CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209091Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 209091
Review #1
Review Date (see last page)

Drug Name/Dosage Form	saxagliptin and dapagliflozin tablets
Strength	5/10 mg/mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Astra Zeneca

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	4/27/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Product	John Amartey	New Drug Products II/ONDP
Facility	Vipulchandra Dholakia	Inspectional Assessment/OPF

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**

   A. **DMFs:** Adequate (see OPQ review of NDA (b) (4))

   B. **Other Documents:**

DOCUMENT	APPLICATION	DESCRIPTION
NDA	(b) (4)	saxagliptin and dapagliflozin tablets (same product, same applicant)

2. **CONSULTS:** not applicable

Executive Summary

I. Recommendation and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the 11/21/16 Overall Manufacturing Inspection Recommendation) is for **APPROVAL**.

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(1) application for a fixed dose combination of two approved drug substances, saxagliptin and dapagliflozin, 5 mg and 10 mg. This is not an NME application because the applicant has several approved NDAs for these drug substances.

The same product in this new NDA was previously submitted in NDA (b) (4) by the same applicant. NDA (b) (4) received a Complete Response on 10/15/2015 (b) (4) OPQ review recommended "approval" at the time of the action with no pending Quality issue.

B. Quality Assessment Overview

The CMC information in the new NDA and the previously reviewed NDA (b) (4) (b) (4)

(b) (4)

The OPQ review of NDA 209091 consists of the drug product review of the new and updated information listed above and a cross-reference to the OPQ review of NDA (b) (4) for the evaluation of all other Quality information. The Overall Manufacturing Inspection Recommendation is updated on 11/21/16 for "approval".

Application Technical Lead Signature:

Suong (Su) Tran, Ph.D.
electronic signature on the last page

CHAPTERS: Primary Quality Assessment

Chapter I: Drug Substance (see OPQ Review of NDA [redacted])
Chaper II: Drug Product
Chapter III: Environmental Assessment (see OPQ Review of NDA [redacted])
Chapter IV: Labeling
Chapter V: Process (see OPQ Review of NDA [redacted])
Chapter VI: Facilities (see OPQ Review of NDA [redacted])
Chapter VII: Biopharmaceutics (see OPQ Review of NDA [redacted])
Chapter VIII: Microbiology (see OPQ Review of NDA [redacted])
Attachment I: Final Risk Assessment (see OPQ Review of NDA [redacted])

CHAPTER II: Drug Product

and

CHAPTER IV: Labeling

Drug Product Review – Memorandum

FROM: John K. Amartey, PhD

CMC-Reviewer/DNDPII/Branch VI

THROUGH: Danae Christodoulou, PhD

Acting Branch Chief/DNDPII/Branch VI

TO: NDA 209091

DATE: 08/14/2016

SUBJECT: **Saxagliptin/Dapagliflozin Fixed-Dose Combination (5 mg/10 mg) tablets**

INTRODUCTION:

The NDA 209091 is seeking market approval for saxagliptin 5 mg and dapagliflozin 10 mg fixed-dose combination (FDC) tablet. The product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Dapagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2). The SGLT2 inhibitors reduce hyperglycemia by promoting glucose excretion by the kidney. Saxagliptin is dipeptidyl peptidase 4 (DPP4) inhibitor. DPP4 inhibitors improve the beta-cell sensitivity to glucose, increase insulin secretion, and decrease glucagon secretion. These inhibitors therefore complement the action of the SGLT2 inhibitors in reducing hyperglycemia. The two drug substances have been approved in several NDA such as in 2009 NDA 22350 to market Onglyza (saxagliptin), 2010 NDA 200678 Kombiglyze XR (saxagliptin/metformin HCl). Dapagliflozin is approved as Farxiga in 2014 NDA 202293. The FDC is submitted in NDA (b) (4)

In NDA 209091 the applicant seeks approval for a single strength saxagliptin 5 mg/ dapagliflozin 10 mg FDC. The drug product is packaged in the container closure systems: HDPE bottle and also in (b) (4) blisters. Portions of this NDA have been previously submitted to NDA (b) (4) (b) (4)

(b) (4)

Referenced DMFs: The cited DMFs are listed in the table below and are adequate.

DMF#	TYPE	Holder	ITEM REFERENCED	STATUS
(b) (4)	III	(b) (4)		ADEQUATE 9/26/2014
(b) (4)	III			ADEQUATE 10/21/2015

Description:

(b) (4)

Revision of Drug Product sections:

Specifications:

(b) (4) The sample chromatogram presented indicated that the method is suitable for the intended use.

Excipients:

(b) (4)

There are no novel excipients. The non-compendial excipients are well controlled (CoA s are provided in the application). The analytical methods used are based on compendial procedures and no need for validation.

