Federal Food, Drug and Cosmetic Act , as amended, the undersigned hereby certifies that to the best of our knowledge, and in Teva Branded Pharmaceutical Products R&D, Inc.'s opinion, there are no listed patents which claim the reference drug **Beconase AQ® (beclomethasone dipropionate monohydrate) Nasal Spray, 42 mcg.**

EXCLUSIVITY STATEMENT

Beclomethasone Dipropionate Nasal Aerosol

The undersigned hereby certifies that, to the best of our knowledge and in Teva Branded Pharmaceutical Products R&D, Inc.'s opinion, there are no exclusivities in effect for **Beconase AQ® (beclomethasone dipropionate monohydrate) Nasal Spray, 42 mcg.**

The undersigned hereby certifies that, to the best of our knowledge and in Teva Branded Pharmaceutical Products R&D, Inc.'s opinion, there are no exclusivities in effect for **Vanceril DS (beclomethasone dipropionate) Inhalation Aerosol, 84 mcg.**

CLAIMED EXCLUSIVITY

Beclomethasone Dipropionate Nasal Aerosol

Teva Branded Pharmaceutical Products R&D, Inc. claims exclusivity, in accordance with 21 CFR 314.50(j) and with reference to 21 CFR 314.108(b)(4). Teva Branded Pharmaceutical Products R&D, Inc. certifies that this application contains new clinical investigations as set forth in 21 CFR 314.108(a), that are essential to approval of the application and were conducted or sponsored by Teva Branded Pharmaceutical Products R&D, Inc.

EXCLUSIVITY SUMMARY

NDA # 202813

SUPPL #

HFD #

Trade Name Qnasl Nasal Aerosol

Generic Name beclomethasone dipropionate

Applicant Name Teva Branded Pharmaceutical Products Research Development, Inc.

Approval Date, If Known March 23, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

Applicant did not specify the number of years.

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

YES NO

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

NA

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 19389 Beconase AQ

NDA# 20911 Qvar

NDA# 20486 Vanceril

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

BDP-AR-201, BDP-AR-301, BDP-AR-302, BDP-AR-303, BDP-AR-304

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

BDP-AR-201, BDP-AR-301, BDP-AR-302, BDP-AR-303, BDP-AR-304

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

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

Investigation #1 !
IND # 101639 YES ! NO
! Explain:

Investigation #2 !
IND # Same YES ! NO
! Explain:

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

Investigation #1 !
!

YES
Explain:

! NO
! Explain:

Investigation #2

!
!

YES
Explain:

! NO
! 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: Carol F. Hill
Title: RPM
Date: March 14, 2012

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Director, Division of Pulmonary, Allergy, and Rheumatology Products

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

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

/s/

CAROL F HILL
03/23/2012

BADRUL A CHOWDHURY
03/23/2012

1.3.3 DEBARMENT CERTIFICATION

On behalf of TEVA Branded Pharmaceutical Products R&D, Inc., the applicant, I hereby certify, pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 335a(k)) as amended by the Generic Drug Enforcement Act of 1992, that it did not and will not use in any capacity the services of any person who has been debarred pursuant to Section 306 of the Federal Food, Drug, and Cosmetic Act, in connection with this application.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202813 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Qnasl Established/Proper Name: beclomethasone dipropionate Dosage Form: nasal aerosol		Applicant: Teva Branded Pharmaceuticals Products R & D, Inc. Agent for Applicant (if applicable):
RPM: Carol F. Hill		Division: Pulmonary, Allergy, and Rheumatology Products
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" 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>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>NDA 19389, Beconase AQ</p> <p>NDA 20-486, Vanceril</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Utilizes the MDI canister coupled with a nasal actuator for nasal administration . Provides a second non-CFC based intranasal corticosteroid aerosol treatment for patients with AR. Product is for 80 mcg strength.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>March 24, 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ 	<input type="checkbox"/> Received
<ul style="list-style-type: none"> Application Characteristics² 	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</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 type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: 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 type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Public communications (<i>approvals only</i>) 	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² 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"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> 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> 	<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"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" 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>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	March 23, 2012
Officer/Employee List	
❖ 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>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP, March 23, 2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	March 21, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	May 24, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.

❖ 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>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	March 21, 2012
<ul style="list-style-type: none"> Original applicant-proposed labeling 	May 24, 2011
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	March 21, 2012
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	August 25, 2011 March 5, 2012, August 25, 2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM July 15, 2011 <input type="checkbox"/> DMEPA October 14, 2011 <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC February 2, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews January 30, 2012 Patient Labeling
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing/Memo September 9, 2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) March 15, 2012
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2) March 23, 2012
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
<ul style="list-style-type: none"> Date reviewed by PeRC <u>January 25, 2012</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" 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>)	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	March 20,16,15, 7, 5, & 2, February 28 & 3, 2012, November 17, October 18, September 12 and 9, August 5, July 13 and May 27, 2012
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg CMC-11/23/10 Clin F/U-11/17/10 Clin-10/18/10
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg Clin-9/9/09 CMC-6/8/09
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None March 23, 2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None March 9, 2012
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None March 22, 2012 (5)
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	March 9, 2012
• Clinical review(s) (<i>indicate date for each review</i>)	February 17, 2012 July 22, 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 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>)	Page 14 of Clinical Rev. 2-17-12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) 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>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <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 checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 14, 2012 July 7, 2011 Filing
Clinical Pharmacology <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 checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 14, 2012 July 1, 2011 Filing
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 17, 2012
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 2, 2012 July 1, 2011 Filing
❖ 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>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None February 7, 2012 BP February 6, 2012 November 9, 2011 Rev II August 30, 2011 Rev I June 28, 2011 Filing
❖ Microbiology Reviews <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 (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None P/T Review November 10, 2011
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		June 28, 2011
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<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 sites⁶)</i>		Date completed: February 3, 2012 <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
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ 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/

CAROL F HILL
04/02/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: March 22, 2012

FROM: Sandy Barnes, Chief, Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products

SUBJECT: Withdrawn of NDA for Vanceril (beclomethasone dipropionate)

TO: NDA 20486

We have concluded that Vanceril (beclomethasone dipropionate) (NDA 20486), approved December 24, 1996 **WAS NOT** withdrawn from sale for reasons of safety or effectiveness.

We carefully reviewed the files for records concerning the withdrawal of **Vanceril** from sale. Vanceril was a CFC Metered-Dose Inhaler and was removed from the market as part of the implementation of the Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol).

Based on a thorough search for records related to the withdrawal from sale of Vanceril and a careful review and evaluation of these records, we conclude that the drug **WAS NOT** withdrawn from sale for reasons of safety or effectiveness.

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/s/

SANDRA L BARNES

03/22/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 20, 2012

To: William Kiddell	From: Carol Hill, M.S. Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-575-6284	Phone number: 301-796-2300

Subject: NDA 202813 – Additional Comments to Teva’s Proposed Labeling dated March 9, 2012

Total no. of pages including cover: 22

Comments: Please confirm receipt.

Document to be mailed: YES xNO

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NDA 202813
Qnasl Nasal Aerosol

Dear Mr. Kiddell:

We are reviewing your proposed labeling dated March 9, 2012 for NDA 202813 submitted in response to the FDA correspondence dated March 7, 2012. Per our telephone conversation on March 19, 2012, we have the following additional comments (highlighted in yellow) in response to your proposed label. Please see the attached package insert. Please note that we may have additional labeling comments as we continue to review the labeling for your product.

We request that you submit draft labeling incorporating all FDA revisions along with your formal submission to the NDA by the close of business on March 20, 2012. If you have any questions, contact Carol Hill, Senior Regulatory Health Project Manager at 301-796-1226.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROL F HILL
03/20/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 16, 2012

To: William Kiddell	From: Carol Hill, M.S. Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-575-6284	Phone number: 301-796-2300

Subject: NDA 202813 – FDA Response to Teva’s Proposed Labeling dated March 9, 2012

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: YES xNO

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NDA 202813
Qnasl Nasal Aerosol

Dear Mr. Kiddell:

We are reviewing your proposed labeling dated March 9, 2012, for NDA 202813 submitted in response to the FDA correspondence dated March 7, 2012. We have the following comments. Please note that additional comments may be forthcoming as we continue to review the labeling for this product.

GENERAL COMMENTS

Minor format and wording changes were made in the label language including use of the preferred term clinical “trial” rather than (b) (4) and removal of the (b) (4)

HIGHLIGHTS

WARNINGS AND PRECAUTIONS

A minor wording change was made (use of term pediatric patients instead of (b) (4) in order to be consistent with the wording in Section 5.6.

ADVERSE REACTIONS

The adverse reaction (b) (4) was removed to be consistent with the information in Table 1.

FULL PRESCRIBING INFORMATION

Section 5 WARNINGS AND PRECAUTIONS

5.2 Glaucoma and Cataracts: The wording regarding the number of patients with increased intraocular pressure was revised to account for patients with mildly elevated IOP at baseline. (b) (4)

(b) (4) s it does not add any additional meaningful information.

5.3 Hypersensitivity Reactions Including Anaphylaxis: Your suggested re-wording is acceptable.

Section 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience:

- The number of patients in the short-term studies was revised to be consistent with the numbers reported in Table 1 based on information in Tables 3 and 6 in the Summary of Clinical Safety, pages 24 of 104 and 28 of 104, respectively.
- The number of patients with epistaxis (45) is based on the safety data submitted by Teva on Feb. 8, 2012 in response to our information request dated February 3, 2012. In that submission, subject 3280/3014 was classified from the original "nasal discomfort" to "epistaxis" in the amendment. In the AE list 16.2.7.1, page 7 of 145, the subject's AE was marked as moderate in severity.

Section 14 CLINICAL STUDIES

14.1 Seasonal and Perennial Allergic Rhinitis:

- The [REDACTED] (b) (4) have been removed. As stated previously, this is consistent with the labels of other marketed nasal corticosteroid products marketed to treat allergic rhinitis (Zetonna, Omnaris, Veramyst, Nasonex). This is also consistent with our comment at the End of Phase 2 meeting on September 9, 2009 in response to Teva's request for clarification for the need to assess rTNNS and iTNSS in the long term safety study. At that time we responded "that efficacy measures rTNSS and iTNSS are needed in the efficacy and safety trials in general" and "The Agency wants to have efficacy measures in the long term safety study primarily for the purpose of compliance monitoring" (End of Phase 2 meeting minutes dated October 7, 2009).
- The patient numbers were changed based on the removal of [REDACTED] (b) (4)
- Your proposal to delete [REDACTED] (b) (4) is acceptable.

CARTON AND CONTAINER

Your proposed Carton and Container labeling is acceptable

PATIENT INSTRUCTION SHEET

Your proposed patient instructions sheet is acceptable.

Submit revised draft labeling by March 20, 2012. If you have any questions, please contact Carol Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LADAN JAFARI
03/16/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2012

To: William Kiddell	From: Carol Hill, M.S. Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-575-6284	Phone number: 301-796-2300

Subject: NDA 202813 – Information Request

Total no. of pages including cover: 4

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NDA 202813
Teva Branded Pharmaceutical R & D Products, Inc.
Qnasl (beclomethasone dipropionate)

Dear Mr. Kiddell:

In your submission dated May 24, 2011 for NDA 202813, you proposed to conduct pediatric studies in patients 2 to 12 years of age. As discussed at the teleconference held on March 15, 2012, we request that you submit your commitment to conduct these pediatric trials and provide the final protocol submission date, trial completion date and the final report submission date for each of the studies listed below.

PMR-1: Conduct a 2-week double-blind, placebo-controlled dose-ranging trial in children 6-11 years of age with seasonal allergic rhinitis. At least 2 doses of BDP-HFA will be evaluated.

Trial Completion: Month Year

Final Report Submission:

PMR-2: Conduct a 12-week double-blind, placebo-controlled safety and efficacy trial in children 6-11 years of age with perennial allergic rhinitis.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

PMR-3: Conduct a 6-week double-blind, placebo-controlled trial to assess the effects of BDP-HFA on the HPA axis in children 6-11 years of age with perennial allergic rhinitis.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

PMR-4: Conduct a 12-week double-blind, placebo-controlled safety trial in children 2-5 years of age with perennial allergic rhinitis.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

PMR-5: Conduct a 6-week double-blind, placebo-controlled trial to assess the effects of BDP-HFA on the HPA axis in children 2-5 years of age with perennial allergic rhinitis.

Final Protocol Submission:
Trial Completion:
Final Report Submission:

Provide the requested information via email by COB on March 20, 2012. Also, formally submit this information to the application. If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Drafted by: CHill/March 15, 2012
Clearance: Jafari/March 15, 2012
 Seymour/March 15, 2012
 Durmowicz/March 15, 2012
Finalized: CHill/March 15, 2012

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/s/

CAROL F HILL
03/15/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2012

To: William Kiddell	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-575-6284	Phone number: 301-796-2300

Subject: NDA 202813 – FDA Response to Teva’s Proposed Labeling dated March 1 & 4, 2012

Total no. of pages including cover: 5

Comments: Please confirmed receipt

Document to be mailed: YES xNO

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Dear Mr. Kiddell:

We are reviewing your proposal for NDA 202813, submitted via email on March 1, 2012, in response to our February 28, 2012 correspondence. We have the following preliminary comments. Your proposal submitted via email on March 4, 2012 regarding the PPI is acceptable. Please note that additional comments will be forthcoming as we continue to review the labeling for this product. Deletions are noted as strikethrough and additions are underlined.

Proposed Change No. 1

Section 5.3 Hypersensitivity Reactions Including Anaphylaxis

(b) (4)

The above wording does not differentiate the AEs observed in the QNASL Nasal Aerosol clinical program vs. the AEs reported for other beclomethasone dipropionate products. We were unable to find an anaphylaxis AE in the QNASL Nasal Aerosol safety database. Therefore, to more accurately reflect the clinical data, Teva proposes the following wording:

*Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, and rash, have been reported following administration of beclomethasone dipropionate nasal and inhalationally administered products. Angioedema, urticaria, and rash, have been reported following administration of QNASL Nasal Aerosol. Discontinue QNASL Nasal Aerosol if any such reactions occur [see *Contraindications (4)*].*

(b) (4)

FDA Response:

See additions and deletions noted in the above paragraph.

Proposed change No. 2

In section 6.1 Clinical Trials Experience, Table 1, Adverse Events With $\geq 1\%$ Incidence and Greater than Placebo in QNASL Nasal Aerosol-Treated Patients with Seasonal or Perennial Allergic Rhinitis in Controlled Clinical Trials of 2 to 6 Weeks Duration are presented. (b) (4) did not occur in $\geq 1\%$ of patients with 320 mcg/day QNASL dose or placebo and Teva proposes removing this adverse reaction from the Table to accurately represent the data.

