

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200678Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED UPON AND
AFTER APPROVAL OF AN NDA OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation or
Composition) and/or Method of Use*

NDA NUMBER

200678

NAME OF APPLICANT/NDA HOLDER

Bristol-Myers Squibb Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME

Kombiglyze XR

ACTIVE INGREDIENT(S)

saxagliptin/metformin HCl

STRENGTH(S)

2.5 mg saxagliptin/1000 mg metformin HCl
5.0 mg saxagliptin/500 mg metformin HCl
5.0 mg saxagliptin/1000 mg metformin HCl

DOSAGE FORM

saxagliptin and metformin HCl extended-release tablet

APPROVAL DATE OF NDA OR SUPPLEMENT

November 5, 2010

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions 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 file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,395,767

b. Issue Date of Patent

May 28, 2002

c. Expiration Date of Patent

February 16, 2021

d. Name of Patent Owner

Bristol-Myers Squibb Company

Address (of Patent Owner)

P.O. Box 4000

City/State

Princeton, NJ

ZIP Code

08543

FAX Number (if available)

609-252-4526

Telephone Number

609-252-4000

E-Mail Address (if available)

patents@bms.com

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

Telephone Number

FAX Number (if available)

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?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

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

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes."
- the answer to 2.7 is "No."

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	<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

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 23 and 24	Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) KOMBIGLYZE XR is a dipeptidyl peptidase-4 inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.
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4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.

Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)

KOMBIGLYZE XR is a dipeptidyl peptidase-4 inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use 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 or supplement approved 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

Terence J. Bogie

11/22/10

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

Terence J. Bogie

Address

P.O. Box 4000

City/State

Princeton, NJ

ZIP Code

08543

Telephone Number

609-252-6385

FAX Number (if available)

609-252-4526

E-Mail Address (if available)

patents@bms.com

The public reporting burden for this collection of information has been estimated to average 5 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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542

PATENT INFORMATION SUBMITTED UPON AND AFTER
APPROVAL OF AN NDA OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.
- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims one or more methods of use of the drug product that is the subject of the approved NDA or supplement.

- 4.2) For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple patent claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the approved drug labeling that is claimed by the patent.
- 4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. Use a maximum of 240 characters for each "use code."

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**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

200678

NAME OF APPLICANT/NDA HOLDER

Bristol-Myers Squibb Company

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)
(b) (4)

ACTIVE INGREDIENT(S)

saxagliptin/metformin HCl

STRENGTH(S)

2.5 mg saxagliptin/1000 mg metformin HCl
5.0 mg saxagliptin/ 500 mg metformin HCl
5.0 mg saxagliptin/1000 mg metformin HCl

DOSAGE FORM

Fixed Dose Tablet saxagliptin immediate release/ metformin HCl-extended release

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 *only* 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.

1. GENERAL

a. United States Patent Number 6,475,521	b. Issue Date of Patent November 5, 2002	c. Expiration Date of Patent March 19, 2018
d. Name of Patent Owner Bristol-Myers Squibb Company	Address (of Patent Owner) P.O. Box 4000	
	City/State Princeton, NJ	
	ZIP Code 08543	FAX Number (if available) 609-252-4526
	Telephone Number 609-252-4000	E-Mail Address (if available) patents@bms.com
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 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.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input 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)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

5. No Relevant Patents

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

6. Declaration Certification	
<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>Date Signed</p> <p><i>December 8, 2008</i></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>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Maureen Gibbons</p>	
<p>Address P.O. Box 4000</p>	<p>City/State Princeton, NJ</p>
<p>ZIP Code 08543</p>	<p>Telephone Number 609-252-3453</p>
<p>FAX Number (if available) 609-252-4526</p>	<p>E-Mail Address (if available) patents@bms.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>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**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

200678

NAME OF APPLICANT/NDA HOLDER

Bristol-Myers Squibb Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (b) (4) PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

saxagliptin/metformin HCl

STRENGTH(S)

2.5 mg saxagliptin/1000 mg metformin HCl
5.0 mg saxagliptin/ 500 mg metformin HCl
5.0 mg saxagliptin/1000 mg metformin HCl

DOSAGE FORM

Fixed dose tablet saxagliptin immediate-release/ metformin HCl extended-release

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 *only* 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.

1. GENERAL

a. United States Patent Number

6,660,300

b. Issue Date of Patent

December 9, 2003

c. Expiration Date of Patent

March 19, 2018

d. Name of Patent Owner

Bristol-Myers Squibb Company

Address (of Patent Owner)

P.O. Box 4000

City/State

Princeton, NJ

ZIP Code

08543

FAX Number (if available)

609-252-4526

Telephone Number

609-252-4000

E-Mail Address (if available)

patents@bms.com

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?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes 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.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 1-7, 16-20, 27-33, and 35-41	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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) (b) (4) [redacted] is a dipeptidyl peptidase-4 inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.	

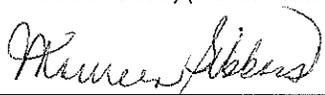
5. No Relevant Patents

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

6. Declaration Certification

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

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

<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p><i>December 8, 2009</i></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).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Maureen Gibbons</p>	
<p>Address P.O. Box 4000</p>	<p>City/State Princeton, NJ</p>
<p>ZIP Code 08543</p>	<p>Telephone Number 609-252-3453</p>
<p>FAX Number (if available) 609-252-4526</p>	<p>E-Mail Address (if available) patents@bms.com</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:

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 200678

SUPPL # N/A

HFD # 510

Trade Name Kombiglyze XR

Generic Name saxagliptin/metformin hydrochloride extended-release tablets

Applicant Name Bristol-Myers Squibb Company

Approval Date, If Known November 5, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

Approvability of this NDA required review of bioavailability/bioequivalence data. Please see attached Figure 1 (from CLINPHARM review) which was uploaded into DARRTs on 11.4.10 entitled "Link between FDC product (Kombiglyze XR) and metformin IR and saxagliptin co-administration used in the Phase 3 trials."

This NDA did not require the review of any other new clinical data (we relied on previously reviewed clinical data from the following NDAs):

NDA # 022350 Onglyza (saxagliptin) approved at doses of 2.5 mg and 5.0 mg

NDA # 020357 Glucophage (metformin HCL) approved at doses of 500 mg, 850 mg, and 1000 mg

NDA # 021202 Glucophage XR (metformin HCL) approved at doses of 500 mg and

750 mg.

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:

Not a supplement. This is a new fixed-dose combination of saxagliptin and metformin HCL XR for the treatment of type 2 diabetes mellitus

d) Did the applicant request exclusivity?

YES NO

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

N/A

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?