Table 3.2.P.5.4-1: Batch Information for Saxa 5/Dapa10

Batch Number	Drug Substance Batch Used		Date of Manufacture	Site of Manufacture	Batch Size (Tablets)	Use of Batch
	Saxa	Dapa				
4D81581S[a]	3E7699NT	4C89280N	(b) (4)		(b) (4)	TT, Experimental
4D78404S[a]	3D77208UN	4C89280N				TT, Experimental
4C88898S	3D77208UN	4C89280N				TT, Clinical
3C82341	2F71028	2F72891				LTSS
3C82340	2F71027	2F71344				LTSS
3B73725[b] / 3C82339[c]	2F71026	2F71034				Clinical, LTSS

[a] Coated (b) (4) tablets

[b] Clinical supplies batch number - coated (b) (4) tablets

[c] LTSS batch number - coated (b) (4) tablets

Stability:

Long term stability:

The long term stability data on three batches of the saxa 5 mg/ dapa10 mg product packaged in the (b) (4) blisters (5°C, 25°C/60%RH and 30°C/75%RH), show that there is essentially little or no change in mean potency (saxa and dapa), impurities (saxa and dapa), (b) (4) mean hardness, disintegration time, or appearance through the 24 months test period (the longest real time data). The data is evaluated in accordance with ICH Q1E. The results show that the predicted values at 36 months are within the acceptance limits under the long term stability storage conditions. Similar results are observed for the saxa 5 mg/ dapa 10 mg tablets when packaged in the HDPE bottles and stored at the long term condition of 25°C/60%RH for 24 months and at accelerated condition 40°C/75%RH for 6 months. Based on the real data presented the proposed 36 months shelf-life is justified.

Post-approval stability protocol and commitment:

The applicant commits to continue with the long-term stability studies following the protocol presented in the application.

Comparability Protocol:

(b) (4)

(b) (4)

NEW LABELING:

The proposed (b) (4) blisters package label is shown below. The label presented in the application is for a tablet count of 7 as a Physician sample. In the labeling the section 3: Dosage Forms and Strength and the section 11: Description lists only the 5 mg/10 mg strength. In section 16: How Supplied/Storage and Handling the three bottle size tablet counts of 30, 90 and 500 are described.

The carton has label is not changed

(b) (4)

RECOMMENDATION: APPROVAL

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 10/04/2016 12 26:24PM
GUID: 5050dd27000012a4c69bfc70b47660b7

John Amartey

Digitally signed by John Amartey
Date: 10/04/2016 10:18:35AM
GUID: 54061eab0009a3906521deca6e5fda70

Su (Suong) Tran

Digitally signed by Su (Suong) Tran
Date: 1/04/2017 11:14:56AM
GUID: 508da71f00029ec8b75e233f12b15339

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: 209091	**Established/Proper Name: saxagliptin and dapagliflozin**
Applicant: Astra Zeneca	**Dosage Form: tablet**
Submission Type: 505(b)(1) –not NME	**Strength(s): 5 mg/10 mg**
Chemical Type: 4	**Cross Referenced Applications: Approved NDA 22350, NDA 200678, NDA 202293, and NDA 205649 Unapproved NDA** (b) (4)

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		x	x

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

B. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS

This is a 505(b)(1) application for a fixed dose combination of two approved drug substances, saxagliptin and dapagliflozin, 5 mg and 10 mg. This is not an NME application because the applicant has several approved NDAs for these drugs.

This new NDA replaces NDA (b) (4) *which received a Complete Response on 10/15/2015 due to* (b) (4)

- *The new NDA 209091, with the only one strength of 5/10, is for the indication of type 2 diabetes* (b) (4)

The CMC information (b) (4) *:*

(b) (4)

Plan for the OPQ review:

(b) (4) ***reference is made to the OPQ review of NDA*** (b) (4) ***with the following addition:***

1. ***Drug product*** *reviewer to evaluate the new/additional information as summarized above.*
2. ***Facilities*** *reviewer to evaluate all commercial testing, manufacturing, and packaging facilities currently in the NDA.*

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 **AND** 25.15(d) been provided?	x			
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?	x			
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	x			
	FACILITY INFORMATION				
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	x			
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	x			
	DRUG SUBSTANCE INFORMATION				
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?			x	NDA 202293 is referenced for all CMC information on the drug substance dapagliflozin. NDA 22350 is referenced for all CMC information on the drug substance dapagliflozin.
	DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	x			See the DRUG PRODUCT review of NDA (b) (4) for the same product- recommending approval with no pending issue. (b) (4)
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?				See the Biopharmaceutics review of NDA (b) (4) for the same product- recommending approval with no pending issue (b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

C. FILING CONSIDERATIONS					
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*				
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.				
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?				
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?				
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?				
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x		
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x			
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			x	
17.	For Biotech Products, is sufficient information provided in compoliance with 21 CFR 610.9 and 601.2(a)?			x	

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Suong T. Tran -S

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Suong (Su) Tran, PhD
Application Technical Lead

QUALITY ASSESSMENT

Recommendation:
APPROVAL

NDA (b) (4)
Review #1
Review Date: (see page 5)

Drug Name/Dosage Form	saxagliptin and dapagliflozin tablets
Strength	5/10 mg/mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	AstraZeneca
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE
NDA	12/15/2014
Amendment	3/13/2015
Amendment	5/11/2015
Amendment	6/15/2015

Quality Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
Drug Substance	n/a	
Drug Product	John Amartey	ONDP/DNDPII
Process	Daniel Peng	OPF/PA II
Microbiology	Daniel Peng	OPF/PAII
Facility	Vipul Dholakia	OPF/IA
Biopharmaceutics	Peng Duan	ONDP/DB
Business Process Manager	Kerri-Ann Jennings Anika Lalmansingh	OPRO/RBPMI
Application Technical Lead	Suong Tran	ONDP/DNDPII
Laboratory (OTR)	n/a	
ORA Lead	n/a	
Environmental Assessment (EA)	n/a	

Table of Contents

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: n/a

2. RELATED/SUPPORTING DOCUMENTS:

1. DMFs:

(Reviewed by Drug Product Reviewer)