FDA Response:

We agree to delete (b) (4)

Proposed change No. 3
Section 8.4 Pediatric Use

In section 8.4 Pediatric Use, Teva would like to add clarifying language to the text in the third paragraph to read:

A 12 month randomized controlled clinical trial evaluated the effects of QVAR, an orally inhaled HFA beclomethasone dipropionate (b) (4) without a spacer versus chlorofluorocarbon-propelled (CFC) BDP with a large volume spacer on growth in children with asthma ages 5-11.

FDA Response:

We agree with the revised language.

Proposed change No. 4
Section 14 CLINICAL STUDIES

(b) (4)

FDA Response:

(b) (4)

We will discuss this issue further internally, but it is likely that we will continue to be consistent with what we have done for similar products.

Proposed change No. 5
Section 14 CLINICAL STUDIES

(b) (4)

Teva proposes removal of the above sentence in Section 14 (b) (4)

FDA Response:

We will discuss this issue further and respond in a future correspondence.

If you have any questions, contact Carol F, Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Drafted by: CHill/March 6, 2012

Clearance: Jafari/March 6, 2012

Durmowicz/March 6 2012

Finalized: CHill/March 7, 2012

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/s/

CAROL F HILL
03/07/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 5, 2012

To: William Kiddell	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: Teva Branded Pharmaceuticals Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-575-6284	Phone number: 301-796-2300

Subject: NDA 202813 – Information Request

Total no. of pages including cover: 3

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NDA 202813
Teva Branded Pharmaceutical R & D Products, Inc.
Qnasl (beclomethasone dipropionate)

Your submissions dated May 24, 2011, is currently under review. We have the following comment and request for information.

You cited reliance and provided patent certification for NDA 19-389, Beconase; however you need to cite reliance and provide patent certification to address reliance on Vanceril, NDA 20-486 since NDA 20-911 was a 505 (b)(2) application that relied on NDA 20-486. Submit an amendment to your pending NDA that identifies Vanceril as a listed drug relied upon for approval and provide an appropriate patent certification or statement accordingly.

Provide this information by COB on March 9, 2012. Also email a copy of the submission. If you have any questions, contact Carol Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Drafted by: CHill/March 5, 2012
Clearance: Jafari/March 5, 2012
Finalized: CHill/March 5, 2012

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/s/

CAROL F HILL
03/05/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 2, 2012

To: William Kiddell	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: Teva Branded Pharmaceuticals Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-575-6284	Phone number: 301-796-2300

Subject: NDA 202813 – Labeling Revisions III

Total no. of pages including cover: 15

Comments: Please confirm receipt.

Document to be mailed: YES xNO

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NDA 202813
Teva Branded Pharmaceutical R & D Products, Inc.
Qnasl (beclomethasone dipropionate)

Dear Mr. Kiddell:

Your submissions dated May 24 and December 13, 2011, are currently under review. We have attached the following proposed recommended revisions to the patient package insert (PPI). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Send revised draft labeling of the PPI by March 7, 2012. If you have any questions, please contact Carol Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROL F HILL
03/02/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: Tuesday, February 28, 2012

To: William Kiddell	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-75-6339	Phone number: 301-796-1226
Subject: NDA 202813 – Labeling Revisions II	

Total no. of pages including cover: 20

Comments: Please acknowledge your receipt.

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NDA 202813
Teva Branded Pharmaceutical R & D Products, Inc.
Qnasl (beclomethasone dipropionate)

Dear Mr. Kiddell:

Your submissions dated May 24 and December 13, 2011, are currently under review. We have the following proposed recommended revisions to the labeling. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forth coming.

General Comment

We have reviewed your proposed prescribing information for QNASL Nasal Aerosol. Due to the large number of edits we are sending you a clean FDA draft version of the QNASL Nasal Aerosol that contains the FDA-suggested label edits. Please use this version to make additional edits. Also, please check and confirm the demographic and adverse reaction data as minor edits have been made based on recently submitted data submitted as well as FDA internal analyses. If changes are made, please support them by citing where the relevant data can be found in the NDA submission.

Section 1 Indications and Usage

1.1: The efficacy data for QNASL support the indication for treatment of nasal symptoms of allergic rhinitis.

Section 5 Warnings and Precautions

Warnings and Precautions are listed in decreasing order of importance and is consistent with the order for similar recently approved products.

Section 8 Use in Specific Populations

8.4 Pediatric Use:

1. Confirm the total number of pediatric patients age 12-17 years (b) (4) enrolled in Studies 201, 301, 302, 303, and 304.
2. Growth study data from the QVAR program are included.

Section 14 Clinical Studies

14.1 Seasonal and Perennial Allergic Rhinitis:

3. Tables 2 and 3 have been revised to depict clinically relevant data. (b) (4)
[Redacted]
4. [Redacted] (b) (4)

Carton Labeling (Trade and Professional Sample)

5. The statement of strength lacks prominence. Increase the space between the dosage form (nasal aerosol) and strength (80 mcg per spray) and place the strength (80 mcg per spray) in bold font.
6. Both side panels contain a dosage statement (i.e., “Recommended Dosage: Two sprays...” and (b) (4) This information is redundant; therefore, delete the (b) (4) statement.
7. On one of the side panels, the strength immediately follows the dosage form. Place the statement of strength on the line below the dosage form as is done on the other three panels. In order to accommodate the move of the statement of strength, consider condensing the manufacturing statement and removing the trademark statement.

Container Labels (Trade and Professional)

8. The statement of strength (80 mcg per spray) lacks prominence. Place the strength in bold font.
9. Debold the storage statement and ensure it is consistent with what is stated on the carton and in the insert labeling. Consider condensing the manufacturing statement in order to accommodate the full storage statement.

Submit revised draft labeling incorporating our comments and recommendations. Provide your response to by COB on Tuesday, March 6, 2012. If you have any questions, please contact Carol F. Hill, Senior Regulatory Project Manager, at 301-796-1226.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROL F HILL
02/28/2012

Hill, Carol

From: Greeley, George
Sent: Wednesday, February 08, 2012 2:45 PM
To: Hill, Carol
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Chowdhury, Badrul A
Subject: NDA 202-813 Beclomethasone Dipropionate

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Carol,

The email serves as confirmation of the review for the Beclomethasone Dipropionate nasal aerosol product conducted by the PeRC PREA Subcommittee on January 25, 2012.

The Division presented a partial waiver for patients ages birth through 23 months because the product would be unsafe, a deferral in patients 2-11 years because the product is ready for approval in adults and an assessment for those patients 12-17 years of age. This product has been studied for the treatment of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.

The PeRC agreed with the Division to grant a partial waiver from birth through 23 months and a deferral for those patients 2-11 years. There are local (nasal) safety concerns with the use of corticosteroids via nasal inhalation in children below 2 years of age. In addition, appropriate alternatives to corticosteroid nasal sprays for use in children below 2 years of age. For patients 12-17 years an adequate assessment has been submitted.

The PeRC recommends the following:

- *The phrase (b)(4) listed in the label is insufficient and so the Division should be more specific regarding what the safety concerns are for this drug.*
- *The Division shall review the safety concern regarding two year olds and their nasal cavity not being advanced.*

The pediatric record is attached for Beclomethasone Dipropionate.



1_Pediatric_Record.pdf (62 KI)

Thanks,

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 3, 2012

To: William Kiddell	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-75-6339	Phone number: 301-796-2300

Subject: NDA 202813 – Clinical Information Request

Total no. of pages including cover: 4

Comments: We request your response by February 7, 2012

Document to be mailed: YES xNO

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NDA 202813
 Teva Branded Pharmaceutical R & D Products, Inc.
 Qnasl
 February 3, 2012

Dear Mr. Kiddell

Your New Drug Application (NDA), NDA 202813 dated May 24, 2011 is currently under review. We have the following request for information.

In reviewing the data submitted in your NDA, we found that key local adverse events were presented inconsistently in terms that were unclear to readers, such as NASAL DISORDER, NASAL MUCOSAL DISORDER, NASAL SEPTUM DISORDER, MUCOSAL EROSION, etc. To assist our review process, reclassify the treatment emerged local AEs as listed in following tables.

For each individual study of 2 – 6 week duration (201, 301, 302) and combined data from all 3 studies

	80 mcg N=	160 mcg N=	320 mcg N=	Placebo N=	Total N=
	n (%)	n (%)	n (%)	n (%)	n (%)
Nasal Mucosal/Septum Disorders					
Non-ulcerative lesions					
Irritation					
Abrasion/excoriation/scabs					
Erosions/ulcerations					
Erosions					
Ulcerations					
Other (specify)					

For the long term safety study (303)

	320 mcg N=	Placebo N=	Total N=
	n (%)	n (%)	n (%)
Nasal Mucosal/Septum Disorders			
Non-ulcerative lesions			
Irritation			
Abrasion/excoriation/scabs			
Erosions/ulcerations			
Erosions			
Ulcerations			
Other (specify)			

We request that you submit your response by COB on February 7, 2012 via facsimile (301-796-9728) or email (carol.hill@fda.hhs.gov). You must also formally submit your response to the application. If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Drafted by: CHill/February 3, 2012
Clearance: Jafari/February 3, 2012
Wang/February 2, 2012
Durmowicz/February 2, 2012
Finalized: CHill/February 3, 2012

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/s/

CAROL F HILL
02/03/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 17, 2011

To: William Kiddell Senior Manager, Regulatory Affairs, GRR&D	From: Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: willam.kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-575-6284	Phone number: 301-796-2300

Subject: NDA 202813 – Label Revisions I

**Total no. of pages including
cover:** 4

Comments: Please acknowledge receipt

Document to be mailed: YES xNO

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Teva Branded Pharmaceuticals Products R & D, Inc.
Qnasl (beclomethasone dipropionate)
NDA 202813

Dear Mr. Kiddell:

Your submission dated May 24, 2011, to NDA 202813, is currently under review. We have the following proposed recommended revisions to the labeling. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

The following comments pertain to the Container Label and Carton Labeling (professional sample and retail).

1. Revise the presentation of the proprietary name from all upper case letters (QNASL), to title case (Qnasl) to improve readability.
2. The ingredient information should appear together, without any intervening written, printed or graphic matter per 21 CFR 201.10(a). [REDACTED] (b) (4)
[REDACTED] Revise the presentation of the proprietary name, so that the entire name is presented in only one color.
3. Revise "(Beclomethasone Dipropionate) Nasal Aerosol" so that the active ingredient and dosage form have the same size and font.
4. Add the product strength to follow the established name in the following manner: Qnasl (Beclomethasone Dipropionate) Nasal Aerosol 80 mcg per spray.
5. On the principal display panel, revise [REDACTED] (b) (4) to read "For Intranasal Use with Qnasl Actuator Only" to prevent misuse of the nasal actuator device with other products.

The following comments pertain to the Container Label (professional sample and retail).

6. Unbold "Rx only" and "120 Metered Sprays" since these statements are overly prominent.
7. Replace [REDACTED] (b) (4) with a statement regarding the usual dosage, such as "See package insert for dosage information" for clarity.

8. Since the font is small, the TM superscript located after Qnasl makes the 'L' look like an 'E'. Move the TM further away from Qnasl to prevent any misinterpretation of the name.

The following comments pertain to the Carton Labeling (professional sample and retail).

9. In order to accommodate the strength expression after the established name, remove or minimize (b) (4)
10. Unbold and decrease the font size of "120" metered sprays since it is overly prominent.
11. The (b) (4) color of "120 metered sprays" and "8.7 g net contents" on a blue background and the (b) (4) color of the NDC number on a yellow background are hard to read. Change the font color for better contrast with the background.
12. Relocate "For optimal results, the device should be at room temperature when used" to immediately follow the statement "Store at 25°C (77°F); excursions are permitted between 15 and 30°C (59 and 86°F). Do not expose to temperatures higher than 49°C (120°F)" to ensure all information regarding storage are presented on the same panel.

If you have any questions, please contact Carol Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Drafted by: CHill/November 8/15, 2011

Clearance History: Jafari/November 15, 2011

Neshiewat (Villanueva)/November 16, 2011

Chan/November 16, 2011

Bertha/November 16, 2011

Schroeder/November 16, 2011

Wang/November 16, 2011

Durmowicz/November 16, 2011

Finalized: CHill/November 17, 2011

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/s/

CAROL F HILL
11/17/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 18, 2011

To: William Kiddell Senior Manager, Regulatory Affairs, GRR&D	From: Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R & D, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: William.Kiddell@tevapharm.com	Fax number: 301-796-9728
Phone number: 305-575-6339	Phone number: 301-796-2300

Subject: NDA 202813 - Statistical Information Request

Total no. of pages including cover: 2

Comments: Please acknowledge receipt

Document to be mailed: YES xNO

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NDA 202813
Teva Branded Pharmaceutical Products R & D, Inc.
Beclomethasone Dipropionate Nasal Spray

Dear Mr. Kiddel:

Please refer to your new drug application (NDA) received on May 24, 2011. We have the following request for information:

For study protocol BDP-AR-302, you provided the following datasets: ADSL (- Sites 1375-1409), ADDY1-Diary (Efficacy.Sites 1375-1381) and ADDY2-Diary (Efficacy.Site -1400-1409). ADDY1-Diary appears to cover sites 1375-1388 and ADDY2-Diary - sites 1400-1401. When the efficacy datasets, ADDY1 and ADDY2 are merged, sites 1389-1399, 1402-1409, and 999 are missing. Provide the entire efficacy dataset for all the sites in the study.

We request that you provide your response by COB on November 2, 2011. If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-796-1226.

Drafted by: CHill/October 18, 2011
Clearance History: Jafari/October 18, 2011
Hamilton/October 18, 2011
Buenconsejo/October 18, 2011
Finalized: CHill/October 18, 2011

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/s/

CAROL F HILL
10/18/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, September 12, 2011 10:04 AM
To: William Kiddell
Subject: FW: Beclomethasone Nasal Aerosol (NDA 202813) IR-9/12/2011

Dear Mr. Kiddell,

We are reviewing the Biopharmaceutics section of your NDA and have following information request. We request a response no later than September 30, 2011. Please acknowledge the receipt and confirm, if a response will be received by September 30, 2011.

- Submit the following information as SAS Transport files. Data in these tables should be arranged in columns as shown in examples. This information is needed to confirm the results of the in vitro BE analysis.

