CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210045Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210045
Review #01

Drug Name/Dosage Form	Amlodipine and Celecoxib Tablets
Strength	2.5 mg/200 mg; 5 mg/200 mg; 10 mg/200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Kitov Pharma Ltd
US agent, if applicable	J. Paul Waymack, M.D., Sc.D.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	31-JUL-2017	*Amendment*	20-FEB-2018
Amendment	20-OCT-2017	*Amendment*	27-MAR-2018
Amendment	27-OCT-2017	*Amendment*	20-APR-2018
Amendment	08-DEC-2017	*Amendment*	20-APR-2018
Amendment	24-JAN-2018		
Amendment	05-FEB-2018		

Quality Review Team

DISCIPLINE	PRIMARY/SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Gaetan Ladouceur/Charles Jewell	ONDP
Drug Product	Milton Sloan/Wendy Wilson-Lee	ONDP
Process	Bo Jiang/Derek Smith	OPF
Facility	Daniel DeCiero/Derek Smith	OPF
Biopharmaceutics	Kaushalkumar Dave/Jing Li	ONDP
Regulatory Business Process Manager	Grafton Adams	OPRO
Application Technical Lead	Wendy Wilson-Lee	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	14-SEP-2017	
	II			Adequate	19-JAN-2018	
	II			Adequate	09-FEB-2018	
	II			Adequate	11-MAR-2017	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	112830	Celecoxib and amlodipine besylate tablets
NDA	20998	Celebrex (celecoxib) Capsules
NDA	19787	Norvasc (amlodipine besylate) Tablets

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends approval of NDA 210045 for amlodipine and celecoxib tablets (2.5 mg/200 mg; 5 mg/200 mg; and 10 mg/200 mg). This action includes two product quality post-marketing commitments (PMC 3387):

- Product Quality PMC #1: Elemental Impurities Assessment
- Product Quality PMC #2: Dissolution Method and Acceptance Criteria Development

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Adult patients for whom treatment with both amlodipine for hypertension and celecoxib for osteoarthritis are appropriate***
Duration of Treatment	(b) (4)
Maximum Daily Dose	***10 mg amlodipine and 200 mg celecoxib***
Alternative Methods of Administration	***None***

B. Quality Assessment Overview

Kitov Pharmaceuticals seeks approval of a fixed-dose combination, immediate-release tablet (KIT-302) containing varying amounts of amlodipine besylate (2.5 mg, 5 mg, and 10 mg) and 200 mg of celecoxib for the (b) (4) treatment of (b) (4) of hypertension (amlodipine) and osteoarthritis (celecoxib). The target population for this product is adults. The expected occurrence of pediatric patients with both hypertension and osteoarthritis is rare.

Both celecoxib and amlodipine besylate are marketed in the United States (US) and worldwide as individual branded and generic prescription drug products (celecoxib was first approved in 1998 and amlodipine besylate was first approved in 1992). In addition, amlodipine besylate is available as a combination drug product with other prescription drugs. The reference listed drugs for this NDA are NDA 020998 for Celebrex® (celecoxib) capsules and NDA 019787 for Norvasc® (amlodipine besylate) tablets. The proposed product is considered a "convenience reformulation" intended to facilitate and improve patient compliance. This product was not granted any regulatory designations.

Key review issues for the product quality assessment included:

1. Suitability of the multiple drug substance suppliers for each active ingredient and the impact of these different sources on final drug product quality and performance.
2. Compatibility of the active ingredients with each other in the formulation as well as the excipients.
3. Suitability of the proposed analytical methods, including dissolution, for quality control, especially with respect to sensitivity and selectivity for each active ingredient.
4. Suitability of the proposed manufacturing process (b) (4)
5. Suitability of the proposed control strategy for critical quality attributes (b) (4) content uniformity, and polymorphism.
6. Qualification and control strategy (b) (4) drug product.
7. Proposal (b) (4) for microbial limits.
8. Stability of the drug product over the proposed shelf-life.
9. Suitability of the proposed container closure(s) to protect the drug product from light (photostability studies identified potential light sensitivity of the product, proposed labeling instructs to protect from light).
10. Adequacy of comparability protocol to support shelf-life extension post-approval.