N/A

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# N/A

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 022350	Onglyza (saxagliptin) approved at doses of 2.5 mg and 5.0 mg
NDA# 020357	Glucophage (metformin HCL) approved at doses of 500 mg, 850 mg, and 1000 mg
NDA# 021202	Glucophage XR (metformin HCL) approved at doses of 500 mg and 750 mg

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:

N/A

(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:

N/A

(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:

N/A

(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:

Study CV181014, Study CV181039, and Study CV181038-- note that all these clinical investigations were previously submitted and reviewed under NDA 022350 (saxagliptin).

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:

Study CV181014-- NDA 022350
Study CV181039-- NDA 022350

Study CV181038-- NDA 022350

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:

N/A

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"):

N/A

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 # N/A YES ! NO ! Explain:

Investigation #2
IND # N/A YES ! NO ! Explain:

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

Investigation #1
!
!
YES ! NO
Explain: ! Explain:
N/A

Investigation #2
!
!
YES ! NO
Explain: ! Explain:
N/A

(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:

N/A

=====
Name of person completing form: Raymond Chiang
Title: Consumer Safety Officer
Date: January 10, 2011

Name of Office/Division Director signing form: Hylton Joffe on behalf of Mary Parks

Title: CDTL

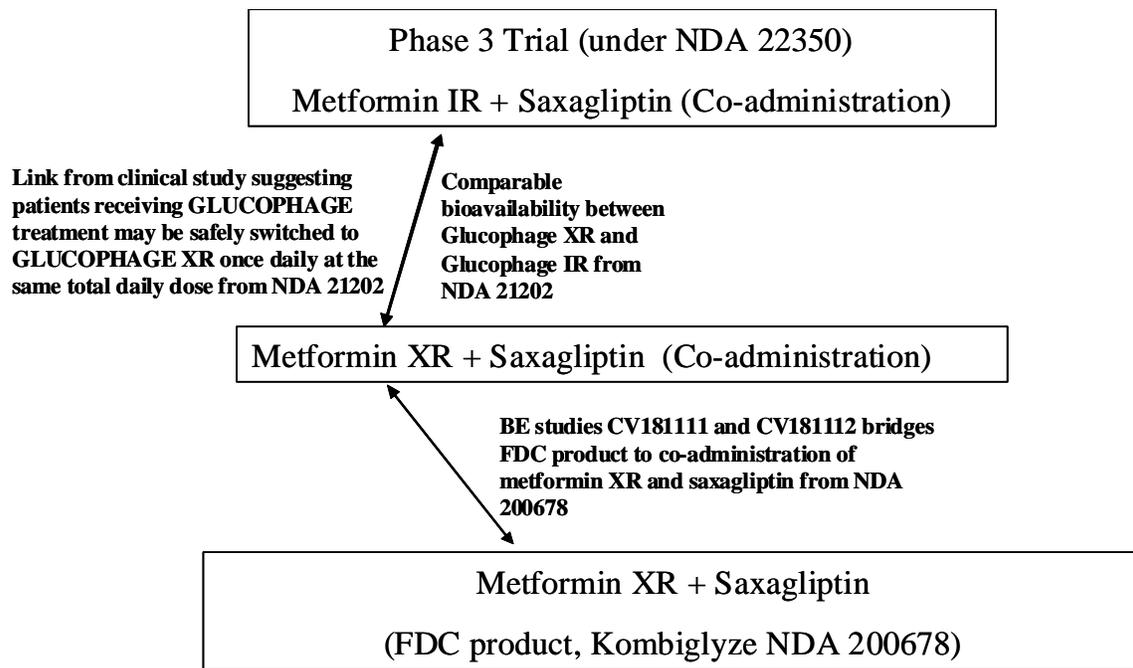
Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

CONCLUSIONS:

NDA 21202 demonstrated the comparable bioavailability between Glucophage XR and Glucophage IR. The differences in C_{max} between the two formulations did not appear to result marked differences in efficacy based on a clinical trial in which patients with T2DM receiving Glucophage IR were either maintained on this regimen or switched to Glucophage XR. Also, the current product label of GLUCOPHAGE XR states that **“In a randomized trial, patients currently treated with GLUCOPHAGE were switched to GLUCOPHAGE XR. Results of this trial suggest that patients receiving GLUCOPHAGE treatment may be safely switched to GLUCOPHAGE XR once daily at the same total daily dose, up to 2000 mg once daily”**

Figure 1 summarizes the bridging between the metformin extended-release and the metformin IR, which was co-administered with saxagliptin in the long term Phase 3 safety and efficacy trials in support of NDA 200678. In addition, the sponsor conducted BE studies comparing metformin XR and saxagliptin co-administered together to the FDC combination product and demonstrated that there was no formulation effect bridging the individual saxagliptin and metformin extended-release to Kombiglyze XR.

Figure 1: Link between FDC product (Kombiglyze XR) and metformin IR and saxagliptin co-administration used in the Phase 3 trials.



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

/s/

RITESH JAIN
11/04/2010

SALLY Y CHOE
11/04/2010

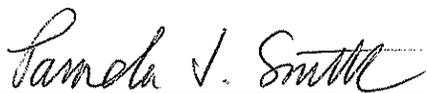
CHANDRAHAS G G SAHAJWALLA
11/04/2010

NDA 200678

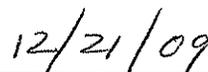
**SAXAGLIPTIN (BMS-477118) AND METFORMIN EXTENDED-
RELEASE FIXED DOSE COMBINATION (FDC)**

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



Pamela J. Smith, M.D.
Group Director, Global Regulatory Sciences
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543
Pamela.Smith@bms.com
609-252-5228



Certification Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 200678 BLA #	NDA Supplement # N/A BLA STN #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Kombiglyze Established/Proper Name: saxagliptin/metformin HCL extended release fixed dose combination (FDC) Dosage Form: tablets		Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):
RPM: Mehreen Hai/ Raymond Chiang		Division: DMEP
<p>NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>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>October 29, 2010</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None

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.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ²</p> <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 BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<p><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</p>

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 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 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 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 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 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 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	Included
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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) 11.5.10
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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. 	See Approval letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12.29.09
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Janumet (not included in Action Package)

³ Fill in blanks with dates of reviews, letters, etc.
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<ul style="list-style-type: none"> ❖ 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 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. 	See Approval letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12.29.09
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ 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 	See Approval Letter
<ul style="list-style-type: none"> ❖ 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>) 	10.29.10, 10.29.10, 8.6.10, 5.27.10 7.13.10, 5.27.10
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 11.4.10 <input checked="" type="checkbox"/> DMEPA 7.2.10 <input checked="" type="checkbox"/> DRISK 10.14.10 (PPI) <input checked="" type="checkbox"/> DDMAC 10.15.10 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	9.2.10
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>October 6, 2010</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
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	10.29.10, 10.28.10, 10.27.10, 9.26.10, 9.24.10, 9.24.10, 9.14.10, 9.10.10, 9.10.10, 9.7.10, 8.27.10,