Table 1. Single Actuation Content through Container Life

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
CONTAIN	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
<i>ACTUAT</i>	<i>Spray Number</i>	<i>Numeric</i>	<i>Numeric values</i>	<i>Actual spray number corresponding to B or E life stages.</i>
AMOUNT	Actual delivered amount of drug mass	Numeric	Numeric values	Drug mass per single actuation
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Example

PRODUCT	SECTOR	LOT	CONTAIN	ACTUAT	AMOUNT	PCTLABEL
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 2. Priming and Repriming

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning. Lifestage not specified for repriming data.
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
CONTAIN	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
<i>ACTUAT</i>	<i>Spray Number</i>	<i>Numeric</i>	<i>Numeric values</i>	<i>Actual spray number</i>
AMOUNT	Actual delivered amount of drug mass	Numeric	Numeric values	Drug mass per single actuation
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Example

PRODUCT	SECTOR	LOT	CONTAIN	ACTUAT	AMOUNT	PCTLABEL
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 3. Droplet Size Distribution by Laser Diffraction

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
DISTANCE	Distance	Numeric	Numeric values	Distance from the actuator tip to the laser beam (cm)
CONTAIN	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref at each distance).
ACTUAT	Spray Number	Numeric	Numeric values	Actual spray number corresponding to B or E life stages.
D10	D10	Numeric	Numeric values	D10
D50	D50	Numeric	Numeric values	D50
D90	D90	Numeric	Numeric values	D90
SPAN	SPAN	Numeric	Numeric values	SPAN calculated as $((D90-D10)/D50)$

Example

PRODUCT	SECTOR	LOT	DISTANCE	CONTAIN	ACTUAT	D10	D50	D90	SPAN
TEST	B	1234		1					
				2					
				3					
				4					
				5					
				6					
				7					
				8					
				9					
				10					

Table 4. Plume Geometry

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning
LOT	Lot number	Alphanumeric/N umeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAIN	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
HEIGHT	Height	Numeric	Numeric values	Plume height
WIDTH	Width	Numeric	Numeric values	Plume width
ANGLE	Angle	Numeric	Numeric values	Cone angle of one side view at one delay time

Example

PRODU CT	SECTOR	LOT	CONTAIN	HEIGHT	WIDTH	ANGLE
TEST	B	1234	1			
			2			
			3			
			4			
			5			
			6			
			7			
			8			
			9			
			10			

Table 5. Spray Pattern

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B, or E	B=Beginning; E=End
LOT	Lot number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
DISTANCE	Distance	Numeric	Numeric values	Distance from the actuator tip to the laser beam (cm)
CONTAIN	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref at each distance).
ACTUAT	Spray Number	Numeric	Numeric values	Actual spray number corresponding to B or E life stages.
DMAX	Dmax	Numeric	Numeric values	Dmax
DMIN	Dmin	Numeric	Numeric values	Dmin
OVALITY	Ovality	Numeric	Numeric values	Ovality ratio (Dmax divided by Dmin)
AREA	Pattern Area	Numeric	Numeric values	Pattern area

Example

PROD	SECTOR	LOT	DISTANCE	CONTAIN	ACTUAT	DMAX	DMIN	OVALITY	AREA
TEST	B	1234		1					
				2					
				3					
				4					
				5					
				6					
				7					
				8					
				9					
				10					

Table 6. Drug in Small Particles/Droplets by Cascade Impactor

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
SECTOR	Lifestage	Character	B	B=Beginning
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAIN	Bottle or container Number	Numeric	Numeric values	Identifier for bottle or container. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
AMT_ACT	Actual Amount of drug	Numeric	Numeric value	Actual amount of drug per spray
AMT_TOT	Total Amount at all Stages and Accessories	Numeric	Numeric values	Drug mass collected on all Stages and Accessories
AMT_LT 9	Amount for Equal or Less Than 9 mm	Numeric	Numeric values	Drug mass collected for particles equal or less than 9 mm
MB_TOTAL	Mass Balance Total	Numeric	Numeric value	Mass balance for total drug mass collected on all stages and accessories

example:

PRODUCT	SECTOR	LOT	CONTAIN	AMT ACT	AMT TOT	AMT LT 9	MB TOTAL
TEST	B	1234	1				
			2				
			3				
			4				
			5				
			6				
			7				
			8				
			9				
			10				

Thank you

Swati Patwardhan
 Regulatory Health Project Manager for Quality
 Office of New Drug Quality Assessment (ONDQA)
 Center of New Drug Evaluation and Research
 Phone: 301-796-4085
 Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
09/12/2011



(b) (4)

NDA 202813
NDA 21457/S-03 and S-013

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Teva Branded Pharmaceutical Products R&D, Inc.
74 NW 176th Street
Miami, FL 33169

Attention: Axel G. Perlwitz, Ph.D
Associate Director, Regulatory Affairs

Dear Dr. Perlwitz:

Please refer to your New Drug Application (NDA) or Supplemental NDA (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following products.

(b) (4)

NDA 202813 beclomethasone dipropionate Nasal Aerosol, 80 mcg
NDA 21457/S-03 and S-013 Proair HFA (albuterol sulfate) Inhalation Aerosol

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

NDA 202813
NDA 21457/S-03 and S-013
Page 2

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Christine Chung, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SANDRA L BARNES
09/09/2011



NDA 202813

DISCIPLINE REVIEW LETTER

Teva Branded Pharmaceutical Products R&D, Inc
Attention: William Kiddell
Sr., Manager, Regulatory Affairs
74 NW 176th Street
Miami, FL 33169

Dear Mr. Kiddell:

Please refer to your May 24, 2011 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnasl (beclomethasone dipropionate) Nasal Aerosol.

We also refer to your submissions dated August 2, and August 4, 2011.

Our review of the CMC section of your submission is complete, and we have identified the following deficiencies:

1. Provide follow-up information on the identification of the [REDACTED] (b) (4) that were identified by the secondary ion mass spectrometry for the foreign particulates filtered from sampled canisters as described in the drug product characterization report.
2. Provide an update with data on the efforts to identify the unspecified leachables compounds found by the HPLC method 07-002174 that were possibly above the Safety Concern Threshold. Provide a summary of the control strategy and any necessary toxicological evaluation.
3. The drug product release and stability acceptance criteria for foreign particulates appears to be in terms of counts per actuation. However, the data provided to justify the acceptance criteria in P.5.6 (p. 17 of 211) would appear to be on a count per canister basis [statistical analysis Section 3.2.P.5.6 Setting Finished Product and Stability Specification Limits for BDP Nasal Aerosol at 24 Months (QDP0031006)]. Provide clarification of this apparent discrepancy and make the appropriate modifications as necessary to the specification acceptance criteria, the method, or the justification in section P.5.6. If the acceptance criteria are truly in terms of counts per actuation, which seems unlikely [REDACTED] (b) (4) [REDACTED] provide a rationale from a [REDACTED]

safety perspective that justifies the proposed acceptance criteria.

4. We acknowledge that you have based your aerodynamic particle size distribution (APSD) acceptance criteria on an extrapolation to 24 months from data (b) (4)
[REDACTED]
[REDACTED] re-analyze these data and revise the acceptance criteria accordingly.
5. Revise the leakage rate acceptance criteria to that which are applied to your QVAR product, which has the same canister/valve/formulation. Otherwise, a 24 month expiry period will not be allowable for this product, considering the minimal fill allowed (b) (4) the maximum leakage rate allowed (b) (4) the target shot weight (59 mg), and the necessity for some overfill due to some undeliverable volume of formulation.
6. It is recommended that you revise the Appearance Internal method QDP0029008 so that it includes a photomicrograph of a typical sample that does not contain any noted foreign particulates.
7. Revise the drug product specification to include acceptance criterion for the identification of the drug substance by infrared spectrophotometry, e.g., the sample spectrum exhibits absorbance maxima only at the same wavelengths as that for the reference standard.
8. From table 4 of the stability report (Stability Report – Exhibit (120-Dose) it does not appear that you would be determining the shot weight for 2nd tier spray content uniformity samples. It is recommended that you revise your procedures to collect this data on 2nd tier samples when you find that you need to proceed beyond the 1st tier SCU testing.
9. You have indicated in the method validation report for the APSD method that you will be undertaking a sample stability study to determine the adequate storage conditions for future samples. Provide the results of these studies and revise the method to include the appropriate recommendations that are determined as appropriate, based on the results.
10. Revise the acceptance criteria for the counter check (method QDP0026668) such that it accounts for the appearance and the persistence of the (b) (4) as indicated in the method.
11. We acknowledge the proposed (b) (4) expiry period for the drug product, regardless of your statistical evaluation of the spray content uniformity data which currently only supports an expiry period of (b) (4) based on the product from one batch stored in the valve up orientation. Reanalyze updated stability data for this parameter to confirm the appropriateness of the proposed expiry

period. Depending on the results, you may also need to include product in the valve up orientation in the routine post-approval stability protocol.

12. Revise the post-approval stability protocol to indicate that you will provide updated stability data in annual reports, regardless of whether or not you propose an extension of the expiration dating period.
13. The following are preliminary comments on the labels and labeling.
 - a. As the drug product only has a single strength, it is not necessary to include the strength in the name. Make the appropriate revisions to the labels and labeling.
 - b. As IVAX (Waterford, Ireland) does not perform any of the applicable manufacturing operations listed in 21 CFR 201.1(b), and 3M performs all of the operations listed in that regulation required to manufacture the drug product (b)(4) revise the labels and labeling to indicate that the drug product is manufactured by 3M.
 - c. Revise the storage statement on the labels (canister and carton) to be consistent with what is included in the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert. For the canister label, reference to the package insert may be used to reference the allowed excursion range.
 - d. Rather than referring, on the carton, to the package insert for the dosage and administration information, it is recommended that you indicate the recommended dosage as two sprays in each nostril once a day.
 - e. Revise the carton and canister (if space allows) labels to include a statement that the drug product canister should only be used with the QNASL™ actuator only, e.g., For nasal inhalation with QNASL™ actuator only.
 - f. Revise the DESCRIPTION section of the package insert to provide the full name of the drug substance, i.e., beclomethasone dipropionate. (b)(4)
(b)(4)
 - g. Revise the DESCRIPTION section of the package insert to provide a statement indicating the amount of medication delivered, e.g., each actuation delivers 'x' mcg of (b)(4) in 'w' mg of solution from the valve and delivers 80 mcg of (b)(4) from the nasal actuator.
 - h. Revise the DESCRIPTION section of the package insert to directly

indicate the number of available actuations, i.e., 120 (currently implied by reference to the counter reading after priming).

- i. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the labeling to include a statement that the canister should only be used with the supplied actuator and not with any other actuator from similar drug products.
- j. With regard to the patient instructions leaflet, it is recommended that you include a statement instructing the patient to check to confirm that there are no foreign objects in the nasal actuator tip prior to use, as some patients may fail to use the protective dust cap.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other 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 not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager-Quality, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
09/09/2011



NDA 202813

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Teva Branded Pharmaceutical Products R&D, Inc.
74 NW 176th Street
Miami, Florida 33169

ATTENTION: William Kiddell,
Sr. Manager, Regulatory Affairs, GRR&D

Dear Mr. Kiddell:

Please refer to your New Drug Application (NDA) dated May 24, 2011, received May 24, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Beclomethasone Dipropionate Nasal Aerosol, 80 mcg per actuation.

We also refer to your May 27, 2011, correspondence, received May 27, 2011, requesting review of your proposed proprietary name, Qnasl. We have completed our review of the proposed proprietary name, Qnasl and have concluded that it is acceptable.

The proposed proprietary name, Qnasl, 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 May 27, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Carol Hill, at (301) 796-1226.

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

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/s/

CAROL A HOLQUIST
08/25/2011



NDA 202813

FILING COMMUNICATION

Teva Branded Pharmaceutical Products R & D, Inc.
74 BW 176th Street
Miami, FL 33169

Attention: William Kiddell
Senior Manager, Regulatory Affairs, GRR&D

Dear Mr. Kiddell:

Please refer to your New Drug Application (NDA) dated May 24, 2011, received May 24, 2011 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for beclomethasone dipropionate (BDP) nasal aerosol, 80 mcg.

We also refer to your amendment dated May 27, 2011.

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**. Therefore, the user fee goal date is March 24, 2011

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 20, 2012.

During our filing review of your application, we identified the following potential review issue.

1. We note that the proposed indication for BDP Nasal Aerosol is “for the treatment (b) (4) seasonal and perennial allergic rhinitis in adult and adolescent patients 12 years of age and older”, which implies (b) (4) of the proposed drug product. It is a review issue whether or not the data support this claim.

We are providing the above comment to give you preliminary notice of a potential review issue. 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.

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

The following comments pertain to the HIGHLIGHTS section:

1. There should be white space between each major heading.
2. The verbatim statement “Initial U.S. Approval XXXX” should be followed by the four-digit year in which the FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients.
3. Delete the manufacturer’s web address from the required adverse reactions verbatim statement.

General Comments

4. You submitted a 'patient instructions leaflet' and 'patient product instructions.' There appears to be duplicate information in these two documents. Clarify how these documents differ and how they will be packaged with the product.
5. We note that the May 27, 2011 submission referenced a 2010 model of the drug product. Provide an updated sample of the product, preferably with all proposed labels and labeling attached.

We request that you resubmit labeling that addresses these issues by August 29, 2011. 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.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if these requests are denied.

We note that you have submitted pediatric studies with this application for pediatric patients 12 to 17 yrs of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LYDIA I GILBERT MCCLAIN
08/05/2011
Acting Division Director

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Tuesday, July 12, 2011 2:33 PM
To: 'william.kiddell@tevausa.com'
Cc: 'Jacqueline Howard'
Subject: RE: Re: IR for NDA 202813

Hi Bill and Jackie,
We are reviewing the CMC section of above referenced NDA and request additional information as follows:

You have stated that the BDP Nasal Aerosol 80 mcg (120-dose) filled canister is the same canister and formulation as approved in NDA 20-911, S-019 for QVAR. As such, it would greatly expedite our review of the application if you would provide us a *detailed list*, with references to relevant parts of the application, of what differs between the CMC information that you have provided in module 3 in the current application from that which is currently applied in the manufacture and control of the approved 120 dose QVAR filled canister from S-019. For example, we noted that [REDACTED] ^{(b) (4)} is referenced for these two applications, as well as a discussion of additional [REDACTED] ^{(b) (4)} for the nasal aerosol product. The early provision of this detailed list will help us to efficiently review your application without duplication of previous effort.

Please acknowledge the receipt.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
07/13/2011



NDA 202813

NDA ACKNOWLEDGMENT

Teva Branded Pharmaceutical Products R&D, Inc.
74 NW 176th Street
Miami, FL 33169

Attention: William Kiddell
Senior Manager, Regulatory Affairs, GRR&D

Dear Mr. Kiddell:

We have received your New Drug Application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Beclomethasone Dipropionate Nasal Aerosol, 80 mcg/actuation

Date of Application: May 24, 2011

Date of Receipt: May 24, 2011

Our Reference Number: NDA 202813

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 July 23, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol F. Hill, M.S.
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CAROL F HILL
05/27/2011



IND 101-639

MEETING MINUTES

Teva Branded Pharmaceutical Product R&D, Inc.
Attention: William Kiddell
Senior Manager, Reg. Affairs
74 NW 176th Street
Miami, FL 33169

Dear Mr. Kiddell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BDP (beclomethasone dipropionate) HFA Nasal Aerosol.

We also refer to the telecon between representatives of your firm and the FDA on November 23, 2011. The purpose of the meeting was to discuss CMC and statistical quality programs to support the NDA for BDP (beclomethasone dipropionate) HFA Nasal Aerosol.

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

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.