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	Adequate	NDA review date	sufficient information in NDA
	III			Adequate	NDA review date	sufficient information in NDA
	III			Adequate	3/21/2012	N/A
	III			Adequate	3/11/05	N/A
	III			Adequate	NDA review date	sufficient information in NDA
	III			Adequate	4/24/12	N/A
	III			Adequate	NDA review date	sufficient information in NDA

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

2. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22350 (same applicant)	Onglyza (saxagliptin)
NDA	202293 (same applicant)	Farxiga (dapagliflozin)
NDA	205649 (same applicant)	Xigduo (dapagliflozin/metformin hydrochloride extended release)

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	n/a			
Pharmacology/Toxicology	n/a			
CDRH	n/a			
Clinical	n/a			
Other				

Executive Summary

1. Recommendation

1. Recommendation and Conclusion on Approvability

NDA [redacted] is recommended for approval from the Quality perspective.
There is no unresolved deficiency.
Labeling comments will be finalized via the OND Division review process.

2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approved – n/a

3. Summary of Quality Assessment

1. Drug Substance Quality Summary

Reference is made to the Quality reviews of the approved NDA 22350 saxagliptin and approved NDA 202293 dapagliflozin.

2. Drug Product Quality Summary

1. Strength: 5 /10 mg/mg saxagliptin/dapagliflozin
2. Description/Commercial Image: light brown to brown, biconvex round film-coated tablets, [redacted] "1122" printed on the other side, in blue ink
3. Summary of Product Design n/a
4. List of Excipients: anhydrous lactose, croscarmellose sodium, iron oxides, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, silicon dioxide, talc, and titanium dioxide.
5. Process Selection (see section "Process" in this review): [redacted]
6. Container Closure: bottles of 30-, 90-, and 500-count in bottles for commercial distribution, and 7-count blisters as samples
7. Expiration Date & Storage Conditions: [redacted] months when stored at room temperature (20-25 °C).
8. List of co-packaged components n/a

9. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	
Non Proprietary Name of the Drug Product	
Non Proprietary Name of the Drug Substance	Saxagliptin and dapagliflozin
Proposed Indication(s) including Intended Patient Population	Adjunct to diet and exercise to improve glycemic control in adutls with type 2 diabetes mellitus
Duration of Treatment	chronic
Maximum Daily Dose	5 /10 mg/mg saxagliptin/dapagliflozin

Alternative Methods of Administration	n/a

10. **Biopharmaceutics Considerations** (see section "Biopharmaceutics" in this review)
    1. BCS Classification: Saxagliptin BCS III, dapagliflozin BCS III

    2. Biowaivers/Biostudies
    1. The results from BE study CV181341 are acceptable. The Saxa [redacted] (b) (4) 5/ Dapa 10 mg FDC tablets are bioequivalent to the respective strengths of Saxa and Dapa mono-tablets in fasted healthy adults. There was no meaningful effect on the peak or total exposure of saxagliptin due to administration in the fed state. High fat meal, however, reduced the peak exposure of dapagliflozin by approximately 50%. In conclusion, the combination of both saxagliptin and dapagliflozin together in one FDC tablet obtains the similar conclusion of the food effect on respective mono-tablet stated in their labeling. See labeling details on food effects of respective mono-tablets.

11. [redacted] (b) (4)

12. **Novel Approaches n/a**

13. **Any Special Product Quality Labeling Recommendations n/a**

14. **Life Cycle Knowledge Information (see Attachment B)**

Application Technical Lead Signature: (Suong Tran)

I concur with the OPQ review team members' recommendations. There is no pending/unresolved deficiency.

Suong T. Tran -S

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ASSESSMENT OF BIOPHARMACEUTICS

In this submission, (b) (4) the Applicant seeks approval for (b) (4) saxagliptin (5mg) and dapagliflozin (10 mg), as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

(b) (4)

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(b) (4)

2. Discriminability of the dissolution method and the application of disintegration test in lieu of dissolution test for quality control

During the development of dissolution method, the Applicant studied the apparatus and paddle speed selection (b) (4) as well as the media selection. (b) (4)

(b) (4)

Similarly, during the long-term stability test for the proposed formulations, the drug release (b) (4) tested is (b) (4) % (b) (4)

(b) (4)

According to ICH Q6A guidance and its Decision Tree #7(1) (Table 8), the proposed Saxa/Dapa commercial tablets meet all the criteria shown in Table 8 below, and are considered qualified for using disintegration as a surrogate for dissolution.

Table 8. Justification for Using Disintegration as a Surrogate for Dissolution for Saxagliptin/Dapagliflozin Proposed Commercial Tablets

ICH Q6A Decision Tree # 7(1)	Criteria Justification for Saxagliptin/Dapagliflozin Proposed Commercial Tablets
The dosage form is not designed to produce modified release.	Criterion is met. (b) (4)
The drug solubility at 37±0.5°C is high (dose/solubility ≤ 250mL) throughout the physiological pH range (pH 1.2 -6.8).	Criterion is met. (b) (4)
Greater than 80% dissolution is achieved in 15 minutes at pH 1.2, 4.0, and 6.8.	Criterion is met. (b) (4)
A relationship has been established between dissolution and disintegration or disintegration is shown to be more discriminating than dissolution.	Criterion is met. (b) (4)

The Applicant tested the discriminability of both dissolution method and disintegration method (b) (4)

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(b) (4)

3. Disintegration acceptance criteria

Disintegration in lieu of dissolution is used as QC method because of meeting the criteria as shown in Table 8. The proposed acceptance criterion for disintegration time is (b) (4) minutes at 37°C water.