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

	8.6.10, 8.4.10, 7.29.10, 7.21.10, 7.16.10, 7.2.10, 6.23.10, 5.27.10, 5.12.10, 3.12.10, 2.13.10, 1.25.10, 1.8.10
❖ 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 October 15, 2009
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• 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 11.4.10
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11.4.10
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	see CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	9.28.10
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input 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 12 (section 3.3) of clinical review
❖ 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
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	REMS Memo 10.7.10
• 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 type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁵ Filing reviews should be filed with the discipline reviews.
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Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 10.1.10 (concurrent by TL)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 11.4.10 addendum (concurrent by TL), 10.15.10 (concurrent by TL)
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None 10.8.10
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 9.22.10 (concurrent by TL)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<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 (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 10.28.10 (biopharm), 10.26.10
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 10.20.10 (biopharm), 9.30.10 (concurrent by TL), 9.28.10 (biopharm), 5.25.10 (concurrent by TL)
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 9.29.10 (concurrent by TL)
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(all original applications and all efficacy supplements that could increase the patient population)	page 82 of primary Product Quality review
<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</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 2.9.10 <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</i>) (<i>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 type="checkbox"/> Not needed (per review)

...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.

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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.



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

Memorandum

Date: November 4, 2010
From: Raymond Chiang, Regulatory Project Manager
Subject: Memo regarding NDA 200678 PI/PPI and Carton and Container labels

BMS made final submission of carton and container labels on October 22, 2010. BMS incorporated all our requested changes as per the FDA information request. See below. The final submission of carton and container labels were determined as acceptable by DMEP RPM, DMEPA AND DDMAC.

BMS made final submission of PI/PPI on November 1, 2010. The label was reviewed by DMEP and deemed acceptable.

From: Chiang, Raymond
Sent: Wednesday, October 20, 2010 3:14 PM
To: 'Lamendola, Joseph'
Cc: Smith, Pamela
Subject: RE: carton and container labels- NDA 200678

Hello Dr. Lamendola,

As per our phone conversation, please see comments/requests regarding your carton and container labels.

1. Increase the prominence of the statement of strength on the trade container labels and professional sample carton labeling.
2. For the carton and container labels, we recommend that K (kombiglyce) should be capital, XR should be capital, and T (tablets) should be capital.

Please email and submit the revised carton and container labels, incorporating these requested changes, no later than noon, Friday, October 22, 2010. To streamline the process, please submit the revised carton and container labels in the same submission as the revised PI.

Also, in the cover letter, please state that no changes have been made to the carton and container labels except what was explicitly requested by FDA as per 10.20.10 email.

thanks!
ray

From: Chiang, Raymond
Sent: Monday, November 01, 2010 9:40 AM
To: 'Lamendola, Joseph'
Cc: 'Smith, Pamela'
Subject: RE: Kombiglyze XR PI/PPI sent to BMS 11.1.10

Hi Dr. Lamendola and Dr. Smith,

Please see attached Kombiglyze XR PI/PPI with DMEP's edits incorporated. Please provide a response by email and as an official amendment to NDA 200678 within the next couple days. If you accept all our edits, please provide a clean Word and pdf copy accepting all our edits.

thanks!
ray

<< File: saxag-metfo-markup sent to BMS 11.1.10.doc >>

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

/s/

RAYMOND S CHIANG
11/04/2010



NDA 200678

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Pamela J. Smith, M.D.
Group Director, Global Regulatory Strategy
Metabolism and Endocrine Products

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) dated December 29, 2009, received December 29, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxagliptin and Metformin Hydrochloride Extended-release Tablets, 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg.

We also refer to your September 29, 2010, correspondence, received September 29, 2010, requesting review of your proposed proprietary name, Kombiglyze XR. We have completed our review of the proposed proprietary name, Kombiglyze XR, and have concluded that it is acceptable.

The proposed proprietary name, Kombiglyze XR, will be re-reviewed 90 days prior to the approval of the NDA.

If **any** of the proposed product characteristics as stated in your September 29, 2010, 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 Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Raymond Chiang at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
10/29/2010

Memo to File

NDA:	200-678
Submission Date:	December 29, 2010
Type of Submission:	Original NDA
Product name	(b) (4) (Saxagliptin/metformin HCl)
Dosage Form:	Extended Release Fixed Dose Combination Tablets
Dosage Strengths:	5mg saxa/500 mg met, 5 mg saxa/1000 mg met, 2.5 mg saxa/1000 mg
Sponsor:	Bristol-Myers Squibb Company

Reference to Biopharmaceutics review dated September 28, 2010, the following two comments are made to clarify recommendations # 2 and # 3 found in the above mentioned review and listed below in [blue color](#) for convenience.

Recommendation #2

The request to waive the requirement to repeat the in vivo BE study using Saxa 5/Met XR 500 manufactured at the commercial scale is not applicable, because the sponsor decided to repeat the study using the to-be-marketed FDC formulation manufactured at the BMS manufacturing facility at Mt Vernon, IN (test) versus 5 mg Onglyza and 500 mg Glucophage XR (Evansville, IN, clinical formulation) using commercial scale batches.

Comment 1 to clarify Recommendation # 2 in the above mentioned review:

The sponsor does not need to repeat the bioequivalence study because of using a small scale batch, as the application contains dissolution data demonstrating that the small scale batch has the same release characteristics of the large scale batch.

Recommendation #3

The request to waive any requirement to conduct an in vivo bioequivalence study of Saxa 5/Met XR 500, Saxa 5/Met XR 1000, and Saxa 2.5/Met XR 1000 manufactured using Mt. Vernon Met XR (b) (4) with the same Saxa/Met XR products manufactured using Evansville Met XR (b) (4) is acceptable.

Comment 2 to clarify Recommendation # 3 in the above mentioned review:

The acceptance of the Biowaiver for manufacturing site change is not applicable because the sponsor provided in-vivo data demonstrating that the to-be-marketed formulation manufactured at the new site (Mt. Vernon) is bioequivalent to the clinical trial formulation.

Houda Mahayni, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.

Biopharmaceutics Lead
Office of New Drug Quality Assessment

APPEARS THIS WAY ON
ORIGINAL

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/s/

HOUDA MAHAYNI
10/28/2010

PATRICK J MARROUM
10/28/2010



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

Memorandum

Date: October 27, 2010
From: Raymond Chiang, Regulatory Project Manager
Subject: Information request NDA 200678 regarding phase 3 trials

From: Chiang, Raymond
Sent: Wednesday, October 27, 2010 2:10 PM
To: 'Lamendola, Joseph'
Cc: 'Smith, Pamela'
Subject: RE: NDA 200678

Hi Dr. Lamendola and Dr. Smith,

We have the following information request:

Clarify which of the completed and ongoing phase 3 trials included in your saxagliptin/metformin FDC initial NDA submission and 120-day safety update used/are using metformin XR. Provide study details for the ongoing trials that are using metformin XR (e.g., study design, treatment groups, population, sample size, current status of trial including number of patients enrolled and when the trial will be completed).