Branch Chief, Branch VIII, Division III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: meeting minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Teva Branded Pharmaceutical Product R&D, Inc
Application Number:	IND 101,639
Product Name:	BDP (beclomethasone dipropionate) HFA Nasal Aerosol
Meeting Requestor:	William Kiddell
Meeting Type:	Type B
Meeting Category:	Pre-NDA CMC
Meeting Date and Time:	November 23, 2010, 2:00 to 3:00 PM
Meeting Location:	Teleconference
Received Briefing Package	October 22, 2010
Meeting Chair:	Prasad Peri, Ph.D.
Meeting Recorder:	Swati Patwardhan

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Office of New Drug Quality Assessment:

- Eric Duffy, PhD. Division Director, Division of New Drug Quality Assessment III
- Prasad Peri, PhD. Acting Branch Chief, Branch VIII
- Alan Schroeder, PhD. CMC Lead, Branch VIII
- Eugenia Nashed, PhD. CMC Reviewer, Branch VIII
- Swati Patwardhan, MS Regulatory Project Manager

Division of Pulmonary, Allergy, and Rheumatology Products

- Xu Wang, MD. Medical Officer

Office of Biometrics

- Meiyu Shen, PhD. Statistician
- Youngsook Joen, PhD. Statistician

EXTERNAL ATTENDEES:

Teva Branded Pharmaceutical Product R&D, Inc.

- Jason Liao, PhD. Director, Nonclinical Statistics
- Mary McKenry, MS Statistician, Biostatistics
- Xian-Ming Zeng, PhD. Senior Director Product Development
- Jade Ly, PhD. Associate Director, Product Development
- Steve Viti, PhD, MBA Senior Director, Regulatory Affairs
- Axel Perlwitz, PhD. Associate Director, Regulatory Affairs
- William Kiddell Senior Manager, Regulatory Affairs

1.0 BACKGROUND

BDP (beclomethasone dipropionate) HFA Nasal Aerosol, 80 mcg is being developed to treat (b) (4) seasonal and perennial allergic rhinitis. The canister is based on the QVAR Inhalation Aerosol, 80 mcg (NDA 20-911) approved for the maintenance treatment of asthma as prophylactic therapy. A meeting request for Pre-NDA CMC meeting was submitted on August 12, 2010 to discuss CMC and statistical quality programs to support the NDA for BDP (beclomethasone dipropionate) HFA Nasal Aerosol.

Teva proposed to discuss the following:
Finished Drug Product Release Specification
Drug Product Characterization Study Protocol
Bridging Study of BDP HFA 100 Dose and 120 Dose Canisters

After receipt of the preliminary responses, Teva requested that the face-to-face meeting be converted to a Teleconference.

2.0 DISCUSSION

2.1 Quality:

2.1.1 Teva proposes to reference the product development section for the canister in the QVAR® 20-911 application with permission from 3M to the product development report in volumes 3 to 5 (owned by 3M) of NDA 20-911? Teva has no rights to see this information and therefore cannot include this information in our application. Is this acceptable?

FDA Pre-meeting Response:

We expect a submission of full and cohesive drug product development section to the NDA. Although some early development data may be reproduced from the original NDA submission, we note that these data are more than twenty years old and some of it may be obsolete now. Address all changes that occurred in the development of drug product (formulation + cartridge + actuator + overwrap) from the pre-clinical to the to-be-marketed phase of development. Provide a table cross-linking the product changes to the pre-clinical, clinical and stability studies.

Teva Response and Request for Guidance:

The proposed canister for BDP HFA Nasal Aerosol contains exactly the same formulation, valve, and can as those originally approved in the QVAR NDA, submitted by 3M. The development of these components was described in the original QVAR NDA Development Report. Since then there have been no changes made to the formulation, valve and the canister. Therefore, Teva proposes only describing in the BDP HFA Nasal NDA, Development Report, the development work we performed starting with the development of the first version of the actuator through the proposed commercial actuator. Teva proposes **not** including a discussion of the studies performed to select the formulation, valve, or can that were originally conducted by 3M and included in the original QVAR NDA. **Is this approach acceptable?**

Meeting Discussion:

The NDA for QVAR was submitted in ~ 1998. The data and methods are almost 20 years old. We would like to see a comprehensive development section for your nasal drug product in relation to the proposed route of administration. We define the drug product as canister, valve, actuator, formulation, and secondary protective packaging, if any. Submission of development for the actuator only with reference to NDA 20-911 is not acceptable, because the NDA 20-911 has different development data. The NDA does not contain any development data for the nasal aerosol that you are developing and seeking approval for marketing. We will take into consideration the fact that the formulation is same. You may reproduce canister related data from the 20-911, as appropriate, and provide detailed references. However, a full discussion of the development of the drug product including appropriateness of the formulation, valve, actuator, storage conditions, priming, in-use conditions etc. should be submitted. We do not expect a complete developmental data for QVAR, but a cohesively written report linking the existing data as it applies for your drug product. Each part of the discussion should encompass (b) (4) to-be-marketed drug product (b) (4) 120 actuations) and the drug product used in the clinical studies. (b) (4)

The

Agency recommended that Teva Include performance data for 100 actuation product used in Phase 3 clinical trials. The later data does not need to be included in the calculation of the expiry period. For the drug product used in the clinical trial stability studies are required and data should be submitted in the NDA submission. Indicate that this product will not be marketed. Teva expressed concern and wanted to know the implication if validation studies did not meet the current standard requirement. The Agency responded that it is premature to speculate at this time. This will be addressed during the review. Agency requested NDA submission with a cohesive overview of the analytical methods and their validation, including data related to method and method validation from the original NDA 20-911 (as needed), as well as detail references to all supporting DMFs.

2.1.2 Are the tests included in the proposed finished drug product release specification still acceptable (refer to Appendix 10.1 and June 10, 2009 FDA response to End of Phase 2 Meeting, page 6, question 2.3.1)?

FDA Pre-meeting Response:

The acceptability of the proposed drug product specifications will be determined during the NDA review process, upon evaluation of the submitted supporting data. Note that data-based acceptance criteria need to be included for each tested attribute, rather than “Report values” entry. Provide justification for adequacy of the selected attributes and clearly identify party responsible for each test.

Note that inclusion of pediatric indication may impact the proposed controls for the drug product if the minimal dose will change from two to one actuation per nostril .

Meeting Discussion:

Participants accepted the preliminary response, no discussion occurred.

2.1.3 Is the proposed Drug Product Characterization Study still acceptable (refer to Appendix 10.2 and June 10, 2009 FDA response to End of Phase 2 Meeting, page 5, question 2.1.4)?

FDA Pre-meeting Response:

The Drug Product Characterization studies will be evaluated in detail during the NDA review in context of other submitted data. Your draft protocol included in Appendix 2 seems to be based on the recommended guidance. Note, that a comparison of characteristics for the to-be-marketed drug product^(b)₍₄₎ (120 ^(b)₍₄₎ actuations), to the 100 actuation drug product used in the Phase 3 trials need to be included if you observe any changes.

Teva Response and Request for Guidance:

Teva will perform full characterization studies on the 120-actuation (b) (4) product (b) (4). In addition, Teva has completed a comparison study between three batches of each of the 100-actuation and the 120-actuation products using the following tests:

- Single Actuation Content through Container Life
- DSD by Laser Diffraction
- APSD by NGI
- Spray Pattern
- Plume Geometry

The results indicate there is no difference in the product performance between the 120-actuation and 100-actuation products. Therefore we would propose that full characterization studies on the 100-actuation product is not necessary and only full characterization studies will be done on the (b) (4) proposed commercial configuration (b) (4) the 120-actuation (b) (4) product (b) (4) intended to be included in the NDA submission. **Is this approach acceptable?**

Meeting Discussion:

The overall approach is acceptable. (b) (4)

(b) (4). For comparison studies and future specification, a submission of detail discussion/assessment of the performance was requested. Also, the Agency noted that the specific cascade impactor groupings will be subject to review evaluation based on adequate data. The Agency requested to include priming/non-priming data in the comparison studies, and clarification if the spray pattern data is obtained manually or by automated mode.

FDA Pre-meeting Response:

In addition, we recommend including stability testing for the overwrapped and unprotected drug products to evaluate the impact of the additional protection. Furthermore, the drug deposition in the nose piece has to be evaluated though the lifetime of the drug product and a characterization of foreign particulates need to be evaluated for changes with time. The latter can be data from your NDA stability studies.

Teva Response and Request for Guidance:

QVAR stability data through 36 months has been submitted to the NDA and the expiration has been well established to be 24 months. As the stability of the BDP Nasal product should be directly related to that of QVAR, we have elected not to overwrap this product on stability and only to collect data from the unwrapped product. From the data we have obtained so far we believe that the 12-month data to be included with the NDA submission and all subsequent stability data will demonstrate that this product does not need to be wrapped to attain at least 24-month expiration dating.

The justification for not collecting any stability data in protective packaging follows: Neither the Nasal Spray Guidance nor the MDI Inhalation Guidance requires collecting data for submission in this situation. The Nasal Guidance states that “Stability studies should be performed on the drug product with the packaging configuration (i.e., primary, protective) for which approval is sought, using the appropriate test storage conditions.” Approval is sought for the product without any protective packaging. There is no mention of the use of protective wrapping of devices. The MDI Inhalation Guidance suggests the “use of a modified or more protective container and closure system” as one of four options when accelerated stability data demonstrates significant change. It also suggests that when both the accelerated stability and controlled room temperature data show significant change “this would indicate that protective packaging or other modification is needed”. Again, neither situation applies to this product.

As this product shows no stability issues, we propose not submitting any stability data from a wrapped product. **Is this approach acceptable for this product?**

Meeting Discussion:

Provide justification along with the supporting data for not overwrapping the drug product. During the review process, we will determine if the additional protection (e.g. overwrapping) would benefit the quality/stability of the drug product based on available real time data, accelerated stability data including storage condition cycling experiments. Provide detailed discussion and assessment of observed changes along with supportive data from the NDA 20-911 application, as needed.

2.1.4 The Sponsor has developed a BDP HFA Nasal Aerosol 80 mcg with various actuation canister products (reference to section 6.1 above):

The Sponsor will perform in vitro testing to demonstrate comparable performance characteristics between the to-be-marketed product (120 actuation), [REDACTED] ^{(b) (4)} and transition product (100

actuation), as per the Agency's response to our EOP II CMC questions (IND 101, 639).

a) Is the bridging protocol between the transition product (100 actuation) and the to-be-marketed product (120 actuation) adequate to establish a comparison between the product presentation^{(b)(4)}(refer to Appendix 10.3)?

b) [Redacted] ^{(b)(4)}

FDA Pre-meeting Response a):

Quality response: The draft protocol seems adequate for comparison of the in vitro dose performance data between the 100 and 120 actuation drug products.

Bio-Stat/Biopharmaceutics response: The Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (2003) clearly states that priming and repriming test is relevant to all nasal aerosols, therefore include this test in your proposed BA/BE in vitro study protocol.

The proposed statistical approach and grouping for the analysis of particle size distribution measured by cascade impaction will be a review issue.

For spray pattern test (Section 9.4 in Appendix 3), it is not clear whether it is automated or manual analysis.

FDA Pre-meeting Response b):

[Redacted] ^{(b)(4)}

Meeting Discussion:

Participants accepted the preliminary response, no discussion occurred.

2.1.5 Teva will submit 12 months of stability data on the 120 actuation (trade) product with the original NDA. [Redacted] ^{(b)(4)}

[Redacted]

Is this approach acceptable to support approval [Redacted] ^{(b)(4)}

[Redacted]

FDA Pre-meeting Response:

We recommend inclusion of a complete stability data package with the original submission. Depending on the availability of the review resources, we may not be able to complete the review of data incoming later than 3-4 months after the original submission. [Redacted] ^{(b)(4)}

(b) (4)

(b) (4)

Meeting Discussion:

Participants accepted the preliminary response, no discussion occurred.

2.2 Statistical:

When there exists an approved specification for the mean of a drug characteristic, does the agency agree that shelf life may be determined as the shortest time point at which the 95% lower (upper, when appropriate) confidence bound of the mean of any of the drug characteristic intersects the approved lower (upper) specification of the drug product (i.e. using the worst case parameter)?

FDA Pre-meeting Response:

Yes. Shelf life is estimated by the intersection of the 95% confidence bound of the regression line with the acceptance criteria. In order to determine a single shelf life of all the future batches of a drug product, FDA request at least three batches of the same product be studied. A common shelf life is determined by the life of the shortest of the three batches for each drug characteristic. Then shelf life of a drug product is determined by the shortest of shelf lives of drug characteristics.

Note: The statistical analysis method for determining the shelf life should be pre determined. We request the sponsor to provide us more detailed statistical analysis plan.

Meeting Discussion:

The Agency requested a clarification on the number of units used for Section 9.3: Particle/Droplet Size Distribution by Cascade Impactor in Appendix 3 since the information provided by the sponsor is not consistent. According to Table 5 on page 57, the number of units used for this study is 5. However, on page 60, the sponsor wrote that 20 units are selected from each canister batch for analysis.

Teva agreed to provide this clarification later.

3.0 CONCURRENCE:

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

4.0 ATTACHMENTS AND HANDOUTS

No Attachments or handouts were provided during the meeting.

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/s/

PRASAD PERI
12/20/2010

MEMORANDUM OF TELECONFERENCE

APPLICATION: IND 101639

SPONSOR: Teva Global Respiratory R&D

DRUG NAME: BDP (beclomethasone dipropionate) HFA Nasal Spray

DATE: November 17, 2010

Teva Global Respiratory R & D Representatives:

Paul Dorinsky, MD, VP, Clinical Research

Sudeesh Tantry, PhD, Associate Director, Clinical Research

Mark Lepore, MD, Clinical Research Physician, Clinical Research

Patrick Darken, PhD, Senior Director, Biostatistics

Stephanie Dunbar, PhD, Director Biostatistics, Women's Health and Allergic Rhinitis

Steve Viti, PhD, MBA, Senior Director, Regulatory Affairs

Axel Perlwitz, PhD, Associate Director, Regulatory Affairs

Shelia Westmoreland, DPM, MPH, PMP Project Leader

William Kiddell, Senior Manager, Regulatory Affairs

Division of Pulmonary, Allergy, and Rheumatology Products Representatives:

Anthony Durmowicz, MD, Clinical Team Leader

Xu Wang, MD, Clinical Reviewer

Carol Hill, MS, Regulatory Health Project Manager

BACKGROUND:

On August 4, 2010, Teva Global Respiratory R & D submitted a request for a pre-NDA meeting. The purpose of the meeting was to discuss pre-clinical, clinical, and statistical programs to support the submission of an electronic NDA in eCTD format that would support NDA approval of BDP (beclomethasone dipropionate) HFA Nasal Aerosol. The preliminary comments for the scheduled October 18, 2010 meeting were provided to Teva by fax on October 14, 2010. Teva responded to the October 14, 2010 correspondence acknowledging their intent to meet with the Agency via teleconference and submitted questions for clarification regarding specific comments from the Agency. The Agency's minutes for the October 18, 2010 meeting were provided to Teva on November 5, 2010. After receipt of the minutes, Teva requested a teleconference to discuss for clarification the post meeting comment included in the Agency's meeting minutes. The post meeting comment and Teva's question for clarification appears below.