The maximum disintegration time was (b) (4) minutes at initial and showed some variability with values ranging from (b) (4) minutes with no major trend observed for tablets stored under all long-term storage conditions through 12 months.

Fig 5a.

(b) (4)

(b) (4)

Fig 5b. Maximum Disintegration Time at 25°C/60%RH for Saxa 5/Dapa 10 Tablets in HDPE Bottles

(b) (4)

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(b) (4)

Furthermore, the statistical analysis conducted by the Applicant based on stability data shows that (b) (4) the disintegration time at release is (b) (4) minutes. The upper side of the 95% confidence/99% coverage tolerance interval of the release disintegration time is (b) (4) minutes. Statistical analysis of the trend of disintegration over time found no significant increase in the disintegration time. Overall, the proposed acceptance criterion (b) (4) minutes at 37°C of water is acceptable.

PART 2. Review of BE studies and Biowaiver request

BE Studies

Bioequivalence study CV181341 has been conducted to demonstrate bioequivalence (b) (4) Saxa 5/ Dapa 10 mg tablets compared with the (b) (4) Saxa and Dapa in fasted state. The food effect on the FDC tablets was also studied.

The saxagliptin and dapagliflozin in study CV181341 were analyzed by LC/MS/MS, and the Applicant provided the validation report and summary as follows:

Document control number	Analyte	Sample matrix	Method[a]	Regression model, weighting	Standard curve range (ng/mL)	Assay precision (%CV) Inter-	Assay precision (%CV) Intra-	Accuracy (% deviation)	Stability (RT[b], F/T[c], LTS[d])	Study No.[e]
930037127	Saxagliptin	Human plasma EDTA	LC-MS/MS[a]	Linear, $1/(Conc)^2$	0.1-50	≤2.8%	≤9.2%	±4.3%	24 h RT[b] matrix stability for saxagliptin and 42 hr for BMS-510849; 401 days LTS at -20°C; 6 cycles F/T at -20°C; post preparative stability 31 hr at RT	CV181191
	5-Hydroxy saxagliptin			Linear, $1/(Conc)^2$	0.2-100	≤4.4%	≤5.2%	±4.2%		
930065686	Dapagliflozin	Human plasma EDTA	LC-MS/MS[a]	Linear, $1/x^2$	0.2-100	≤4.9%	≤3.8%	±2.0%	RT = 24 h, 5 cycles F/T at -20°C & -70°C; 337 days LTS at -20°C & -70°C; Post Preparative extract stability, 72 h at RT and 141 h at 2 to 8°C	CV181191 CV181341
930081712	Saxagliptin	Human [lasma EDTA	LC-MS/MS[a]	Linear, $1/(Conc)^2$	0.1-100	≤5.2%	≤8.2%	±8.6%	RT = 6 h, F/T = 5 cycles at -20°C & -70°C, 171 days LTS at -20°C and 615 days at -70°C; Post Preparative extract stability, 91.25 Hours at 2 to 8°C	CV181341
	5-Hydroxy saxagliptin			Linear, $1/(Conc)^2$	0.2-200	≤4.4%	≤5.2%	±6.5%		

The incurred sample reproducibility is determined with 10% of the study sample reassayed, the ISR met the acceptance criteria of (b) (4)%. The analytical report for the BE study is acceptable.

The pharmacokinetic (PK) results from the study cohort 1 are shown as below:

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Table 2 : Statistical Analysis Results of Dapagliflozin for Cohort 2 (dosed with Saxa 5/Dapa 10 FDC or Saxagliptin 5 +Dapaglifloxin 10 mg)

PK Parameter	Treatment and Comparison	Adjusted Geometric Mean	90% CI
Cmax (ng/mL)	D (Saxa + Dapa fasted)	149	(134, 166)
	E (Saxa/Dapa fasted)	141	(125, 158)
	F (Saxa/Dapa fed)	91.3	(81.1, 103)
	E versus D	0.946	(0.878, 1.019)
	F versus E	0.648	(0.565, 0.743)
AUC(0-T) (ng·h/mL)	D (Saxa + Dapa fasted)	577	(542, 615)
	E (Saxa/Dapa fasted)	598	(562, 636)
	F (Saxa/Dapa fed)	557	(526, 589)
	E versus D	1.036	(1.010, 1.062)
	F versus E	0.931	(0.908, 0.955)
AUC(INF) (ng·h/mL)	D (Saxa + Dapa fasted)	596	(559, 635)
	E (Saxa/Dapa fasted)	617	(579, 656)
	F (Saxa/Dapa fed)	582	(550, 615)
	E versus D	1.035	(1.008, 1.063)
	F versus E	0.943	(0.919, 0.968)

Treatment D: 5-mg saxagliptin + 10-mg dapagliflozin tablets under fasted conditions
Treatment E: Saxa 5/Dapa 10 FDC tablet under fasted conditions
Treatment F: Saxa 5/Dapa 10 FDC tablet under fed conditions

The reviewer's own analysis is as follows:

PK parameter	Treatment and comparison	Adjusted Geometric mean	90% CI
Cmax ng/mL	D	150	
	E	141	
	F	91.3	
	E vs D	0.944	0.878-1.016
	F vs E	0.648	0.565-0.743
AUC (0-T)	D	591	
	E	613	
	F	573	
	E vs D	1.038	1.011-1.065
	F vs E	0.938	0.912-0.965
AUC(INF)	D	610	
	E	632	
	F	598	
	E vs D	1.038	1.011-1.065
	F vs E	0.949	0.923-0.976