Please confirm receipt of this email.
We request a response ASAP.

thanks!
ray

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/s/

RAYMOND S CHIANG
10/27/2010

**DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS
SAFETY TEAM
MEMO TO THE FILE**

NDA#/Submission #/Submission type: 200678/000/N

Product Name: (b) (4) (saxagliptin/metformin HCl extended-release) tablets

Application submission date: 29 December 2009

Safety team reviewer: Amy G. Egan, M.D., M.P.H.

Safety review completion date: 4 October 2010

Action goal date: 29 October 2010

Reason for Review: New PPI

Items Reviewed: PI/PPI/Clinical review

Synopsis of Findings: (b) (4) is a fixed-dose combination of saxagliptin, a DPP-4 inhibitor, and extended-release metformin, a biguanide. There are 3 proposed dosage strengths, 5mg/500mg, 5mg/1000mg, and 2.5mg/1000mg. Saxagliptin was approved July 31, 2009 with a PPI; metformin HCl extended-release was approved October 13, 2000 without a PPI or a Medication Guide; however, Medication Guides are approved with other metformin-containing combination products including Janumet (sitagliptin/metformin HCl), ActoplusMet (pioglitazone/metformin HCl), ActoplusMet XR (pioglitazone/metformin HCl XR), and Avandamet (rosiglitazone/metformin HCl). Metaglip (glipizide and metformin HCl) and Glucovance (glyburide and metformin HCl) have PPIs.

According to the medical review, no new safety issues were identified with co-administration of saxagliptin and metformin XR. The known safety issues with saxagliptin include: hypersensitivity, and lymphopenia; dosage adjustment is required for moderate or severe renal impairment. The known safety issues with metformin XR include: lactic acidosis due to metformin accumulation, especially in the setting of compromised renal function, and a decrease in Vitamin B12 levels.

Unlike sitagliptin, saxagliptin remains unlabeled with respect to the occurrence of pancreatitis. At the time of approval, there were 6 (0.2%) cases of pancreatitis in patients treated with saxagliptin versus 2 (0.2%) cases in patients treated with comparator. An OSE review of AERS was conducted in May 2010 that revealed two reports of acute pancreatitis associated with saxagliptin use. In the last PSUR (dated January 31, 2010 to April 30, 2010), there were 7 cases of pancreatitis reported. The sponsor has been asked to provide a summary/analysis of all postmarketing pancreatitis cases along with drug

utilization data, and to provide a cumulative summary of the data on pancreatitis in future PSURs. Additionally, saxagliptin will undergo a 915 review beginning 31 January 2011 at which time a more comprehensive approach to this safety issue will be undertaken to determine if the saxagliptin label should be revised to include language regarding acute pancreatitis and whether a Medication Guide-only REMS should be required.

At this time, I do not recommend that the PPI be converted to a Medication Guide or that a REMS be required.

Determination:

REMS triggered: Y N I

If yes (Y) or indeterminate (I), was submission referred to the SRT?: Y N

Date submitted:

Date response received:

SRT response:

If no (N), why not?:

If no (N), please check one (or more) of the following reasons below:

No significant safety issue identified

Only editorial changes made

Changes pertain only to proper use of a device

Other:

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/s/

AMY G EGAN
10/07/2010

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Sunday, September 26, 2010 5:53 PM
To: 'Smith, Pamela (pamela.smith@bms.com)'
Cc: Hai, Mehreen; Chiang, Raymond
Subject: NDA 200678 saxagliptin + metformin XR FDC information request

Hi Pam,

Re: NDA 200678 saxagliptin + metformin XR FDC information request

We have noted at least 3 cases of tuberculosis among saxagliptin-treated patients in the clinical trials submitted to support your saxagliptin + metformin XR fixed-dose combination tablet. One saxagliptin-treated patient in Study 181014 discontinued due to tuberculosis meningitis, one saxagliptin-treated patient in Study 181064 discontinued due to pulmonary tuberculosis, and one saxagliptin-treated patient in Study 181054 had a serious adverse event of pulmonary tuberculosis. Please provide an analysis of tuberculosis adverse events among saxagliptin treated patients and among comparator treated patients from your entire controlled clinical trial database available to date. Provide narratives for all cases of tuberculosis. Include information on lymphocyte counts at baseline and during treatment with study medication as well as information on other risk factors, if available. Present data individually by trial and also pooled across your database and clearly show saxagliptin dose. Include an additional analysis that incorporates other atypical infections.

I would also like to take this opportunity to introduce you to Raymond Chiang. Mehreen will be going on maternity leave in just a few days, and Ray will be picking up her applications, including this NDA. Please contact him in lieu of Mehreen from here on out.

Ray's email address: cc'd on this email
Ray's phone #: 301.796.1940

Best,
Lina

***Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
l.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)***

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/s/

LINA ALJUBURI
09/26/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
cc: [Chiang, Raymond;](#)
Subject: Another info request
Date: Friday, September 24, 2010 10:04:38 PM

Hi Pam,

We received your submissions today containing the pediatric protocol submission date, and the responses to our info requests, so thank you for that.

I have another info request for you. Back on May 12, 2010, I had sent you an info request regarding batch sizes for studies CV181111 and CV181112, in response to which you had emailed me a document on May 17, 2010. We want to follow up on that document: the table for the tablet batch size has both dots and commas which doesn't make any sense. Could you please check on this and verify the exact batch sizes of the tablets. Also, could you please submit your response officially to the NDA?

Thank you, and as you can imagine, we would really appreciate a quick turnaround on this.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
09/24/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
Subject: RE: Pediatric synopsis
Date: Wednesday, September 22, 2010 4:26:58 PM

Pam,
I'm afraid we need the protocol submission date as well. Is it too late to include that in the letter?

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Smith, Pamela [<mailto:pamela.smith@bms.com>]
Sent: Wednesday, September 22, 2010 4:03 PM
To: Hai, Mehreen
Subject: RE: Pediatric synopsis

Hi Mehreen,

The letter will include day, month, year of study start and final CSR. It also includes the deferral certification in the format you provided (Thank you!)

Pam

From: Hai, Mehreen [<mailto:Mehreen.Hai@fda.hhs.gov>]
Sent: Wednesday, September 22, 2010 3:26 PM
To: Smith, Pamela
Cc: Chiang, Raymond
Subject: RE: Pediatric synopsis

Thanks, Pam.