Post Meeting Comment

We have concerns with the design of your proposed nasal inhaler because it resembles and performs in a similar manner as other oral inhalers frequently used by patients with respiratory diseases. As such there is the potential that it may be confused as an oral

inhaler, which may result in an incorrect route of administration and drug medication errors. You will need to address this issue in the NDA for your proposed beclomethasone nasal aerosol spray including consideration of conducting usability and labeling comprehension studies to evaluate patients' ability to use the inhaler correctly with the proposed labels and content of labeling.

Teva's Question for Clarification

Teva believes that there should not be confusion on use versus other orally inhaled products that could not be addressed by labeling (i.e., without a study). Is the concern to ensure patients are not spraying in their mouths or something else? Teva would like to further discuss this with the agency.

Discussion:

The Agency stated that the issue of the potential for confusion and medication errors would need to be addressed in the NDA. One method to address the concern is to conduct a usability study but that is not necessarily the only means to address the issue. Teva stated that none of the issues for concern were observed in the clinical program and that the issues could be addressed by labeling. Teva asked would it be acceptable to use pictorial wording that indicates for nasal use only. Teva also inquired would the 74-Day letter notify Teva whether the Division of Medication Error Prevention and Analysis (DMEPA) accepted the justification they would make in the NDA submission. The Agency noted that the 74-Day letter is an early notification of the most prominent issues seen during the preliminary review of the application. Potentially, comments by DMEPA may be included regarding the justification provided but no assurance can be given. The usability study is the gold standard but, as mentioned above, not necessarily the only means to support your nasal administration device. As previously discussed, you should justify the lack of device confusion in the NDA submission.

Carol Hill, MS
Regulatory Health Project Manager

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/s/

CAROL F HILL
12/08/2010



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: pre-NDA
Meeting Date: October 18, 2010
Meeting Location: Teleconference
Application Number: IND 101639
Product Name: BDP (beclomethasone dipropionate)
Received Briefing Package September 20, 2010
Sponsor Name: Teva Global Respiratory R & D
Meeting Requestor: William Kiddell, Senior Manager, Regulatory Affairs
Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Carol Hill, M.S.
Meeting Attendees:

FDA Attendees

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products

Anthony Durmowicz, M.D., Clinical Team Leader, DPARP

Xu Wang, M.D., Clinical Reviewer, DPARP

Mamata De, Ph.D., Acting Pharmacology/Toxicology Supervisor, DPARP

Virgil E. Whitehurst, Ph.D., Pharmacology/Toxicology Reviewer, DPARP

Joan Buenconsejo, Ph.D., Statistical Team Leader, Division of Biometrics II

Robert Abugov, Ph.D., Statistical Reviewer, DOB II

Prasad Peri, Ph.D., Acting Branch Chief, Branch VIII, Division of New Drug Quality Assessment III

Eugenia M. Nashed, Ph.D., CMC Reviewer, Branch, DNDQA III

Yun Xu, Ph.D., Acting Team Leader, Division of Clinical Pharmacology 2

Kristina Toliver, Team Leader, Division of Medication Error Prevention and Analysis

Loretta Holmes, BSN, Pharm.D., Safety Evaluator, DMEPA

Carol Hill, M.S., Regulatory Health Project Manager, DPARP

Teva Attendees

Tushar Shah, M.D., Senior Vice President

Paul Dorinsky, M.D., Vice President, Clinical Research

Sudeesh Tantry, Ph.D., Associate Director, Clinical Research

Mark Lepore, M.D., Clinical Research Physician, Clinical Research

Patrick Darken, Ph.D., Senior Director, Biostatistics

Stephanie Dunbar, Ph.D., Associate Director, Biostatistics

Steve Viti, Ph.D., MBA, Senior Director, Regulatory Affairs

Axel Perlwitz, Ph.D., Associate Director, Regulatory Affairs

William Kiddell, Senior Manager, Regulatory Affairs

Harry Geyer, Ph.D., Senior Manager, Regulatory Affairs

1.0 BACKGROUND

On August 4, 2010, Teva Global Respiratory R & D submitted a request for a pre-NDA meeting. The purpose of the meeting was to discuss pre-clinical, clinical, and statistical programs to support the submission of an electronic NDA in eCTD format that would support NDA approval of BDP (beclomethasone dipropionate) HFA Nasal Aerosol. The preliminary comments for the scheduled October 18, 2010 meeting were provided to Teva by fax on October 14, 2010. Teva responded to the October 14, 2010 correspondence acknowledging their intent to meet with the Agency via teleconference. Teva also submitted a list of the Agency's comments to be discussed for clarification along with their response to each of these followed by the specific question to be clarified (see attachment).

2.0 DISCUSSION

2.1 General

1. *Information from QVAR[®] NDA 20-911 may be cross referenced in this NDA. Teva proposes to provide the date of submission, volume number and page number as reference for the reviewers rather than scanning and submitting the same documents again. For example, if in Module 2.7.5 we reference a section in QVAR[®] Clinical Study 1162 we propose only to provide the specific reference for this report, and not an electronic copy of this reference.*

Is this approach acceptable to the Agency?

FDA Response:

While you may reference information from the QVAR NDA, we prefer all data necessary to support your allergic rhinitis program be submitted with the NDA, including data from the QVAR program.

Teva's Clarification:

NDA 20-911 for QVAR exists in paper format. In the event that we make Reference to a Clinical Study Report (CSR) in NDA 20-911, we will provide a copy of the CSR in our NDA as a Legacy Report (single pdf file, scanned content).

1. *Would the FDA require just the report body or would FDA require the Entire CSR inclusive of all Appendices?*

Discussion:

The Agency agreed with Teva's proposal to provide a scanned pdf file copy of the Clinical Study Report (CSR) in the NDA as a Legacy Report.

2. Given that electronic datasets may not be available to Teva, would the FDA require these to be submitted as well?

Discussion:

The Agency confirmed that electronic datasets would not have to be submitted.

9.2 Regulatory

Content of Clinical Study Report Appendix 16.1.4:

In section 6 of the Clinical Study Report as per ICH E3, information about the Investigators and Sites is presented in the following type of format:

Investigator or Number	Principal Investigator Study Site Address	Sub-Investigators Identified on Form FDA 1572	Date Signed ¹
3187	<p>Paul Ratner, MD, MBA</p> <p>Sylvana Research Associates 7711 Louis Pasteur Dr, Suite 406 San Antonio, TX 78229, USA</p> <p>and</p> <p>dgd Research, Inc. 5109 Medical Drive San Antonio, TX 78229</p>	<p>(b) (4)</p> 	<p>15 Jan 2009 15 Jan 2009 15-Jan-2009 15-Jan-2009 02-Mar-2009</p>

¹ Date the Principal Investigator signed the version of the Form FDA 1572 on which the identified Sub-investigators were added.

² Although  was designated Sub-Investigator on Form FDA 1572, he did not participate in the study.

In Appendix 16.1.4. (List and Description of Investigators and Sites) we intend to provide Forms 1572, Investigator Curriculum Vitae (CV) and Investigator Medical License:

Forms 1572:

We propose not to include any forms 1572 in the NDA. All Forms 1572 have been submitted to the IND, and are available upon request.

Is this approach acceptable?

FDA Response:

Your approach is acceptable.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred.

Investigator CV and Medical License:

We propose to include CVs and Licenses for only the Principle Investigators, not for any Sub-Investigators. All Sub-Investigator CVs and Licenses are available upon request.

Is this approach acceptable?

FDA Response:

Your approach is acceptable.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

Informed consent forms (ICFs) are provided in Appendix 16.1.3 (IRB information and written information for subjects and sample consent forms) of Clinical Study Reports. ICFs were approved for a clinical study by a central IRB responsible for the entire study. ICFs can vary slightly from site to site, based on local site requirements and copies of all site-specific approved ICFs are kept on file at Teva. We propose to provide in Appendix 16.1.3 only one representative IRB-approved ICF.

Is this approach acceptable?

FDA Response:

Your approach is acceptable. However, individual patient ICFs should be available upon request.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

9.3 Pre-Clinical:

In the Pre-IND meeting briefing package (March 4, 2008, Question 5), Teva proposed that no additional preclinical tests are required because BDP HFA Nasal Aerosol product utilizes the same aerosol canister as QVAR[®] HFA Inhalation Aerosol. Several studies performed in the QVAR NDA (20-911) included dosing of the product to the nasal passages of animals. FDA agreed to this proposal in the April 1, 2008 FDA response to Teva's Pre-IND Meeting Briefing Package for Question 5. Therefore, Teva will include in the proposed NDA only a Non-Clinical Overview (Module 2.4), but no Module 2.6 or Module 4 will be included, as there will be no new studies.

Is this an acceptable approach to providing the supportive Pre-Clinical information?

FDA Response:

We do not agree with your approach. For your NDA submission, include Module 2.6 and Module 4.

Additional Non-clinical Comments:

- 1. Provide structures of any impurities and degradants of the drug substance and drug product in your NDA submission. Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance [ICH Q3A(R) and ICH Q3B(R)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA, as described in the draft FDA Guidance for Industry “Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008)”.*
- 2. Additionally, the NDA submission must contain information on potential leachables from the drug container-actuator system. Provide a toxicological evaluation of those substances identified as leachables to determine the safe level of exposure via the labeled specific route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and takes into account the specific container-actuator system, drug product formulation, dosage form and dose regimen.*

Teva’s Clarification:

- 1. Is FDA requesting that Teva provide in Module 4 of this NDA a full copy of all toxicological reports and information provided in NDA 20-911 (QVAR MDI)?*

Discussion:

The Agency clarified that a full copy of all toxicological reports and information provided in NDA 20911 should be submitted in the Module 4 of the NDA. Teva stated that a full copy would be provided.

- 2. If a full copy of all pre-clinical information provided in NDA 20-911 is not requested in Module 4 of this NDA, are FDAs “Additional Non-Clinical Comments” intended to convey the information that FDA is requesting in Module 4?*

Discussion:

The Agency stated that all of the non-clinical information from NDA 20-911 should be provided in Module 4. The information requested in the Additional Non-Clinical comments may also be addressed in Module 4.

- 3. Please clarify the last sentence in item 2:
“The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and takes into account the Specific container-actuator system, drug product formulation, dosage*

form and dose regimen.”

Discussion:

Teva asked the Agency to provide clarification for the last sentence in comment number 2 of the Additional Non-Clinical Comments. The Agency clarified that an evaluation of potential leachables and extractables as well as novel excipient should be qualified per ICH guidelines. The toxicity studies (if needed) should comply with good laboratory practices (GLP). If published literature will be the source to qualify the components, the literature should be peer reviewed. Teva asked would carcinogenicity (CARC) studies be required and if required, would it be acceptable to provide the data in pdf format. The Agency confirmed that CARC studies are required and that pdf format would be acceptable.

9.4 Clinical:

1. *In the Pre-IND Meeting Briefing Package (March 4, 2008, Question 4), Teva proposed that this drug product will not be studied in infants (0-2 years of age) in the pediatric program and that we would request a waiver from these studies. The FDA agreed to allow Teva to request a waiver in the April 1, 2008 FDA response to Question 4.*

“At this time of NDA filing, a pediatric waiver will be requested for pediatric Patients 0 to 2 years of age in view of low disease prevalence and difficulty in diagnosis and treatment of AR in this age group.”

Therefore, the NDA will include a request for a waiver for study in infants 0-2 years of age based on supporting information in accordance with 21 CFR 314.55.

Is this approach still acceptable to the Agency?

FDA Response:

Yes, the approach is acceptable.

Discussion:

The Sponsor accepted the Agency’s responses. No discussion occurred

2. *In the End of Phase 2 Clinical Meeting Briefing Package (August 7, 2009, Question 6), it was proposed to conduct a dose-range finding study in the 6-11 year old age group as part of the pediatric clinical development program.*

“The Sponsor is considering evaluating 2 doses (160 mcg and 80 mcg, once daily) in a pediatric dose-range-finding study (6-11 years of age) to determine the optimal safe and effective pediatric dose in this age group. The optimal dose for 2-5 years of age pediatric subjects will depend on the results of the dose-range-finding study in the 6-11 year old age group (BDP-AR-305).

The Sponsor is currently planning to conduct the Phase 3 adult and adolescent program first, followed by the pediatric clinical development program. Thus, the adult and adolescent data is currently planned to be submitted as the primary NDA submission followed by a supplemental NDA (sNDA) submission for the pediatric program. Therefore, once the data from the pediatric dose-range-finding study (BDP-AR-305) becomes available, the Sponsor would request another EOP2 meeting at a later date to discuss the entire pediatric program in detail.

The Agency agreed with this approach in the FDA response on September 3, 2009. At the time of NDA submission, a pediatric deferral will be requested for pediatric patients 2-11 years of age because Teva is not planning to conduct the pediatric program until the adult studies are completed. The pediatric program will include pediatric patients 2-5 and 6-11 years, and we anticipate submission of a sNDA in 2013.

Does the Agency agree with this request for a pediatric deferral and the overall pediatric clinical development proposal?

FDA Response:

It is acceptable to request a pediatric deferral when you submit your NDA.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

Is this proposed dose-range for the pediatric dose-ranging study (BDP-AR-305) acceptable to the Agency for selecting the optimal dose for the pediatric program?

FDA Response:

While your general approach appears reasonable, we cannot agree that your proposed pediatric dose-ranging study is acceptable as you have submitted no data to support the doses selected for the study.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

- 3. As a result of the End of Phase 2 Clinical Meeting (Question 7), the Agency agreed (in the September 3, 2009 FDA response) that the outline of the program was reasonable to support an indication for allergic rhinitis. Based on the clinical development program discussed and agreed to with the Agency, the Sponsor will seek to obtain a labeled indication as follows:*

“BDP HFA nasal aerosol is indicated for (b) (4) nasal symptoms of seasonal allergic and perennial allergic rhinitis in adult/adolescent patients 12 years of age and older.”

Does the Agency agree that the proposed clinical program is adequate to support this indication?

FDA Response:

The general outline of your program is reasonable to support an indication for allergic rhinitis. Whether the data from your clinical program is adequate to support this indication is a review issue.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

9.5 Statistical

1. ***Based on the "Guidance to the Industry – Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document", Teva proposes that the Integrated Summary of Safety analysis plan (refer to Appendix 10.1 and Appendix 10.2), including the combination of planned measures, study pools, and subgroups, will sufficiently address the requirements to evaluate the safety of BDP nasal aerosol using integrated data.***

Does the Agency agree with this approach?