Table 4 : Statistical Analysis Results of Saxagliptin for Cohort 2 (Dosed with Saxa 5 mg/Dapa 10 mg FDC or Saxagliptin 5 mg + Dapaglifloxin 10 mg)

PK Parameter	Treatment and Comparison	Adjusted Geometric Mean	90% CI
Cmax (ng/mL)	D (Saxa + Dapa fasted)	26.1	(23.7, 28.8)
	E (Saxa/Dapa fasted)	27.6	(25.2, 30.3)
	F (Saxa/Dapa fed)	25.6	(23.2, 28.2)
	E versus D	1.059	(0.993, 1.129)
	F versus E	0.925	(0.837, 1.022)
AUC(0-T) (ng·h/mL)	D (Saxa + Dapa fasted)	95.8	(90.3, 102)
	E (Saxa/Dapa fasted)	96.4	(90.7, 102)
	F (Saxa/Dapa fed)	111	(106, 117)
	E versus D	1.007	(0.973, 1.042)
	F versus E	1.155	(1.117, 1.194)
AUC(INF) (ng·h/mL)	D (Saxa + Dapa fasted)	97.3	(91.8, 103)
	E (Saxa/Dapa fasted)	97.6	(91.9, 104)
	F (Saxa/Dapa fed)	113	(107, 119)
	E versus D	1.003	(0.969, 1.038)
	F versus E	1.155	(1.118, 1.194)

Treatment D: 5-mg saxagliptin + 10-mg dapagliflozin tablets under fasted conditions
Treatment E: Saxa 5/Dapa 10 FDC tablet under fasted conditions
Treatment F: Saxa 5/Dapa 10 FDC tablet under fed conditions

The reviewer's own analysis is as follows:

PK parameter	Treatment and comparison	Adjusted Geometric mean	90% CI
Cmax ng/mL	D	26.1	
	E	27.6	
	F	25.6	
	E vs D	1.056	0.987-1.129
	F vs E	0.927	0.837-1.028
AUC (0-T)	D	98.0	
	E	98.9	
	F	114.6	
	E vs D	1.009	0.969-1.050
	F vs E	1.124	1.115-1.200
AUC(INF)	D	99.4	
	E	99.8	
	F	115.8	
	E vs D	1.004	0.965-1.045
	F vs E	1.125	1.116-1.200

As all above tables show, although there are slightly differences in the values calculated by the reviewer and values provided by the Applicant, the overall trend and conclusion are the same:

1. The (b) (4) Saxa 5/ Dapa 10 mg FDC tablets are bioequivalent to the (b) (4) Saxa and Dapa mono-tablets in fasted healthy adults.
2. There was no meaningful effect on the peak or total exposure of saxagliptin due to administration in the fed state.
3. High fat meal, however, reduced the peak exposure of dapagliflozin by approximately 50%. In conclusion, the combination of both saxagliptin and dapagliflozin together in one FDC tablet obtains the similar conclusion of the food effect on respective mono-tablet stated in their labeling. Please refer to labeling details on food effects of respective mono-tablets.

Biowaiver Issues

The bioequivalence studies only studied the (b) (4) Saxa 5.0 mg / Dapa 10.0 mg (b) (4)

(b) (4)

The composition of saxa/dapa FDC tablet is as shown in Table 5 (b) (4) The saxagliptin/dapagliflozin FDC tablet consists of (b) (4)

(b) (4)

Based on the *Guidance for Industry-bioavailability and Bioequivalence Studies Submitted in NDAs or INDs-General Considerations*, the justifications from the Applicant are acceptable.

Table 5 The Composition Of Saxa/Dapa FDC Tablet

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature: (Peng Duan)

Peng Duan -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peng Duan -S, 0.9.2342.19200300.100.1.1=2001127615
Date: 2015.07.20 10:23:41 -04'00'

1. The dissolution method (as below) and the application of disintegration test in lieu of dissolution method are acceptable.
2. The acceptance criterion for disintegration time (b) (4) minutes at 37°C of water is appropriate.
3. The results from BE study CV181341 are acceptable;
a. The (b) (4) Saxa 5/ Dapa 10 mg FDC tablets are bioequivalent to the (b) (4) Saxa and Dapa mono-tablets in fasted healthy adults.
b. There was no meaningful effect on the peak or total exposure of saxagliptin due to administration in the fed state.
c. High fat meal, however, reduced the peak exposure of dapagliflozin by approximately 50%. In conclusion, the combination of both saxagliptin and dapagliflozin together in one FDC tablet obtains the similar conclusion of the food effect on respective mono-tablet stated in their labeling. Please refer to labeling details on food effects of respective mono-tablets.

4. (b) (4)

5. The following dissolution method is reviewed and accepted.

USP Apparatus	Agitation Speed (RPM)	Media Volume (mL)	Temperature (C)	Medium
(b) (4)				

6. Finally, the proposed disintegration method and its acceptance criterion (b) (4) minutes at 37°C of water are acceptable for implementation upon NDA approval.

Supervisor Comments and Concurrence: (Tien Mien Chen)
The Biopharmaceutics review is complete and I concur.