And just as a quick reminder, it needs to be day, month and year.

Also, any update on the deferral certification?

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

From: Smith, Pamela [mailto:pamela.smith@bms.com]

Sent: Wednesday, September 22, 2010 3:22 PM

To: Hai, Mehreen

Subject: RE: Pediatric synopsis

Hi Mehreen,

Apologies that "in our haste" to submit the study synopsis we omitted the proposed study timelines. We will be submitting a letter to the NDA with the timelines today.

Pam

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]

Sent: Tuesday, September 21, 2010 4:52 PM

To: Smith, Pamela

Cc: Chiang, Raymond

Subject: Pediatric synopsis

Hi Pam,

We received the synopsis for the second study a little while ago, so thank you for that. Unfortunately, I wasn't able to find any dates for protocol submission, study start date, and study report submission date in there. Did I miss something? Could you please send these dates as soon as possible, maybe along with the other info request I sent earlier today, regarding the deferral certification. We

need to have all our pediatric paperwork in order by Monday at the latest.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
09/24/2010

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/s/

MEHREEN HAI
09/22/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
cc: [Chiang, Raymond;](#)
Subject: Deferral certification for NDA 200678
Date: Tuesday, September 21, 2010 2:48:50 PM

Hi Pam,

I'm afraid there's something else we need from you for the pediatric studies, and that too pretty quickly. We need certification for the deferral of the pediatric studies from you. You may already know what this looks like, but in case you don't, here's an example. You obviously don't need to follow it word for word.

Request for Deferral of Pediatric Studies

<<Name of company>> is requesting deferral of pediatric studies for <<NDA #>>. This application requests approval of <<name of drug product>> as an adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization. No pediatric data, therefore, have been included in this application in accordance with the provisions of 21 CFR 314.55.

In accordance with 21 CFR 314.55(b)(1) FDA may, at the request of an applicant, defer submission of some or all assessments of safety and effectiveness in pediatric patients until after approval of the drug product for use in adults. At the End-of-Phase 2 meeting, the sponsor proposed a deferral of submission of pediatric data with the initial application on grounds that pediatric studies should be delayed until adequate safety and effectiveness data have been collected in adults. This proposal was agreed by the Agency at the End of Phase 2 Meeting and the Agency's agreement was confirmed at the Type C meeting held on

<<Name of company>> certifies that pediatric studies are planned and will be conducted with due diligence. Specific details about planned pediatric studies have recently been submitted to ... etc, etc.

Since this consists of just a cover letter, it would be great if you could submit this within the next couple of days. We are preparing the paperwork for the pediatric committee, and this is one of the necessary items that we have just discovered is missing.

Thank you, and please let me know if you have any questions.

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

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/s/

MEHREEN HAI
09/24/2010

MEMORANDUM OF TELECON

DATE: September 7, 2010 (3:00 – 4:00 P.M. EST)

APPLICATION NUMBER: NDA 200678

DRUG NAME: Saxagliptin and Metformin Extended-Release Fixed-Dose Combination

BETWEEN:

Pamela Zee (Clinical, BMS)
Roland Chen (Clinical, BMS)
Ronald Portman (Clinical, BMS)
Robert Wolf (Clinical, BMS)
Fred Fiedorek (Clinical, BMS)
Peter Ohman (Clinical, AZ)
David Henry (Biostatistics, BMS)
Susan Harris (Biostatistics, AZ)
Anther Keung (Clinical Pharmacology, BMS)
Frank LaCreta (Clinical Pharmacology, BMS)
Pamela Smith (Regulatory, BMS)
Joseph Lamendola (Regulatory, BMS)
Deborah McGill (Regulatory, AZ)
Annette Mattsson (Regulatory, AZ)

Bristol-Myers Squibb Company (BMS) and collaborators from AstraZeneca (AZ)
P.O. Box 4000
Princeton, NJ 08543-4000
(732) 863-0037

AND

Hylton Joffe, M.D. (Diabetes Clinical Team Leader, DMEP)
Arlet Nedeltcheva-Peneva, M.D. (Clinical Reviewer, DMEP)
Ritesh Jain, Ph.D. (Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II)
Hari Sachs, M.D. (Team Leader, Pediatric and Maternal Health Staff)
George Greeley (Regulatory Project Manager, Pediatric and Maternal Health Staff)
Mehreen Hai, Ph.D. (Regulatory Project Manager, DMEP)
Lina AlJuburi, Pharm.D., M.S. (Chief, Project Management Staff, DMEP)

SUBJECT: Discussion regarding pediatric study requirement under PREA for this pending NDA.

Background

Bristol-Myers Squibb (BMS) submitted NDA 200678 for the saxagliptin and metformin extended-release fixed-dose combination tablet on December 29, 2009. Saxagliptin was approved by the FDA in July 2009, under the tradename Onglyza (NDA 022350). Extended-release metformin was approved by FDA in October 2000, under the tradename Glucophage XR (NDA 021202). Both drugs are for the treatment of type 2 diabetes mellitus (T2DM), and the NDAs for both are held by Bristol-Myers Squibb.

Saxagliptin was approved with a Post-Marketing Requirement (PMR) that a randomized and controlled pediatric study be conducted in patients ages 10-17 with T2DM. The protocol for this study (to be conducted under IND 63634) has not been submitted to date.

(b) (4)

On July 20, 2010, BMS submitted a proposed pediatric plan. This plan consisted of a pharmacokinetic study in pediatric patients

(b) (4)

On July 27, 2010, the DMEP clinical and clinical pharmacology reviewers and team leaders met internally with reviewers from the Pediatric and Maternal Health Staff to discuss this submission. Following this meeting, a letter was issued to BMS on July 29, 2010, containing further information requests and comments.

(b) (4)

In addition, the letter stated that the add-on to metformin arm should include patients on metformin XR to provide further supportive data for the FDC tablet.

BMS submitted their response to our letter on August 13, 2010.

(b) (4)

It was decided that an internal discussion followed by a teleconference with BMS would be held, and was scheduled for September 7, 2010.

Teleconference

[REDACTED] (b) (4)

The FDA reviewers recommended that the patients in that arm be randomized, and also that the patients be divided between metformin XR as well as metformin IR, in order to obtain clinical efficacy data in pediatric patients with the FDC product.

BMS explained that it was difficult for them [REDACTED] (b) (4) and inquired whether it would be acceptable for them to conduct the metformin arm as a separate study. FDA informed them that it would be acceptable, pending approval from Dr. Mary Parks (Division Director).

FDA suggested that BMS submit a synopsis for the separate study, including the necessary Postmarketing Requirement dates. BMS also inquired whether the negotiations over the details of the second study would delay the action taken on the NDA for the FDC product. FDA informed them that the action goal date should not be affected, as details of the study are usually worked out at the time of submission of the protocol (postapproval).