The Applicant referenced Drug Master Files (DMFs) for the chemistry, manufacturing, and controls information for each of the drug substance. The DMFs supporting this NDA were found adequate based on recent reviews (see 1.A. in the Quality Data Sheet). The Applicant provided supporting information in the NDA – namely general drug substance properties and the regulatory specification for each drug substance.

The Applicant identified assay, content uniformity, and drug release as critical quality attributes. The drug product critical quality attributes are justified based on the drug product design. (b) (4) The tablets are not film-coated. The compatibility between the excipients and the drug substance were confirmed by compatibility studies. The drug product manufacturing process (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The drug product specification is adequate to ensure quality for the dosage form. The proposal (b) (4) for microbial limits was deemed acceptable. (b) (4) the drug substance and excipient specifications. The analytical procedures that are applied for the immediate release (IR) solid oral dosage forms are appropriate for the intended use. The reference standards are all USP-grade and acceptable. The Applicant did not include the elemental impurities risk assessment for the drug product. Agreement to accept the risk assessment as a post-marketing commitment was reached by the Agency and the Applicant during review (Product Quality PMC 3387).

The dissolution method [USP Apparatus 2 (paddle) at 75 rpm; 900 ml of pH 6.8 phosphate buffer with 0.5% sodium lauryl sulfate at 37.0 ± 0.5°C] currently proposed for the proposed fixed-dose combination (FDC) product, Amlodipine and Celecoxib Tablets, 2.5 mg/200 mg, 5 mg/200 mg, 10 mg/200 mg strengths, under the NDA 210045 is not an optimal method for the evaluation of the dissolution characteristics of each drug component of the proposed FDC product. Therefore, the current dissolution method has been accepted only on an interim basis, and the Applicant has been recommended to develop separate dissolution methods for each drug component of the combination product as a PMC (Product Quality PMC 3387).

The dissolution acceptance criteria of 'not less than (NLT) (b) (4)% (Q) in 20 minutes' for amlodipine, and 'NLT (b) (4)% (Q) in 30 minutes' for celecoxib, revised as per FDA's recommendation, are acceptable on an interim basis. We recommended the Applicant (b) (4)

new dissolution methods (to be developed as a PMC). We also recommended that the Applicant submit the final report (b) (4)

The Applicant requested biowaiver for the middle strength (5 mg/200 mg) of the proposed product. The proposed product does not have classical proportionality between the strengths, due to the constant celecoxib dosage of 200 mg across the three strengths. The Applicant adopted the approach of bracketing for the in vivo pharmacokinetic studies and provided data to demonstrate bioequivalence of the highest and the lowest proposed strengths compared to their corresponding listed drug products. The Applicant provided data showing similar dissolution profiles in multi-media (b) (4) between the highest strength (10 mg/200 mg) and the middle strength (5 mg/200 mg) of the proposed product. Also, the Applicant provided data showing similar dissolution across all three strengths of the proposed product in the proposed dissolution medium. Based on the provided data/information, the biowaiver request for Amlodipine and Celecoxib Tablets, 5 mg/200 mg, is granted.

The characterization of the degradation products and impurities information in drug product is provided. The Applicant has indicated that there are no new impurities resulting in the new fixed combination drug product. The results of (b) (4)% for amlodipine related compound A and total related substances of (b) (4)% was observed only at the three-month time point for lots BY341015A and BY341015A. The values had returned to more consistent levels of (b) (4)% at the 12-month time point. The Applicant deemed the (b) (4)% results out of trend and indicated that there is insufficient data to confirm the one time out of trend result. The Applicant agreed to review the 24 -month stability data with consideration of tightening the related individual and total impurity acceptance criteria if warranted.