FDA Response:

While in general your approach appears reasonable, we have the following comments with regard to your Safety Statistical Analysis Plan:

- a. *Submit safety data for subjects treated with all doses, not just those with 320 mcg BDP HFA (refer to section 2.2 on page 17 of the Briefing Package);*

Teva's Clarification:

BDP-AR-201 is the only study in the pooled analysis with BDP HFA doses other than 320 mcg. As such, an assessment of dose-response with respect to safety would be best done using the BDP-AR-201 data alone, as the studies included in the pooled analyses vary in terms of duration, leading to differences in average exposure and making dose to dose comparisons harder to interpret.

In light of this, is it necessary to include the other BDP HFA doses in the pooled analyses or is it sufficient just to discuss any differences in safety due to dose in the ISS?

Discussion:

The Agency clarified that each clinical study in their allergic rhinitis program will be reviewed both individually and as part of the integrated summary of safety (ISS).

Thus, the pooled analyses should include not only the 320 mcg dose but all the doses used in study BDP-AR-201. Teva stated that they have concerns over pooling of adverse event data from studies of different lengths. The Agency stated that one way

to alleviate this concern would be to present the safety data according to dose and length of exposure in the ISS. The Agency stressed that AEs from all doses will need to be provided.

- b. *Submit all adverse events (AEs) that occurred in the studies, not just “treatment emergent” AEs. Subsequent sub-grouping AEs into those that are treatment emergent is acceptable (refer to section 2.7 on page 18 of the Briefing Package);*

Teva’s Clarification:

It would be difficult to summarize AE’s by treatment if the Sponsor were to combine the AE’s from the Placebo Run-in Period with those that are treatment emergent, as there will be many Subjects who participated in the Placebo Run-in Period, who were never randomized, and hence were never assigned to treatment. Additionally, since AE’s occurring prior to administration of randomized medication are clearly not caused by BDP, inclusion of them with the treatment emergent AE’s might cloud the assessment of potential drug-related effects. The Sponsor proposed to provide integrated summaries of AE’s during the placebo run-in periods, but to keep them summarized separately from the treatment emergent AE’s .

Thus, the Sponsor proposes to submit the following AE Table in addition to those currently planned: Summary of Adverse Events During the Placebo Run-in Period.

Is this approach acceptable to the FDA?

Discussion:

The Agency agreed that the approach is acceptable.

- c. *AE data should be presented by number of subjects and by total counts as well (refer to section 2.7.1 on page 18 of the Briefing Package);*

Discussion:

The Sponsor accepted the Agency’s responses. No discussion occurred

- d. *Submit ear, nose and throat (ENT) exam data from every exam conducted, not only during screening, randomization, and the final visit (refer to section 2.8 on page 18 of the Briefing Package).*

Discussion:

The Sponsor accepted the Agency’s responses. No discussion occurred

2. *Teva proposes that the Summary of Clinical Efficacy (Module 2.7.3) is sufficient to evaluate the efficacy of BDP nasal aerosol, since most clinical studies are not poolable and subgroups (age, gender, race) have been reported*

in individual studies. Therefore, a separate Integrated Summary of Efficacy (ISE) will not be included in Module 5.

Is this approach acceptable?

FDA Response:

We agree with you that integrating statistical analyses for disparate studies is not likely to provide useful information. While both the Summary of Clinical Efficacy and Integrated Summary of Efficacy are required components of this submission, there is no need for them to be markedly different.

Teva's Clarification:

Teva intends to use the Summary of Clinical Efficacy (SCE) (Section 2.7.3) as the Integrated Summary of Efficacy (ISE) (Module 5 Section 5.3.5.3)

1. Is the Agency expecting to see information in the ISE that would not be appropriate in the SCE?

Discussion:

The Agency stated that FDA regulation [21 CFR 314.50 (d)(5)(vi)] requires inclusion of an ISE in the NDA submission. As efficacy in the allergic rhinitis studies will not be pooled, the information provided in the ISE may be the same as that in the Summary of Clinical Efficacy.

Teva's Clarification:

If the two documents can in fact be identical, to facilitate this we intend to place the SCE in Section 2.7.3 and place a reference leaf in the eCTD backbone in Sections 5.3.5.3.

2. Is this approach acceptable?

Discussion:

Teva asked if the SCE and ISE are identical and a narrative is provided in section 2.7.3 would it be acceptable to place a reference leaf in the eCTD backbone in Section 5.35.3 for the ISE. The Agency stated that this may be allowable; however, the electronic submission staff would have to be consulted to confirm whether the proposed format to submit SCE and ISE data is acceptable. Follow-up will be provided in the meeting minutes as a post meeting comment.

Post Meeting Clarification:

If the ISS and/or ISE meet the exception in the referenced guidance listed below, then the approach is acceptable. Module 2.7 can not exceed 400 pages. Also, any supportive data files or tabular listings for the ISS or ISE should reside under 5.3.5.3 and be referenced in an ISE and /or ISS study tagging file and have the appropriate study tag applied to those files. Refer to the following 2 links for additional

information on the specific contents of the Clinical Summary and Integrated Summary sections of the NDA:

[Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document \(PDF - 98KB\)](#) (April 2009)

[Clarification for question #10 of "ICH M4: The CTD -- Efficacy Q&As" on submitting integrated summaries of safety and effectiveness \(ISS/ISE\) in the eCTD format](#) (9/12/2006)

- 3. Teva proposes that data from individual clinical studies (CDISC compliant) will be submitted in a format like the sample dataset package (refer to enclosed disc).***

Does the Agency agree that this is sufficient for review of the submission?

FDA Response:

In general, your proposed format for the submitted data is acceptable. However, check the diarysample.xpt file as it could not be read into SAS. Also, ensure that the computational method/algorithm for each variable named in the define.xml file analysis datasets consistently includes the name of the variable or variables employed for each calculation, the name of the tabulation or analysis dataset on which each of these variables resides, and the calculation formula applied to those variables. Any intermediate tables/metadatasets referred to in your computational methods should be provided and similarly documented.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

- 4. Teva proposes that if data sets are submitted in the NDA, individual patient profiles are not necessary.***

Does the Agency agree with this?

FDA Response:

We request that individual patient profiles be submitted for patients with AEs leading to withdrawal, serious adverse events, and deaths.

Teva's Clarification:

It is the Sponsor's understanding that with a data submission package formatted according to CDISC standards that the data would be loaded into the FDA's data warehouse. This then allowed reviewers to create customized patient profiles using available tools, and so exemptions for providing patient profiles were typically granted.

Teva would like to clarify if this understanding is incorrect and that the creation of patient profiles is truly required.

Discussion:

The Agency stated that while not required, we request that individual patient profiles for patients with AEs leading to withdrawal, serious adverse events, and deaths be included in the NDA submission. In case the Agency could not construct the patient profiles from the data files, it would have to request the information during the review cycle which may adversely affect the review of the application. Teva stated it was concerned that submitting lengthy diaries would be an unnecessary burden for the company. The Agency commented that because a program for allergic rhinitis is conducted in people who are generally healthy, there should not be many SAEs or deaths and the burden should therefore not be so high.

5. ***Teva proposes to only submit CRFs for AE's leading to withdrawal, deaths and SAE's.***

Does the Agency agree that this is sufficient?

FDA Response:

We agree with your proposal to submit CRFs for AEs leading to withdrawal, serious adverse events, and deaths.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

6. ***Teva proposes to only provide SAS programs for the primary and secondary analyses for each study.***

Does the Agency agree that this is sufficient?

FDA Response:

Provision of SAS programs for primary and secondary analyses, plus those for tables concerning patient demographics, baseline characteristics, and disposition by treatment will be sufficient. We also note that inclusion of programs employed for any additional calculations or for construction of your analysis datasets may facilitate review of your submission by resolving any ambiguities in documentation. Be sure to document what each program does, how it is called, and any dependencies, e.g., order in which programs should be run.

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

Additional Comments:

1. *The effects of your proposed BDP HFA Nasal Aerosol on the HPA Axis and growth should be addressed in the NDA submission. One method to do so would be to link your BDP Nasal Aerosol program to data generated from the QVAR inhalation aerosol program.*
2. *Note that the ex-actuator dose of the delivered drug substance will be used in the future labeling of the drug product. Report the ex-actuator dose consistently throughout the medical studies to avoid any confusion with data interpretation.*
3. *Clarify if any changes to the formulation and/or device are planned for the drug product to be used in the pediatric population. If so, include the supporting data in the Pre-NDA package. Note, that the dose uniformity controls for the individual actuations have to be met in respect to the lowest proposed numbers of sprays per nostril.*

Discussion:

The Sponsor accepted the Agency's responses. No discussion occurred

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that required further discussion. However, the teleconference was shortened due to failure of the Agency's telephone system. The Review Team expressed that if the discussion provided in the minutes regarding statistical question 9.5.4. did not address Teva's question, a teleconference would be scheduled to clarify any outstanding issue(s).

4.0 POST MEETING COMMENTS

We have concerns with the design of your proposed nasal inhaler because it resembles and performs in a similar manner as other oral inhalers frequently used by patients with respiratory diseases. As such there is the potential that it may be confused as an oral inhaler, which may result in an incorrect route of administration and drug medication errors. You will need to address this issue in the NDA for your proposed beclomethasone nasal aerosol spray including consideration of conducting usability and labeling comprehension studies to evaluate patients' ability to use the inhaler correctly with the proposed labels and content of labeling.

5.0 ATTACHMENTS AND HANDOUTS

See the attachment below of the October 15, 2010 emailed version of Teva's selection of Agency's comments for which for which requested to be discussed for clarification at the October 18, 2010.

9. Specific Questions:

9.1 General:

1. Information from QVAR[®] NDA 20-911 may be cross referenced in this NDA. Teva proposes to provide the date of submission, volume number and page number as reference for the reviewers rather than scanning and submitting the same documents again. For example, if in Module 2.7.5 we reference a section in QVAR[®] Clinical Study 1162 we propose only to provide the specific reference for this report, and not an electronic copy of this reference.

Is this approach acceptable to the Agency?

FDA Response:

While you may reference information from the QVAR NDA, we prefer all data necessary to support your allergic rhinitis program be submitted with the NDA, including data from the QVAR program.

Clarification:

NDA 20-911 for QVAR exists in paper format. In the event that we make reference to a Clinical Study Report (CSR) in NDA 20-911, we will provide a copy of the CSR in our NDA as a Legacy Report (single pdf file, scanned content).

1. **Would FDA require just the report body or would FDA require the entire CSR inclusive of all Appendices?**
2. **Given that electronic datasets may not be available to Teva, would the FDA require these to be submitted as well?**

9.3 Pre-Clinical:

In the Pre-IND meeting briefing package (March 4, 2008, Question 5), Teva proposed that no additional preclinical tests are required because BDP HFA Nasal Aerosol product utilizes the same aerosol canister as QVAR[®] HFA Inhalation Aerosol. Several studies performed in the QVAR NDA (20-911) included dosing of the product to the nasal passages of animals. FDA agreed to this proposal in the April 1, 2008 FDA response to Teva's Pre-IND Meeting Briefing Package for **Question 5**. Therefore, Teva will include in the proposed NDA only a Non-Clinical Overview (Module 2.4), but no Module 2.6 or Module 4 will be included, as there will be no new studies.

Is this an acceptable approach to providing the supportive Pre-Clinical information?

FDA Response:

We do not agree with your approach. For your NDA submission, include Module 2.6 and Module 4.

Additional Non-clinical Comments:

1. Provide structures of any impurities and degradants of the drug substance and drug product in your NDA submission. Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance [ICH Q3A(R) and ICH Q3B(R)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA, as described in the draft FDA Guidance for Industry “Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008)”.
2. Additionally, the NDA submission must contain information on potential leachables from the drug container-actuator system. Provide a toxicological evaluation of those substances identified as leachables to determine the safe level of exposure via the labeled specific route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and takes into account the specific container-actuator system, drug product formulation, dosage form and dose regimen.

Clarification:

1. **Is FDA requesting that Teva provide in Module 4 of this NDA a full copy of all toxicological reports and information provided in NDA 20-911 (QVAR MDI)?**
2. **If a full copy of all pre-clinical information provided in NDA 20-911 is not requested in Module 4 of this NDA, are FDAs “Additional Non-clinical Comments” intended to convey the information that FDA is requesting in Module 4?**
3. **Please clarify the last sentence in item 2:**

“The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and takes into account the specific container-actuator system, drug product formulation, dosage form and dose regimen.”

9.5 Statistical:

1. Based on the “*Guidance to the Industry – Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*”, Teva proposes that the Integrated Summary of Safety analysis plan (**refer to Appendix 10.1 and Appendix 10.2**), including the combination of planned measures, study pools, and subgroups, will sufficiently address the requirements to evaluate the safety of BDP nasal aerosol using integrated data. ***Does the Agency agree with this approach?***

FDA Response:

While in general your approach appears reasonable, we have the following comments with regard to your Safety Statistical Analysis Plan:

- a. Submit safety data for subjects treated with all doses, not just those with 320 mcg BDP HFA (refer to section 2.2 on page 17 of the Briefing Package);

Clarification:

BDP-AR-201 is the only study in the pooled analysis with BDP HFA doses other than 320 mcg. As such, an assessment of dose-response with respect to safety would be best done using the BDP-AR-201 data alone, as the studies included in the pooled analyses vary in terms of duration, leading to differences in average exposure and making dose to dose comparisons harder to interpret.

In light of this, is it necessary to include the other BDP HFA doses in the pooled analyses or is it sufficient just to discuss any differences in safety due to dose in the ISS?

- b. Submit all adverse events (AEs) that occurred in the studies, not just “treatment emergent” AEs. Subsequent sub-grouping AEs into those that are treatment emergent is acceptable (refer to section 2.7 on page 18 of the Briefing Package);

Clarification:

It would be difficult to summarize AE's by treatment if the Sponsor were to combine the AE's from the Placebo Run-in Period with those that are treatment Emergent, as there will be many Subjects who participated in the Placebo Run-In Period, who were never randomized, and hence were never assigned to treatment. Additionally, since AEs occurring prior to administration of randomized medication are clearly not caused by BDP, inclusion of them with the treatment emergent AEs might cloud the assessment of potential drug-related effects. The Sponsor proposes to provide integrated summaries of AE's during the placebo run-in periods, but to keep them summarized separately from the treatment emergent AEs.

Thus, the Sponsor proposes to submit the following AE Table in addition to those currently planned:

Summary of Adverse Events During the Placebo Run-in Period

Is this approach acceptable to the FDA?

2. Teva proposes that the Summary of Clinical Efficacy (Module 2.7.3) is sufficient to evaluate the efficacy of BDP nasal aerosol, since most clinical studies are not poolable and subgroups (age, gender, race) have been reported in individual studies. Therefore, a separate Integrated Summary of Efficacy (ISE) will not be included in Module 5. *Is this approach acceptable?*

FDA Response:

We agree with you that integrating statistical analyses for disparate studies is not likely to provide useful information. While both the Summary of Clinical Efficacy and Integrated Summary of Efficacy are required components of this submission, there is no need for them to be markedly different.