Post-teleconference note:

Dr. Joffe spoke with Dr. Mary Parks about whether she thought it was acceptable for BMS to conduct the saxagliptin add-on to metformin scenario as a separate study, and she said that it was acceptable. This was communicated to BMS by email on September 10, 2010.

Memo prepared by: Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Concurrence: Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
09/14/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
Subject: Tcon follow-up
Date: Friday, September 10, 2010 1:54:40 PM

Hi again Pam,

As I told you over the phone, following the teleconference we had on Tuesday (9/7/10) about your pediatric plan for saxagliptin and saxagliptin-metformin FDC, Dr. Joffe spoke with Dr. Mary Parks about whether she thought it was acceptable for you to conduct the saxagliptin add-on to metformin scenario in a separate study, and she said that it was acceptable.

Also, could you please email me the list of attendees from your end who were present at the tcon?

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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MEHREEN HAI
09/10/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
Subject: Information Request for NDA 200678
Date: Friday, September 10, 2010 1:47:06 PM

Hi Pam,

We have the following information request for NDA 200678:

With regard to your response dated 8/3/10 to question #6 of our information request dated 7/2/10, we are requesting that you resubmit the table for the drug product specifications (Table 2.3.P.5.T01) with the following addition:

An asterisk (*) at the "Metformin HCl Weight Variation" corresponding to a footnote at the bottom of the table:  (b) (4)

Also, we sent you an information request letter dated July 21, 2010. Can we expect a response to this soon?

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

Application
Type/Number

Submission
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Submitter Name

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NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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MEHREEN HAI
09/10/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
Subject: Pediatric plan
Date: Friday, August 27, 2010 1:37:55 PM

Hi Pam,

We reviewed your submission dated August 13, 2010, containing responses to the additional information we had requested in our July 29, 2010 letter, regarding the pediatric plan for NDA 200678.

Since you are planning to submit the protocol for the (b) (4) pediatric study by mid-September, we request that you submit a **synopsis** of this study to NDA 200678 as soon as possible. We need this information for the pediatric committee. Could you also please let me know how soon you can get that synopsis to us, so that we can plan things at our end?

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Application
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Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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MEHREEN HAI
08/27/2010



NDA 200678

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Pamela J. Smith, M.D.
Group Director, Global Regulatory Strategy
Metabolism and Endocrine Products

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) dated December 29, 2009, received December 29, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxagliptin and Metformin Hydrochloride Extended-release Tablets, 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg.

We also refer to your June 16, 2010, correspondence, received June 16, 2010, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable (b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Mehreen Hai at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

CAROL A HOLQUIST
08/06/2010

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Wednesday, August 04, 2010 4:27 PM
To: 'Smith, Pamela (pamela.smith@bms.com)'
Cc: Hai, Mehreen
Subject: RE: Letter re. pediatric plan

Hi Pam,

We have the following comments to the statements included in your July 29, 2010 email regarding the pediatric plan for the saxagliptin + metformin FDC.

(b) (4)

(b) (4)

FDA response: (b) (4)

The fact that effectiveness and safety of metformin XR has not been established in children is reason enough for obtaining some clinical data in patients co-administered saxagliptin and metformin XR to support your saxagliptin/metformin XR FDC tablet.

Please contact Mehreen and/or me if you have questions.

Best,
Lina

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research

8/4/2010

Food and Drug Administration
I.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)

From: Smith, Pamela [mailto:pamela.smith@bms.com]
Sent: Thursday, July 29, 2010 10:14 PM
To: Hai, Mehreen
Subject: RE: Letter re. pediatric plan

Dear Mehreen,

As discussed in our phone conversation today, please see below for an initial comment regarding the pediatric advice letter you sent today by email:

Re comment 3:

[Redacted content] (b) (4)

[Redacted content] (b) (4)

We will provide full responses to the comments in your letter re the Saxagliptin/Metformin XR pediatric plan, and we will submit the responses within two weeks of the date of your letter (July 29).

Pam Smith
Bristol-Myers Squibb
609-252-5228

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

LINA ALJUBURI
08/04/2010



NDA 200678

GENERAL ADVICE

Bristol-Myers Squibb Company
Attention: Pamela J. Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for saxagliptin and metformin HCl extended-release tablets (5/500 mg, 5/1000 mg and 2.5/1000 mg).

We also refer to your submission dated July 16, 2010, containing a proposal for a study in pediatric patients ages 10-^(b)₍₄₎ years, (b) (4)

We have reviewed this submission and have the following comments and recommendations.

Please submit the following information regarding the pediatric plan for the saxagliptin/metformin XR fixed dose combination (FDC) tablet:

1. The ages for which you are requesting a waiver and for which you are requesting a deferral. Include a rationale for the partial waiver. The rationale for the waiver should address at least one of the following four criteria: (1) studies are impossible or highly impractical (e.g., too few pediatric patients), (2) the product would be ineffective or unsafe in the pediatric group for which a waiver is being requested, (3) the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients, or (4) reasonable attempts to produce a pediatric formulation have failed.
2. Clarify the dimensions of the saxagliptin/metformin XR FDC tablet compared to the saxagliptin tablet and compared to the metformin XR tablet. Clarify what is planned with regard to the formulation if the swallowability test results show that children cannot swallow the FDC tablet.

(b) (4)

(b) (4)

(b) (4) In addition, the add-on to metformin arm should include patients on metformin XR to provide further supportive data for your FDC tablet.

Regarding your proposed clinical pharmacology study:

4. Please provide the dates by when you will (a) submit the final protocol, (b) enroll the first patient and (c) submit the complete study report.
5. Based on the known half-lives of saxagliptin and metformin IR, your proposed two consecutive day dosing seems reasonable. However, because of the uncertainty of saxagliptin's half-life in the pediatric population, we recommend that you consider adding a wash-out period between the two dosing regimens (e.g., a three-day wash-out).
6. We recommend that you evaluate the active metabolite of saxagliptin in this study.

We request that you provide a response within two weeks from the date of this letter.

If you have any questions, please contact Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MARY H PARKS
07/29/2010



NDA 200678

GENERAL ADVICE

Bristol-Myers Squibb Company
Attention: Pamela J. Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for saxagliptin/metformin HCl extended-release tablets (5/500 mg, 5/1000 mg and 2.5/1000 mg).

We are in the process of reviewing your NDA and have the following comments and recommendations.

Your proposal to (b) (4) for the Microbial Limits test is unacceptable because it does not comply with 21 CFR 211.165(a) and (b).