Based on review of suitability and stability data, the primary HDPE bottle provides adequate protection from light and no additional measures to protect the tablets from light during commercial distribution and use are warranted based on the stability results. No secondary packaging is proposed. The proposed container closure system is acceptable.

The Applicant proposed an expiry period of 24 months based on 12 months long-term and six months accelerated stability data. The long-term data showed little to no variability and conformed to the acceptance criteria. **Based on this data and in accordance with ICH Q1E, we grant a 24-month shelf life for the drug product.** The post-approval stability protocol adequately defines the storage conditions, container closure system, quality test attributes, and time intervals for evaluation throughout the stability program and aligns with ICH guidance.

(b) (4)

The comparability protocol for extension of drug product expiry post-approval is approved.

The Applicant submitted a request for categorical exclusion based on 21 CFR 25.31 (a) "No Increased Use" based on the combination drug definition of "a single product substituting directly for two approved products that would be administered separately." The Applicant also included a statement regarding no extraordinary circumstances in accordance with 21 CFR 25.15(d). **The claim of categorical exclusion is acceptable.**

In response to an information request, the Applicant agreed to reverse the order of the drug substances (b) (4) in the established name (b) (4) .

The Applicant proposed four drug substance manufacturing sources. The facilities were assessed and found acceptable based on their previous inspectional history which either covered the APIs under review or demonstrated capabilities to synthesize these APIs through coverage of similar APIs with a lack of quality defect signals. During the drug substance assessment, two intermediate manufacturing facilities were identified as potentially being critical and needing an evaluation. However, after assessment of the review and previous facility evaluations for DMF (b) (4) it was determined that appropriate controls were in place such that no further evaluation of the facilities is necessary.

The drug product manufacturing, packaging, and testing facilities were also assessed and found acceptable based on their previous inspectional history demonstrating capabilities and lack of quality defect signals for the proposed operations in this NDA. **All manufacturing, testing, and packaging facilities associated with NDA 210045 are acceptable and in good standing.**

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment (see Attachment I)

Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 4/27/2018 11:15:45AM
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ATTACHMENT I: Final Risk Assessment

Final Risk Assessment - NDA 210045 Amlodipine and Celecoxib Tablets; 2.5 mg/200 mg; 5 mg/ 200 mg; 10 mg/200 mg

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Assay	Formulation Container closure Raw materials Process/Scale/Equipment Site	**Medium**	End product testing	**Acceptable**	
(b) (4)	Formulation Container closure Raw materials Process/Scale/Equipment Site	**Medium**	(b) (4)	**Acceptable**	
Content Uniformity	Formulation Raw materials Process/Scale/Equipment Site	**High**	End product testing in compliance with USP <905>	**Acceptable**	
(b) (4)	Formulation Raw materials Process/Scale/Equipment Site	**High**	(b) (4)	**Acceptable**	
Microbial Limits	Formulation Container closure Raw materials Process/Scale/Equipment Site	**Low**		**Acceptable**	
Dissolution	Formulation Raw materials Process/Scale/Equipment Site	**High**	Interim dissolution method and acceptance criteria implemented based on FDA guidance	**Acceptable**	PMC for dissolution method and acceptance criteria development

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
(b) (4)	Formulation Raw materials Process/Scale/Equipment Site	**Low**	(b) (4)	**Acceptable**	
Photostability	Formulation Container closure Raw materials Process/Scale/Equipment Site	**Medium**		**Acceptable**	
Friability	Formulation Container closure Raw materials Process/Scale/Equipment Site	**Low**		**Acceptable**	
Compatibility	Formulation Raw materials Process/Scale/Equipment Site	**Medium**	Compatibility studies showed no interaction expected for commercial formulation	**Acceptable**	
Elemental Impurities	Formulation Container closure Raw materials Process/Scale/Equipment Site	**Not assessed**	Risk assessment and evaluation in accordance with ICH Q4D	**Acceptable**	PMC for elemental impurities assessment