Tienmien Chen -S
Digitally signed by Tienmien Chen -S
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Date: 2015.08.10 11:50:01 -04'00'

ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: Adequate

(b) (4)

- The excipients used in the manufacture of Saxa/Dapa are tested for microbial growth as required by their respective compendial requirements. (b) (4)
- Bulk containers of tablets at the manufacturing site include (b) (4) appropriate packaging (b) (4)
- The Saxa/Dapa tablets are packaged in HDPE bottles (b) (4) and in (b) (4) blister packs (b) (4)

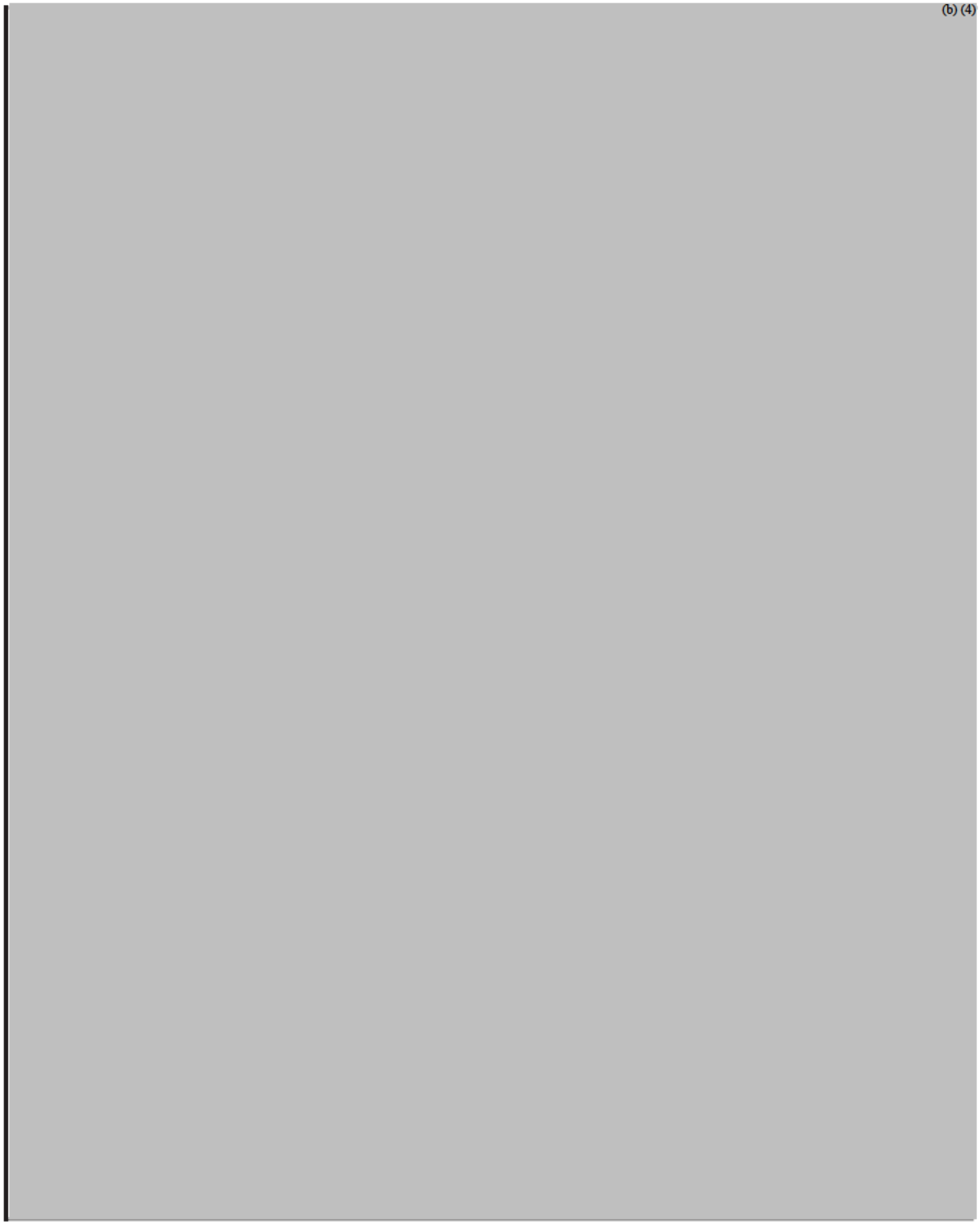
(b) (4)

(b) (4)

The firm conducted (b) (4)

(b) (4)

(b) (4)



2. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: Adequate

The commercial presentation for Saxa/Dapa tablets is (b) (4) high density polyethylene (HDPE) bottle (b) (4) Saxa/Dapa tablets may also be presented in (b) (4) blisters.

The suitability of the packaging components and container closure systems has been demonstrated by the results of the stability studies reported in Section 3.2.P.8, Stability.

The materials used in the fabrication of the packaging components conform to the requirements in the applicable sections of the Code of Federal Registration, Title 21, Indirect Food Additives. Letters from the vendors with the specific references of compliance are provided on the following pages. The Drug Master Files (DMF) and Letters of Authorization (LOA) for the primary packaging components are provided in Module 1.4.1.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: Adequate

(b) (4) The adventitious Agents Safety Evaluation reports are provided in 3.2.R. *Regional Information* section. The (b) (4) statements are provided.