(b) (4)
(b) (4) The product specification should state that the product will meet the requirements of USP<1111>, if tested. These process controls, tests and acceptance criteria should be identified in the batch release criteria, and include, for example:

- Microbial limits data for critical raw materials,
- Microbiological environmental monitoring data for critical processing steps that can be related to the batch, and
- In-process control parameters (b) (4) that may affect product quality microbiology.

In addition, microbial limits testing should be performed at the initial time point (at a minimum) on stability samples.

If you have any questions, please contact Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MARY H PARKS
07/21/2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
07/19/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
Subject: Comments on carton and container labels
Date: Friday, July 16, 2010 3:12:50 PM
Attachments: NDA 200678 Carton Container label comments.pdf

Hello Pam,

We have finished our review of the carton and container labels that you submitted for NDA 200678. Please see our comments in the attached document. While we're aware that the tradename (b) (4) has been found unacceptable, most of these comments will apply to whichever name is finally approved. We recommend that when an alternate name is found acceptable that you submit revised labels and labeling with the new name for our review and comment.

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

A. General Comments on the Container Labels, Professional Sample Blister Labels, and Professional Sample Carton Labeling

1. The (b) (4) and (b) (4) portions of the name are presented in two different colors and fonts on the container labels and professional sample carton labeling. The (b) (4) portion of the name is highlighted and more prominent since it is in a darker color and heavier font than the remaining portion of the name. This may make product selection from a shelf more difficult. Therefore, we request you present the entire name in the same color and font in a manner that gives equal prominence to all the letters in the name.
2. The established name has (b) (4) that separates the two ingredients (i.e., (b) (4)). Replace (b) (4) with the word “and” so that the established name reads as: (Saxagliptin and Metformin HCl Extended-release) Tablets.
3. The dosage form statement “tablets” is part of the established name but appears smaller in size as compared to the established name and is difficult to read. Increase the size of the dosage form statement so that it is commensurate with the size of the active ingredients.
4. Include instructions that state the product “must be swallowed whole and never crushed, cut or chewed”. Place this information on the principal display panel.

B. Container Labels and Professional Sample Carton Labeling

1. Each strength is presented in a color block. However, the color blocks used for each strength are green, purple or blue. Green and purple are also the colors used in the trade dress and blue is a color that can look similar to green and purple. This use of color minimizes the effectiveness of color to differentiate the strengths. In order to better differentiate the strengths, present the strength in color blocks that are not the same or similar in color to those colors used in the trade dress.
2. The statement of strength is located at the very top of the labels and labeling, above the net quantity statement and NDC number. This is not the usual location of the statement of strength. Relocate the statement of strength to appear on the line below the established name and dosage form so that patients and healthcare providers can easily find this information.
3. Specify the location for the lot number and expiration date on the labels and labeling.

C. Bulk Container Label (500-count)

On the 500-count bulk bottle, place instructions to the pharmacist concerning the type of container in which the tablets should be dispensed.

D. Professional Sample Blister Labels

1. Each blister card contains either 6 or 7 tablets and there is one label that covers the blister. Thus, as the tablets are used the label can be torn, ripped, or punched out. This can interfere with the product identifying information on the label such as the

proprietary name, established name, dosage form and strength and render it unreadable. We recommend that each tablet be packaged in its own blister with its own label such that as the tablets are used the product identifying information for the remaining tablets stays intact. Alternatively, at a minimum, repeat the product information over and over so that as the tablets are removed there is product identifying information that remains intact on the label.

2. Include instructions on the label that instruct patients on how to remove the tablets from the blister.

E. Professional Sample Carton Labeling

On each carton there is a round color graphic that contains the strength. Delete the graphic. Relocate the statement of strength from the top of the carton labeling to appear on the line below the established name. See comment B-2, above.

Application
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Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
07/16/2010



NDA 200678

INFORMATION REQUEST

Bristol-Myers Squibb Company
Attention: Pamela J. Smith, M.D
Group Director, GRS
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your December 29, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for saxagliptin/metformin HCl extended-release tablets.

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

[Redacted] (b) (4)

2. It is noted in table 3.2.P.2.3.3.T11, that for one of the design space confirmatory batches (batch #8, [Redacted] (b) (4) the saxagliptin content uniformity %RSD is [Redacted] (b) (4) the allowable limit of [Redacted] (b) (4) Comment on this discrepancy. In addition provide the individual tablet data for saxagliptin content for each of the eight batches.
3. If applicable, describe how the [Redacted] (b) (4) would be used to support movements within and outside the design space for this application.
4. Provide data to demonstrate that variations in [Redacted] (b) (4) hold times would have no adverse impact on finished product quality.
5. Provide details about the [Redacted] (b) (4) procedure that was adopted to obtain the design space ranges at commercial scale for the [Redacted] (b) (4) from the pilot scale ranges. For example, indicate how pilot scale experimental data, information from vendors, knowledge of [Redacted] (b) (4) principles and the [Redacted] (b) (4) were used in tandem to derive the design space ranges at commercial scale. Additionally, explain your approach when moving to other equipment or scales.
6. [Redacted] (b) (4)
[Redacted] (b) (4). To ensure the content of the metformin HCl in the final product remains consistent, institute dose uniformity for metformin HCl content on the finished tablet.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

ALI H AL HAKIM
07/02/2010

MEMORANDUM OF TELECON

DATE: June 18, 2010 (2:30 – 3:15 P.M. EST)

APPLICATION NUMBER: NDA 200678

DRUG NAME: Saxagliptin and Metformin Extended-Release Fixed-Dose Combination

BETWEEN:

Names Pamela J. Smith, M.D.
Group Director, Global Regulatory Strategy
Metabolism and Endocrine Products
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
Phone: (732) 863-0037

AND

Mehreen Hai, Ph.D. (Regulatory Project Manager, DMEP)
Lina AlJuburi, Pharm.D., M.S. (Chief, Project Management Staff, DMEP)

SUBJECT: Discussion regarding the request for (b) (4) pediatric studies for this pending NDA.

Background

Bristol-Myers Squibb (BMS) submitted NDA 200678 for the saxagliptin and metformin extended-release fixed-dose combination tablet on December 29, 2009. Saxagliptin was approved by the FDA in July 2009, under the tradename Onglyza (NDA 022350). Extended-release metformin was approved by FDA in October 2000, under the tradename Glucophage XR (NDA 021202). Both drugs are for the treatment of type 2 diabetes mellitus (T2DM), and the NDAs for both are held by Bristol-Myers Squibb.

Saxagliptin was approved with a Post-Marketing Requirement (PMR) that a randomized and controlled pediatric study be conducted in patients ages 10-17 with T2DM. The protocol for this study (to be conducted under IND 63634) has not been submitted to date.

(b) (4)

(b) (4)

DMEP will review the pediatric protocol and provide comments to BMS upon receipt of the submission.