Clarification:

Teva intends to use the Summary of Clinical Efficacy (SCE) (Section 2.7.3) as the Integrated Summary of Efficacy (ISE) (Module 5 Section 5.3.5.3).

1. Is the Agency expecting to see information in the ISE that would not be appropriate in the SCE?

If the two documents can in fact be identical, to facilitate this we intend to place the SCE in Section 2.7.3 and place a reference leaf in the eCTD backbone in Section 5.3.5.3.

2. Is this approach acceptable?

4. Teva proposes that if datasets are submitted in the NDA, individual patient profiles are not necessary. *Does the Agency agree with this?*

FDA Response:

We request that individual patient profiles be submitted for patients with AEs leading to withdrawal, serious adverse events, and deaths.

Clarification:

It is the Sponsor's understanding that with a data submission package formatted according to CDISC standards that the data would be loaded into the FDA's data warehouse. This then allowed reviewers to create customized patient profiles using available tools, and so exemptions for providing patient profiles were typically granted.

Teva would like to clarify if this understanding is incorrect and that the creation of patient profiles is truly required.

Drafted by: chill/October 20, 2010

Clearance History: Holmes/November 4, 2010

Toliver/November 4, 2010

Abugov/October 21, 2010

Buenconsejo/October 21, 2010

Whitehurst/October 21, 2010

De/October 21, 2010

Wang/October 21, 2010

Durmowicz/October 21, 2010 & November 4, 2010

Chowdhury/November 5, 2010

Finalized: chill/November 5, 2010

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

/s/

CAROL F HILL
11/05/2010



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: September 9, 2009, 3-4:30 PM
Meeting Location: White Oak Building 22, Room 1419
Application Number: IND 101639
Product Name: Beclomethasone dipropionate HFA Nasal Aerosol
Received Briefing Package August 10, 2009
Sponsor Name: Teva Global Respiratory
Meeting Requestor: William Kiddel
Meeting Chair: Badrul A. Chowdhury
Meeting Recorder: Carol Hill
Meeting Attendees:

FDA Attendees

Badrul A. Chowdhury, MD, Director, DPAP
Lydia I. Gilbert-McClain, MD, Deputy Director, DPAP
Xu Wang, MD, Clinical Reviewer, DPAP
Brian Porter, MD, Clinical Reviewer, DPAP
Eugenia Nashed, PhD, CMC Reviewer, ONDQA
Yun Xu, PhD, Clinical Pharmacology Reviewer, OCP
Qian H. Li, ScD, Statistical Team Leader, OBII
Dongmei Liu, PhD, Statistical Reviewer, OBII

Teva Global Respiratory

Tushar Shah, MD, Sr., VP
Paul Dorinsky, MD, VP
Mark Lepore, MD, Clinical Research Physician

Sudesh Tantry, PhD, Clinical Program Leader

Jade Ly, PhD, Acting Head, Product Development

Xian-Ming Zeng, PhD, Sr. Dir. Product Development

Patrick Darken, PhD, Sr. Dir., Biostatistics

Stephanie Dunbar, PhD, Assoc. Dir., Biostatistics

Steve Viti, PhD, MBA, Sr. Dir., Regulatory Affairs

William Kiddell, Sr. Mgr., Regulatory Affairs

1.0 BACKGROUND

Teva submitted on July 10, 2009 a request for an EOP 2 clinical meeting. On August 7, 2009 Teva forwarded the background materials for the meeting scheduled for September 9, 2009. In the meeting package, Teva referenced the EOP2 meeting held with CMC on June 8, 2009. Teva requested attendees from ONDQA to obtain clarification for two questions addressed at the June 8, 2009 meeting. The Agency's responses for the September 9, 2009 meeting were faxed to Teva on September 3, 2009. Teva responded on September 4, 2009 their intent to attend the meeting and requested to address the following questions for clarification, 1, 4, 5b, 5c, and the Agency's additional comments.

2.0 DISCUSSION

GENERAL

Question 1:

(b) (4)

(b) (4)

Does the Agency agree with this approach?

Agency's Comments:

(b) (4)

TEVA's Response:

Question 1.

(b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Discussion:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Question 2:***120-actuation trade pack with non-removable (fixed) nosepiece:***

The Sponsor is developing a 120-actuation canister that will be inserted into an actuator with a fixed nosepiece. The 120-actuation product with fixed nosepiece is intended to be the marketed product (trade) and intended to provide at least one month's supply of the medication to the patient. The manufacturing process used to produce the 120-actuation canister is identical to that of the approved 100- and 200-actuation canisters of QVAR oral inhalation aerosol with the exception of having a different fill weight. The Sponsor will perform adequate in vitro testing to demonstrate comparable performance between the 100-actuation product with a removable nosepiece (used in all phases of clinical studies) and the 120-actuation product with a fixed nose piece (that will be used in one Phase 3 clinical study - BDP-AR-302). The fixed nosepiece is the same as the removable nosepiece with the exception of three clips which lock the nosepiece to the lower base. The addition of the fixed nosepiece does not affect the air flow, drug path flow and performance of the device. Teva plans on conducting an in vitro characterization study to demonstrate comparability between the removable and fixed nosepiece products. Samples of both devices (with fixed and removable nosepieces) are being provided in this briefing package for reference. The tests planned for the in vitro comparative study are based on the Guidance for Industry: BA and BE Studies for Nasal Aerosol and Nasal Sprays for Local Action, April 2003. The current device containing the 100-actuation canister and removable nosepiece was used in the Phase 1 and Phase 2 studies and will be used in several Phase 3 studies as well (BDP-AR-301, 303, 304 – see table on page 26 of the briefing document). The Sponsor is also planning to use the to-be-marketed product – 120-actuation product with a fixed nosepiece – in one Phase 3 PAR efficacy study (BDP-AR-302).

Does the Agency agree with this approach?

Agency's Comments:

The approach seems reasonable. The acceptability of the data will be subject to the review. Refer to our previous comments of June 8, 200, about device differences in terms of cleaning feasibility and provide comparative data.

Discussion:

The sponsor accepted the Agency's response, no discussion occurred.

Question 3:***Stability Study on Exhibit Batches – Actuator-Related Tests and Canister-Related Tests:***

The Sponsor intends to conduct stability studies on 3 lots of exhibit batches of the to-be-marketed product, which is a combination of 3M's BDP HFA canister (120-dose) assembled with a (b) (4) nasal actuator (fixed nosepiece with a dose counter).

3M's QVAR® 100-Dose and 200-dose canisters are stable and have undergone multiple stability studies. The 120-dose canisters use the same canister, formulation, valve and process as the 100-dose and 200-dose QVAR® canisters. Therefore, the Sponsor intends to conduct both the actuator-related and canister-related tests on all three exhibit batches for initial product release but perform the actuator-related tests only during stability studies. The actuator-related tests include Appearance, Spray Content Uniformity, Microscopic Evaluation, Shot Weight, Number of Actuations, Aerodynamic Particle Size Distribution by NGI and Leakage Rate. The canister-related tests include Drug Content Assay, Drug Related Impurities, Ethanol Content, (b) (4) Microbial Limits, Foreign Particulates and Aluminum Content.

Does the Agency agree with this approach?

Agency Comments:

The approach of reduced stability testing for the canister-related attributes seems reasonable due to the same manufacture, formulation, vial and valve. However, we recommend submission of the canister-related stability data for a minimum of one batch of the 120-actuation product and/or providing reference to canister-related stability data for the 100-actuation and 200-actuation batches manufactured concurrently with the 120-actuation exhibit batches. Include results for leachable testing in the canister-related stability studies and data. (b) (4)

Discussion:

The sponsor accepted the Agency's response, no discussion occurred.

CLINICAL**Question 4:*****Dose Selection – Adult and Adolescent Program (12 years of age and older):***

The Phase 2 DRF study (BDP-AR-201) has identified a dose of 320 mcg/day as the lowest safe and effective dose. See Section 9.3, Summary of the Phase 2 Dose-Range-Finding Efficacy Study, for a summary of the Phase 2 study results supporting the optimal dose selection to be further evaluated in the Phase 3 adult and adolescent program.

Does the Agency agree that 320 mcg/day is the single dose appropriate for further evaluation in the Phase 3 program for adults and adolescents (12 years and older) for both SAR and PAR?

Agency's Comments:

We concur that the data indicate that 320 mcg daily is the lowest effective dose. However, it may not be optimal to carry forward only this single dose in your Phase 3 studies. Your dose ranging study (BDP-AR-201) showed that the 320 mcg dose had a relatively small effect size of -0.63 (point estimate) in rTNSS difference compared to placebo. This suggests that a single dose of 320 mcg daily may not be the most effective dose for your Phase 3 studies. Consider including higher doses in your Phase 3 program. Since BDP is dosed twice daily for the asthma indication, the relatively modest efficacy seen with the 320 mcg dose may also indicate that once daily dosing may not be the most appropriate dosing interval for allergic rhinitis. Consider modifying the dose frequency to twice daily.

TEVA's Response***Question 4. Dose Selection – Adult and Adolescent Program (12 years of age and older):***

TEVA wants to clarify the possibility of getting approval of the product with a 320 mcg/day QD dose. TEVA would like to further discuss the small treatment effect found in the Phase II study, and the dose level and dose frequency proposed for the Phase III studies.

Discussion:

Teva stated that they are not interested in studying doses above 320 mcg for rhinitis because of the safety concerns for higher steroid doses. Teva acknowledged that the effect size of 320 mcg dose was smaller than their expectation in the rhinitis trial. Teva believes that a larger scale trial will show efficacy measures of 320 mcg dose comparable

to currently marketed products with regard to the effect size in treatment of rhinitis. The Agency commented that the data for the 320 mcg dose is not optimal and suggested that a higher dose or an increase in dosing frequency might be more appropriate. The Agency commented (b) (4)

(b) (4) TEVA commented that the (b) (4) TEVA noted that the choice of the 320 mcg once daily dose is their risk. They acknowledge the small sample size in the dose ranging study but believe that with larger studies, a more robust effect will be seen. The Agency reminded TEVA that the drug would need to show efficacy on both the rTNSS and on iTNSS.

Question5:

Phase 3 Program – Adult and Adolescent (12 years and older):

The Sponsor has demonstrated in the Phase 1 PK study (BDP-AR-101) that the systemic exposure following intranasal administration of 320 mcg/day of BDP is approximately 27% of that following the same dose administered by the orally inhaled route (see Section 9.2, Summary of the Phase 1 Pharmacokinetic Study (BDP-AR-101), for a summary of the Phase 1 study results). Thus, the Sponsor is proposing to use the systemic safety data available from the QVAR® program (NDA20-911) as supportive information for the current nasal development program. As per the recommendations of the Agency during the pre-IND meeting, and based on the results from the Phase 1 and Phase 2 studies, the Phase 3 Adult and adolescent (12 years and older) clinical development plan has been modified.

Major changes based on the Agency recommendations are summarized below:

- ***Ocular Safety Assessments (LOCS III and IOP evaluations) are included in the long term safety study (BDP-AR-303) in a subset of approximately 250 subjects (See Section 10.1.3, BDP-AR-303 Study Full Protocol).***
- ***The long term safety (BDP-AR-303) study has been modified to be a 52 week, double-blind study (see Section 10.1.3. BDP-AR-303 Study Full Protocol).***
- ***Additional safety assessments (Labs, ECGs) have been added to the Phase 3 program (BDP-AR-302 study – See Section 10.1.2, BDP-AR-302 Study Synopsis).***
- ***The HPA-axis study (BDP-AR-304) has been modified to include subjects down to 12 years of age and the sample size has been increased to 40 subjects per arm. Compliance will be assessed using the dose counter, videophone technology and PK assessments (See Section 10.1.4 BDP-AR-304 Study Synopsis).***

Does the Agency concur that the modified clinical program is adequate to support the indication for both SAR and PAR in this age group?

Specifically, does the Agency agree with the following?

- ***The proposed overall safety evaluations including the planned ocular assessments, laboratory assessments and ECG assessments?***
- ***The design and planned safety evaluations in the long-term safety study?***
- ***The HPA axis study design, sample size and endpoints?***

Agency's Comments:

In general, your modified clinical program is reasonable to support the indication for both SAR and PAR in adults and adolescents (12 years and older). We have the following general comments to the proposed clinical program:

- a. *Refer to our response to Question 4 regarding the appropriate dose selection and dosing frequency.*
- b. *In addition to the proposed primary efficacy endpoint rTNSS, an improvement in instantaneous total nasal symptom score (iTNSS) is needed to support the efficacy of the test drug product.*
- c. *We note that PK sampling is to be conducted only at the end of the treatment period in your proposed HPA axis study. Include additional PK assessments at other timepoints during the 42-day treatment period. In addition, we suggest you also evaluate efficacy as another measure to assess compliance.*
- d. *If doses higher than 320 mcg daily are selected for the Phase 3 studies, you will need to study the highest dose in the HPA axis study.*
- e. *The primary focus of the safety assessment is local toxicity. Therefore, the clinical program should include adequate safety measures to capture local nasal safety events such as epistaxis, nasal irritation, nasal ulcerations and perforations.*

TEVA' Response***Question 5. Phase 3 Program – Adult and Adolescent (12 year and older):***

b. TEVA wants to clarify the need for rTNSS and iTNSS in the long term safety study.

c. TEVA wants to clarify the use of videophone technology instead of efficacy evaluations or additional PK assessments to verify compliance

Discussion:

Teva asked the Agency to clarify the need for rTNSS and iTNSS in the safety study. The Agency responded that efficacy measures rTNSS and iTNSS are needed in the efficacy and safety trials in general, not specifically required in the long term safety study. The Agency wants to have efficacy measures in the long term safety study primarily for the purpose of compliance monitoring.

Teva stated that to address the issue of compliance visual evidence of patient dosing and administration will be employed. Teva commented that 10 hours post intranasal dose, the plasma drug concentrations are already below quantitative limits, so additional PK samples during the treatment is unlikely to provide additional information. The Agency stated that the additional PK assessments, efficacy evaluation, and direct visualization are a matter of redundancy to ensure compliance, but acknowledged TEVA's explanation of the BDP PK profile.

Question 6:***Phase 3 Program – Pediatric (2-11 years of age)***

The Sponsor is considering evaluating 2 doses (160mcg and 80 mcg, once daily) in pediatric dose-range-finding study (6-11 years of age) to determine the optimal safe and effective pediatric dose in this age group. The optimal dose for 2-5 years of age pediatric subjects will depend on the results of the dose-range-finding study in the 6-11 year old age group (BDP-AR-305).

The Sponsor is currently planning to conduct the Phase 3 adult and adolescent program first, followed by the pediatric clinical development program. Thus, the adult and adolescent data is currently planned to be submitted as the primary NDA submission followed by a supplemental NDA submission for the pediatric program. Therefore, the Sponsor would request another EOP2 meeting at a later date to discuss the pediatric program in detail.