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of

the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate (Daniel Y. Peng)
The application is adequate from Microbiology perspective.

see signatures on page 63

Supervisor Comments and Concurrence: Adequate
I concur with the primary reviewer's assessment. The information provided is adequate (Ubrani V. Venkataram, 16-Jun-2015).

see signatures on page 63

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

1. Is the applicant's claim for categorical exclusion acceptable?
   Yes.
2. Is the applicant's Environmental Assessment adequate for approval of the application?
   n/a

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. **Package Insert**

(a) "Highlights" Section (21CFR 201.57(a))

QTERN (saxagliptin and dapagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (b) (4)

Limitations of Use:

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: QTERN Established Name: Saxagliptin/Dapagliflozin Fixed Dose Combination	Adequate
Dosage form, route of administration	Dosage: Tablet Route: Oral	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Fixed dose combination tablets have been developed (b) (4) 5 mg saxagliptin/10 mg dapagliflozin.	Adequate

Conclusion: (b) (4) the applicant has indicated that approval is being sought for (b) (4) (5 mg Saxagliptin/10 mg Dapagliflozin).The information provided is adequate.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

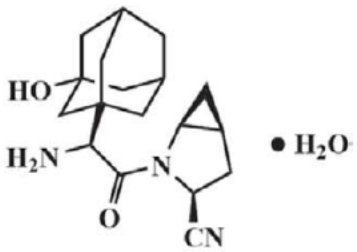
QTERN tablets containing 5 mg saxagliptin and 10 mg dapagliflozin are light brown to brown, biconvex, round, film-coated tablet, with (b) (4) "1122" printed on the other side, in blue ink.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	QTERN Tablets	Adequate
Strengths: in metric system	(b) (4) 5 mg Saxa/10 mg Dapa	(b) (4) described in the application as well and acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Table 3.3.P.1-1 of the application describes in detail the information. The summary description of the highest strength tablet is indicated above.	Adequate

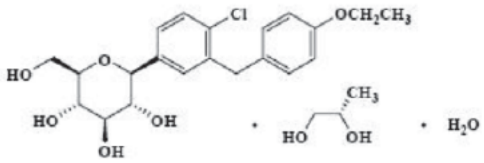
Conclusion: (Reviewed by Drug Product Reviewer).
The strengths of the tablets are described in the application as well as the full description of the different tablet strengths. However, the applicant is seeking market approval for the Saxa 5/Dapa10 tablet. The information is acceptable.

#11: Description (21CFR 201.57(c)(12))

QTERN tablets contain (b) (4) saxagliptin and dapagliflozin.
Each film-coated tablet of QTERN for oral administration contains (b) (4)
Inactive ingredients: The product contains anhydrous lactose, croscarmellose sodium, iron oxides, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, silicon dioxide, talc, and titanium dioxide.
Saxagliptin
Saxagliptin is an active inhibitor of the dipeptidyl-peptidase-4 (DPP4) enzyme.
Saxagliptin is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxytricyclo [3.3.1.1] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate.
Empirical formula: $C_{18}H_{25}N_3O_2 \cdot H_2O$. Molecular weight: 333.43.
Structural formula:



Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).
Dapagliflozin
Dapagliflozin is an active inhibitor of sodium-glucose cotransporter 2 (SGLT2).
Dapagliflozin propanediol is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1).
Empirical formula: $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$. Molecular weight: 502.98.
Structural formula:



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary: QTERN Established Name: Saxagliptin/Dapagliflozin Fixed Dose Combination	Adequate
Dosage form and route of administration	Tablet Oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	This information is provided in section 2.3.P.1 *Description and Composition of the Drug Product*	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	N/A	
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Antihyperglycemic	Adequate
Chemical name, structural formula, molecular weight	Information is provided above	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Dapagliflozin is not ionizable between pH 2-11. Saxagliptin is a primary amine with a pKa = 7.3. Saxagliptin and Dapagliflozin are considered BCS Class III (high solubility and high bioavailability)	Acceptable

Conclusion: (Reviewed by Drug Product Reviewer).
The required information has been provided in the application, and is adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

QTERN™ (saxagliptin and dapagliflozin) tablets (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	5 mg/10 mg	(b) (4) described in the application and are acceptable.
Available units (e.g., bottles of 100 tablets)	Bottles of 30 Bottles of 90 Bottles of 500	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Light brown to brown, biconvex, round (b) (4) "1122" printed on the other side, in blue ink. NDC Codes:0310-6780-30; 0310-6780-90; 0310-6780-50	(b) (4) Adequate
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	The storage condition set is supported by data and is acceptable.