On May 20, 2010, BMS was informed by email that for the pediatric study requirement, a deferral (b) (4) was possible, and therefore, BMS should submit a proposed pediatric plan to NDA 200678. On June 11, 2010, BMS informed FDA by email that they would submit this plan by July 31, 2010.

On June 15, 2010, the clinical and clinical pharmacology reviewers and team leaders met internally with reviewers from the Pediatric and Maternal Health Staff to discuss the appropriate recommendations to be made to the Pediatric Review Committee for this NDA. (b) (4)

This brought up the issue of whether the larger tablets of this new formulation are feasible for younger patients to swallow.

It was decided that a teleconference between the regulatory contact at BMS and members of the DMEP Project Management Staff would be held and the following information would be communicated/requested:

- 1) (b) (4), the pediatric requirement for this pending NDA would be deferred. (b) (4)
- 2) Please describe any pediatric data (either clinical or pharmacokinetic), or data comparing pediatric patients to adult patients, for metformin XR.
- 3) Please submit a proposal for a feasibility study using the fixed-dose combination tablet for pediatric patients down to 10 years old at the same time as your proposed pediatric plan.

Teleconference

All three items listed above were communicated to the sponsor during the teleconference. In response to comment #2, BMS informed FDA that there were no such data available for metformin XR. However, the requirement for a pediatric study with metformin XR was previously waived (see letter from FDA dated April 20, 2006, under NDA 021202 for

Glucophage XR). Also, BMS had found that for metformin IR, the pharmacokinetics in pediatric patients were similar to that in adults.

The sponsor was told that a direction regarding the required pediatric studies would be discussed further internally within the Agency upon receipt and review of their pediatric plan (and the feasibility study as part of that pediatric plan). The sponsor was asked to submit this earlier in July, if possible, in order to provide the division with time for review prior to the scheduled meeting with PeRC at the end of August.

Memo prepared by:

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
06/23/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 200678

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Pamela J. Smith, MD
Group Director, Global Regulatory Strategy
Metabolism and Endocrine Products

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) dated December 29, 2009, received December 29, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Saxagliptin and Metformin Hydrochloride Extended-release Tablets, 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg.

We also refer to your February 5, 2010, correspondence, received February 5, 2010, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Mehreen Hai at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200678	ORIG-1	BRISTOL MYERS SQUIBB	(b) (4) (saxagliptin + metformin XR) Tablets

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/s/

MARGARITA V TOSSA
05/26/2010

CAROL A HOLQUIST
05/27/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
Subject: NDA 200678 info request
Date: Wednesday, May 12, 2010 1:40:11 PM

Hi Pam,

Got your voicemail today. I checked with OSE and they said that although they're aware that they've missed the date, the review is still ongoing. They hope to get a decision to you within the next week or two.

We also have an information request for you:

We can't find the batch size information of formulations used in study CV181111 and CV181112 (submitted in March 2010).

CV181111: 500 metformin/5 mg saxagliptin, batch:9L50239

Saxagliptin 5 mg, batch: 9D4707B

Metformin 500 mg, batch: 8L3022A

CV181112: 1000 mg metformin/5 mg saxagliptin, batch:9L51087

Could you please let me know where in the submission this is located, and if it's not, could you please submit this information?

Thank you,

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
05/12/2010



NDA 200678

FILING COMMUNICATION

Bristol-Myers Squibb Company
Attention: Pamela J. Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your new drug application (NDA) dated and received December 29, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for [REDACTED] (b) (4) [REDACTED] (saxagliptin/metformin HCl extended-release) Tablets (5/500 mg, 5/1000 mg and 2.5/1000 mg).

We also refer to your submissions dated January 12 and February 5, 2010.

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 **October 29, 2010**.

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 October 1, 2010.

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

- A. [REDACTED] (b) (4)
[REDACTED] The expiry should be calculated from the date of manufacture. [REDACTED] (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Provide all available stability data to support the comparability of the metformin (b) (4) manufactured at the BMS-Evansville, Indiana site and those manufactured at the BMS-Mount Vernon, Indiana site.
2. Provide the (b) (4) in the finished drug product.
3. Provide the microbial limits test validation studies or a summary of these studies.
4. Provide the microbial limits testing protocols 5450A, 249965, 249966, and 249967.

(b) (4)

If you have not already done so, you must 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional 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.

(b) (4)

REQUIRED PEDIATRIC ASSESSMENTS

(b) (4)

If you have any questions, please contact Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MARY H PARKS
03/12/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
Subject: Problem with electronic datasets
Date: Saturday, February 13, 2010 3:23:12 PM

Hi Pam,

We are not able to access the electronic datasets for NDA 200678. Please re-submit usable SAS transport files as soon as possible.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
02/13/2010

REQUEST FOR CONSULTATION

TO (Office/Division):

Jim McVey
New Drug Microbiology Staff
Attn: Sylvia Gantt

FROM (Name, Office/Division, and Phone Number of Requestor):

Mehreen Hai (Regulatory Project Manager)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Ph: 301-796-5073

DATE
February 2, 2009

IND NO.

NDA NO.
200678

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
December 29, 2009

NAME OF DRUG
**Saxagliptin-Metformin
extended-release fixed-dose
combination**

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
**DPP-4
inhibitor/Biguanide**

DESIRED COMPLETION DATE
July 30, 2010

NAME OF FIRM: **Bristol-Myers Squibb**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input checked="" type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: DMED requests a Microbiology Consult for new NDA 200678 (Saxagliptin-Metformin extended-release fixed-dose combination) to review the proposed limit of ^{(b) (4)} and the proposed microbial limit. The 10-month goal date is October 29, 2010. The filing meeting is on February 9, 2010. The NDA submission is in the EDR: \\CDSESUB1\EVSPROD\NDA200678\200678.enx

SIGNATURE OF REQUESTOR
Mehreen Hai

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
02/02/2010

From: [Hai, Mehreen](#)
To: ["Smith, Pamela";](#)
Subject: Information Request for NDA 200,678
Date: Monday, January 25, 2010 4:10:17 PM

Hi Pam,
We had the following request for information for NDA 200678 (b) (4)

Please confirm that the formulation of the primary stability batches (used in the long term stability studies) is the commercial formulation, or indicate the differences.

Please provide a response as soon as possible.
Thank you!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Application
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Submission
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/s/

MEHREEN HAI
01/25/2010



NDA 200678

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Pamela J. Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (saxagliptin/metformin HCl extended-release)
Tablets 5/500 mg, 5/1000mg and 2.5/1000 mg

Date of Application: December 29, 2009

Date of Receipt: December 29, 2009

Our Reference Number: NDA 200678

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 **February 27, 2010**, 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.

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 Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
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Submitter Name

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NDA-200678

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/s/

MEHREEN HAI
01/08/2010