Does the Agency agree with this overall approach and the Sponsor's plan to evaluate 80 mcg and 160 mcg once daily in the dose-range-finding study in the 6-11 year old age group?

Agency's Comments:

We agree with the approach to conduct the adult program first before conducting the pediatric program. Refer to our response to Question 4 regarding the appropriate dose selection in the adult and adolescent clinical program. Evaluate doses for the pediatric dose-range-finding study (6-11 years of age) based on the appropriate dose(s) selected in the adult and adolescent clinical program.

Discussion:

The sponsor accepted the Agency's response, no discussion occurred.

Question 7:***Proposed Indication:***

Based on the proposed clinical development program, the Sponsor will seek to obtain a labeled indication as follows:

“BDP HFA nasal aerosol is indicated for [REDACTED] ^{(b) (4)} nasal symptoms of seasonal allergic and perennial allergic rhinitis in adult/adolescent patients 12 years of age and older.”

Does the Agency concur that the proposed adult and adolescent clinical program is adequate to support this indication?

Agency's Comments:

The general outline of your program is reasonable to support an indication for allergic rhinitis. However, we have reservations about the proposed dose and dosing frequency selected for the Phase 3 adult studies. See our response to Question 4.

Discussion:

The sponsor accepted the Agency's response, no discussion occurred.

Question 8:***Patient Exposure – Adult and Adolescent Program:***

Approximately 1128 patients/subjects will be exposed to various doses of BDP HFA nasal aerosol during the proposed adult and adolescent clinical development program.

Does the Agency concur that the overall patient exposure to HFA-BDP nasal aerosol will be acceptable for approval in patients 12 years of age and above?

Agency's Comments:

In general, the number of patients exposed to BDP nasal aerosol in the proposed adult and adolescent clinical development program appears reasonable. However, depending on the local safety findings in the clinical program, additional safety studies with a larger sample size may be needed. Further, if a higher dose is selected for the Phase 3 program, then the higher dose should be studied in the one year safety study.

Discussion:

The sponsor accepted the Agency's response, no discussion occurred.

ADDITIONAL COMMENTS

 (b) (4)
. Provide development data to justify the appropriateness of the selected formulation-device combination for this nasal delivery drug product. Submit information/data characterizing possible in vivo deposition of the drug product, i.e., local versus systemic, and nasal versus lung.

We expect the drug development program to characterize the drug product robustness during clinical trials. A representative number of drug products used in the clinical trial should be returned and evaluated for in vitro performance characteristics (APSD and DDU). In addition, all malfunctioning devices will need to be evaluated and the results provided in the NDA.

TEVA's Response

FDA Additional Comments:

 (b) (4)
. Provide development data to justify the appropriateness of the selected formulation-device combination for this nasal delivery drug product, i.e., local versus systemic, and nasal versus lung.

TEVA:

TEVA wants to clarify that the clinical development program addressing the Safety, Efficacy and PK of the product will determine the approvability of this drug product.

Discussion:

(b) (4)

The Agency commented that there is no data to assess the pulmonary delivery of the formulation delivered via the nose. The Agency also asked if Teva plans to conduct studies using an active comparator and will studies demonstrate how much of the product is deposited in and retained by the lungs and nose. Teva responded that particle size studies are planned. TEVA noted that wash out of medication poses a problem for comparative studies. (b) (4)

(b) (4)

The Agency commented that the reason for asking about the particle size is because of the small effect size seen in the dose ranging study and the concern that the formulation may be a factor affecting overall efficacy. Teva commented that in vivo studies in phase 3 will show how much drug is released through the nose compared to the lungs. Regarding the patient population for their phase 3 studies, the Agency recommended that TEVA conduct at least one of their seasonal allergic rhinitis studies in a patient population other than patients with Mountain Cedar allergy.

Drafted: chill/October 1, 2009

Initialed: Xu/October 2, 2009

Liu/October 2, 2009

Li/October 2, 2009

Nashed/October 6, 2009

Peri/October 5, 2009

Al Hakim/October 6, 2009

Wang/October 2, 2009

Gilbert-McClain/October 4, 2009

Chowdhury/October 7, 2009

Finalized: chill/October 7, 2009

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-101639

GI-1

TEVA GLOBAL
RESPIRATORY
RESEARCH LLC

(b) (4)

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

/s/

CAROL F HILL
10/07/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 101,639

Teva Global Respiratory Research, LLC
Attention: William Kiddell, Senior Manager, Global Respiratory Regulatory Affairs
74 NW 176th Street
Miami, FL 33169

Dear Mr. Kiddell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for beclomethasone dipropionate (BDP) HFANasal Aerosol.

We also refer to the meeting between representatives of your firm and the FDA on June 8, 2009. The purpose of the meeting was to discuss the Chemistry, Manufacturing, and Controls (CMC) quality program to support their proposed plan for Phase III and to support a NDA submission.

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, call me at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Don L. Henry
Regulatory Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Teva Global Respiratory Research LLC
Application Number:	IND 101,639
Product Name:	Beclomethasone dipropionate HFA Nasal Aerosol
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls, End of Phase 2 Meeting
Meeting Date and Time:	Monday, June 8, 2009, 15:30 – 17:00 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	May 1, 2009

FDA ATTENDEES

Ali Al-Hakim, Ph.D, Branch Chief, DPMA I, Branch 2
Prasad Peri, Ph.D, Pharmaceutical Assessment Lead
Eugenia Nashed, Ph.D, Senior Chemistry Reviewer
Sandra Suarez, Ph.D, Office of Clinical Pharmacology
Don Henry, Regulatory Project Manager

TEVA GLOBAL RESPIRATORY RESEARCH ATTENDEES

Xian-Ming Zeng, PhD, Senior Director, Global Respiratory R&D
Jade Ly, PhD, Acting Head of Nasal Sprays, Global Respiratory R&D
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1. BACKGROUND

Teva submitted IND 101,639 in January 2009, for Beclomethasone dipropionate (BDP) HFA Nasal Aerosol. The formulation of the drug product is the same as the approved QVAR Inhalation Aerosol; however, the actuator is designed for nasal delivery. Teva has completed the Phases I and II clinical trials using a non-functional dose counter. For Phase III, Teva proposes to use a functional dose counter. In addition, the sponsor is planning to use a fixed-in-place nosepiece (*versus* removable nosepiece used in the trials) in the to-be-marketed drug product (b) (4)

(b) (4) Teva has requested this meeting to discuss their CMC program to support their proposed plan for Phase III and to support a NDA submission. The proposed bridging studies were outlined in a Briefing Package dated May 1, 2009, and additional amendment dated May 6, 2009.

2. DISCUSSION

2.1. Development

2.1.1. Briefing Package Question 1: Is the Bridging Study Protocol acceptable?

FDA Response:

1. *We assume that you will be using the modified drug product in the phase III studies. Based on this statement, we recommend that you perform only in-vitro performance evaluation for the phase II device, phase III device and the to-be-marketed device as per the draft MDI/DPI guidance (e.g., test to specification and perform applicable drug product characterization studies), instead of a full BA/BE program.*

Meeting Discussion: The Agency clarified that based on the proposed change to the drug product, an in-vitro performance evaluation is the only requirement needed to bridge the Phase II and Phase III clinical studies.

2. *We strongly recommend using the to-be-marketed product (non-removable nosepiece, (b) (4) (b) (4) in the Phase III clinical studies to minimize the extent of the bridging studies necessary.*

Meeting Discussion: The Agency emphasized that any changes introduced to the drug product between the Phase III studies and the to-be marketed product will need to be adequately supported by the bridging data. The review outcome of these studies will be highly critical to the approval process. For this reason the Agency strongly recommends to use the final device in the Phase 3 trials. (b) (4)

(b) (4)

3. *Perform device robustness testing. Evaluate all devices that were considered to be defective or malfunctioning in terms of performance (APSD, DDU) in the clinical trials settings, and submit the report to the NDA. In addition, we recommend that you evaluate the performance of a sample number (e.g., 100) devices used in the clinical trial that were returned by the patients.*

Meeting Discussion: There was no further discussion on this topic.

4. *Provide in-vitro CMC performance data (APSD, DDU, Spray Pattern, Plume Geometry) for multiple batches of the drug product with a functional and non-functional dose counter.*

Meeting Discussion: The Agency clarified that Teva should evaluate the parameters (APSD, DDU, Spray Pattern, Plume Geometry) and compare the data for both the functional and non-functional dose counter. The acceptance of the data should be justified.

5. *In addition, provide comparative CMC data (mean and individual values for multiple batches) for the force to actuate versus the force to fire, for your drug product with a functional, non-functional dose counters, and the to-be marketed device. Provide an assessment of the risk for under-count versus over-count (e.g., FMEA type of risk assessment) for drug product with the functional dose counter. These tests may also include measurements of the canister weight before and after actuating the devices, which can serve as an assessment of accuracy, precision, etc. of the dose counter.*

Meeting Discussion: Teva indicated that this information is available. The assessments have been conducted by the manufacturer of the device.

6. *Clearly identify a sampling plan (number of units) you will choose to select the devices from multiple lots of actuators used to make the drug product and test for the above mentioned CMC studies. Identify the strategy and rationale you will use to reach a conclusion that the drug product with the functional dose counters is indeed comparable or different from the drug product with non-functional dose counters.*

Meeting Discussion: Teva indicated that a beginning, middle, and end sample plan has been developed and will be provided.

7. Clarify if the dose counter is triggered by [REDACTED] (b) (4)

Meeting Discussion: The dose counter is triggered by [REDACTED] (b) (4)

2.1.2. **Briefing Package Question 2:** Are the proposed in-vitro comparative study test planned to justify this change acceptable?

FDA Response:

1. See response 1 above.

Meeting Discussion: There was no further discussion on this topic.

2. *In addition, we suggest you perform evaluation of APSD through container life (beginning, middle, end) and assess any necessary cleaning needed to assure reproducibility in this delivery parameter for the non-removable actuator.*

Meeting Discussion: Teva indicated that the cleaning process is for hygiene purposes, and consists of wiping the outside of the nosepiece, only. Teva will evaluate the container life as part of the stability program.

3. *Provide in the description section the force necessary to insert and remove the canister in the actuator. Submit samples of the drug product to the review team.*

Meeting Discussion: Teva clarified that the canister is inserted as part of the manufacturing assembly process. The patient will not need to insert or remove the canister. However, Teva agrees that removal of the canister may occur, and will provide the force needed to remove the canister. Teva will provide a prototype of the Phase III and to-be marketed drug product at the clinical end of Phase II meeting.

2.1.3. **Briefing Package Question 3:** [REDACTED] (b) (4)

FDA Response:

1. [REDACTED] (b) (4)

Meeting Discussion: There was no further discussion on this topic.

2. [REDACTED] (b) (4)

Meeting Discussion: There was no further discussion on this topic.

3. *We recommend adding a 6 month time point for the accelerated stability conditions (40°C/75% RH).*

Meeting Discussion: There was no further discussion on this topic.

2.1.4. **Briefing Package Question 4:** Is the proposed Drug Product Characterization Study acceptable?

FDA Response:

1. *We concur with proposed test protocol with the following clarifications.*

- a. *The acceptability of the data will be a review issue in the NDA.*
- b. *Clarify the cleaning protocol as it pertains to the to-be-marketed device with a nosepiece that cannot be removed from the actuator.*

Meeting Discussion: Teva clarified that the cleaning process is for hygiene purpose, and consist of wiping the outside of the nosepiece.

2. We strongly recommend using each of the to-be marketed drug products in the Phase III clinical studies.

Meeting Discussion: This topic will be further discussed at the clinical end of Phase II meeting.

2.2. Specifications for Components

- 2.2.1. **Briefing Package Question 5:** Are the tests included in the proposed specification for the nasal actuator acceptable?

FDA Response:

In addition to the test listed, we recommend that you perform airflow testing on 100% of the actuators to assure the accuracy of the orifice diameter. We also recommend you perform, assess and include plume geometry and velocity of the spray for the actuator.

Extractables/leachables should be evaluated for the actuator; see the draft MDI/DPI guidance document.

See comments above with regards to the force necessary to insert and remove the canister from the actuator. You may include these attributes in the specifications as appropriate (in lieu of other dimensional parameters).

Meeting Discussion: Teva indicated that the 100% airflow testing is performed by the manufacturer of the actuator. The plume geometry and spray velocity will be performed as part of a characterization study, and Teva will provide rationale for not include these tests as part of the release specifications for the actuator. The extractables/leachables will be evaluated. The Agency and Teva agreed that leachables may not be seen in the drug product, but recommended following the requirements of the draft guidance. The force needed to remove the canister will be conducted as part of a characterization study.

2.3. Specifications for Finished Drug Product

- 2.3.1. **Briefing Package Question 6:** Are the tests included in the proposed finished drug product release specification acceptable?

FDA Response:

Based on the submitted information and data the selected attributes seem to be adequate, however the acceptability of the results will be a review issue.

As requested in Response 2, above, provide samples of both presentations of the drug product.

Meeting Discussion: There was no further discussion on this topic.

2.4. Stability

- 2.4.1. **Briefing Package Question 7:** Are the tests in the proposed finished drug product stability protocol acceptable?

FDA Response:

Based on the submitted information and data the selected attributes seem to be adequate, however the acceptability of the results will be a review issue.

Evaluate the possibility of leachables in the drug product as it pertains to safety.

(b) (4)

Meeting Discussion: There was no further discussion on this topic.

- 2.4.2. **Briefing Package Question 8:** Is the proposed finished drug product stability protocol acceptable?

FDA Response:

See response to Question 7.

Meeting Discussion: There was no further discussion on this topic.

2.5. Additional Questions

- 2.5.1. **Briefing Package Question 9:** Is the grouping described above acceptable for an in-vitro BA/BE study?

FDA Response:

See response to question 1. The acceptability of the acceptance criteria will be a NDA review issue. Provide the complete APSD profile (stage by stage) data in the IND and NDA.

Meeting Discussion: There was no further discussion on this topic.

- 2.5.2. **Briefing Package Question 10:** Is the Population Bio-equivalence (PBE) described above acceptable for comparison of batches for Aerodynamic Particle Size Distribution by NGI?

FDA Response:

See response to question 1. The acceptability of the stage groupings and acceptance criteria will be a NDA review issue. Provide the complete APSD profile (stage by stage) data in the IND and NDA.

Meeting Discussion: There was no further discussion on this topic.

3. ADDITIONAL COMMENTS/ISSUES REQUIRING FURTHER DISCUSSION

There are no additional comments to discuss

4. ACTION ITEMS

Teva will provide a prototype of the Phase III and the to-be marketed drug product at the clinical End of Phase II meeting.

5. CONCURRENCE:

{See appended electronic signature page}

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Linked Applications

Sponsor Name

Drug Name / Subject

IND 101639

TEVA GLOBAL
RESPIRATORY
RESEARCH LLC

(b) (4)

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/s/

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06/10/2009

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