Manufacturer/distributor name listed at the end of PI, following Section #17

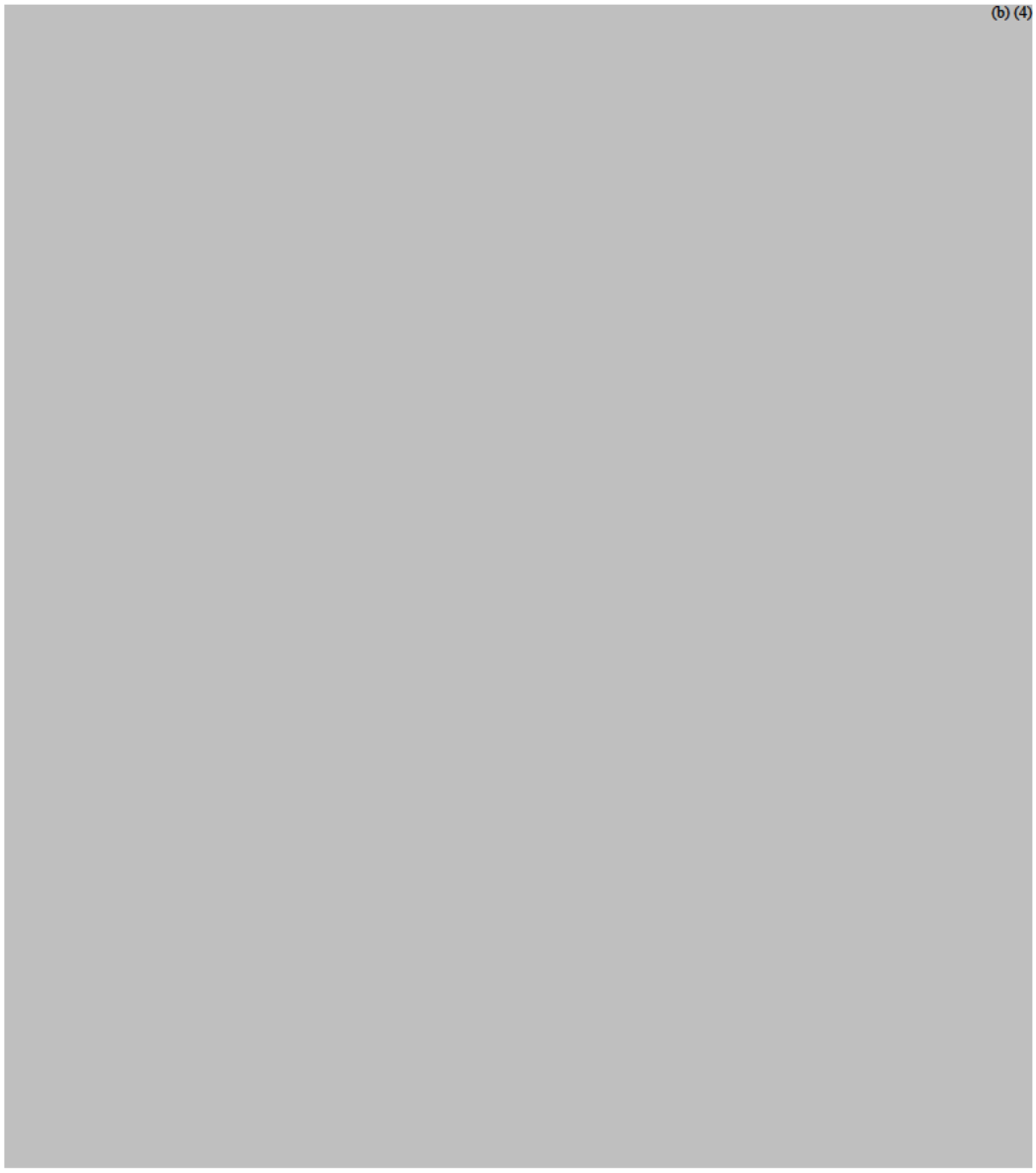
Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	AstraZeneca Pharmaceuticals LP Wilmington, DE 19850	Adequate

Conclusion: (Reviewed by Drug Product Reviewer).
The required information has been provided in the application and is adequate.

2. **Labels**

(b) (4)

(b) (4)



Reviewer's Assessment:
The immediate label for the (b) (4) *blisters has all the relevant information for this section in accordance with regulatory requirements. The font size differential between the proprietary and the established names are acceptable.*
No deficiencies are noted in the bottle labels for the 30 ct, 90 ct and 500 ct tablets. The labels are acceptable from the DP reviewer perspective.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name QTERN and the established name Saxagliptin/Dapagliflozin satisfy the font size deferential required by 21CFR 210.10(g)(2)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b) (4) the applicant is seeking approval for (b) (4) (Saxa 5/Dapa 10)	Adequate
Net contents (21 CFR 201.51(a))	The net contents I terms of weight and counts are indicated as per regulation	Adequate
Lot number per 21 CFR 201.18	Provision for lot number is indicated in the label	Acceptable
Expiration date per 21 CFR 201.17	Location for expiration date is provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The statement "Rx only" is indicated on the label	Adequate
Storage (not required)	The storage condition is indicated	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number is provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The position for a bar code is provided on the label	Adequate
Name of manufacturer/distributor	AstraZeneca Pharmaceuticals LP Wilmington, DE 19850	Adequate
Others	Do not use if printed inner seal of bottle is broken or missing.	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: (Reviewed by Drug Product Reviewer).

The information provided on the label met the regulatory requirements and is acceptable

2) **Cartons**

(b) (4) blister carton is shown below:

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The proprietary (QTERN) and the established (Saxagliptin/Dapagliflozin) names are indicated on the carton label. The font size differential is adequate in accordance with regulatory requirement.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The strength is indicated.	Adequate
Net contents (21 CFR 201.51(a))	The content is indicated (7 tablets)	Adequate
Lot number per 21 CFR 201.18	The lot number location is indicated	Acceptable
Expiration date per 21 CFR 201.17	The expiration date location is indicated	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	N/A	N/A
Sterility Information (if applicable)	N/A	N/A
"Rx only" statement per 21 CFR	The statement "Rx only" is indicated	Adequate
Storage Conditions	Statement for storage is indicated	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number is present	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Bar code sample is provided	Adequate
Name of manufacturer/distributor	Name is provided	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	The statement "dispense with enclosed medication guide" is indicated, although this package is not for sale as is a Physician sample.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	The warning is indicated	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	N/A	N/A

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Adequate (John Amartey)

John Amartey -S

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Secondary Review Comments and Concurrence: Adequate (Danae Christodoulou)

Danae D. Christodoulou -S

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Date: 2015.08.07 17:21:13 -04'00'

1. List of Deficiencies To Be Communicated

None

2. Attachments

A. Lifecycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay-stability	(b) (4)	L	See specific discussion in the review.	Acceptable	See specific discussion in the review.
Content uniformity		M	See specific discussion in the review.	Acceptable	See specific discussion in the review.