LABELING

{For NDA only}

R Regional Information

1.14 Labeling

Highlights of Prescribing Information

----------DOSAGE FORMS AND STRENGTHS----------
Tablets (amlodipine /celecoxib): 2.5 mg/200 mg, 5 mg/200 mg, and 10mg/200 mg (3)

FULL PRESCRIBING INFORMATION: CONTENTS

3 DOSAGE FORMS AND STRENGTHS

CONSENSI (amlodipine and celecoxib) tablets, (b) (4)

(b) (4)

Reviewer's Assessment: Adequate

Recommendation: See tracked changes

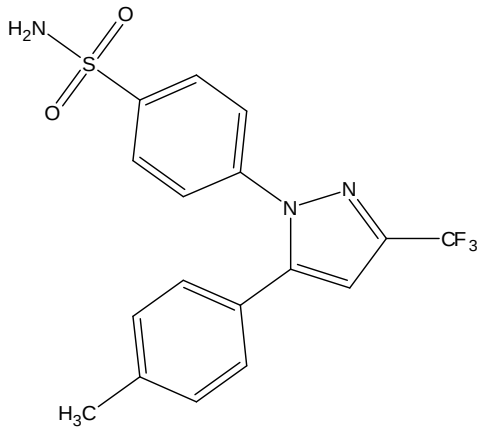
(b) (4)

(b) (4)

11 DESCRIPTION

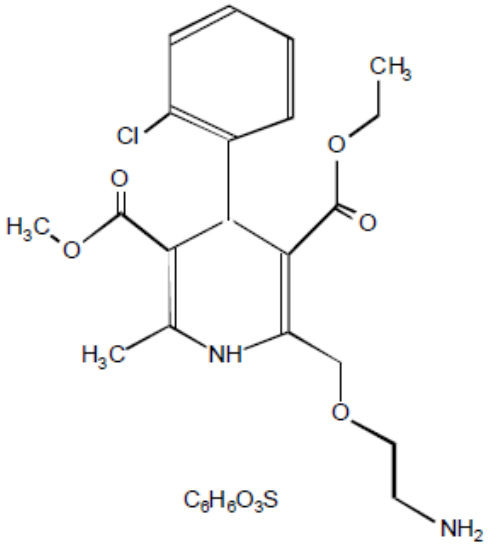
CONSENSI (amlodipine and celecoxib) tablet is an NSAID and long-acting calcium channel blocker for oral administration.. Each tablet contains amlodipine besylate and celecoxib 3.47 mg/200 mg, 6.93 mg/200 mg, and 13.87 mg/200 mg and is equivalent to 2.5 mg/200 mg, 5 mg/200 mg, and 10 mg/200 mg amlodipine/celecoxib respectively.

Celecoxib is chemically designated as 4-[5-(4-methylphenyl)- 3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The empirical formula is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38; the chemical structure is as follows:



Celecoxib is a white to off-white powder with a pKa of 11.1 (sulfonamide moiety). Celecoxib is hydrophobic (log P is 3.5) and is practically insoluble in aqueous media at physiological pH range.

Amlodipine besylate is chemically designated as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. The molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and the molecular weight is 567.1; the chemical structure is as follows:



Amlodipine besylate is a white crystalline powder. It is slightly soluble in water and sparingly soluble in ethanol.

The inactive ingredients in CONSENSI include: mannitol DC 200, croscarmellose sodium, povidone K-30, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide.

Reviewer's Assessment:

Recommendation: See tracked changes

The package insert comments were additionally added to the SharePoint document for consolidation of label revisions for team review.

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

CONSENSI (b) (4) tablets are white, (b) (4) biconvex, (b) (4)

(b) (4)

Storage

Store at room temperature 20°C to 25°C (68°F to 77°F); [see USP Controlled Room Temperature].

Dispense in tight, light-resistant containers (USP).

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

Distributed by

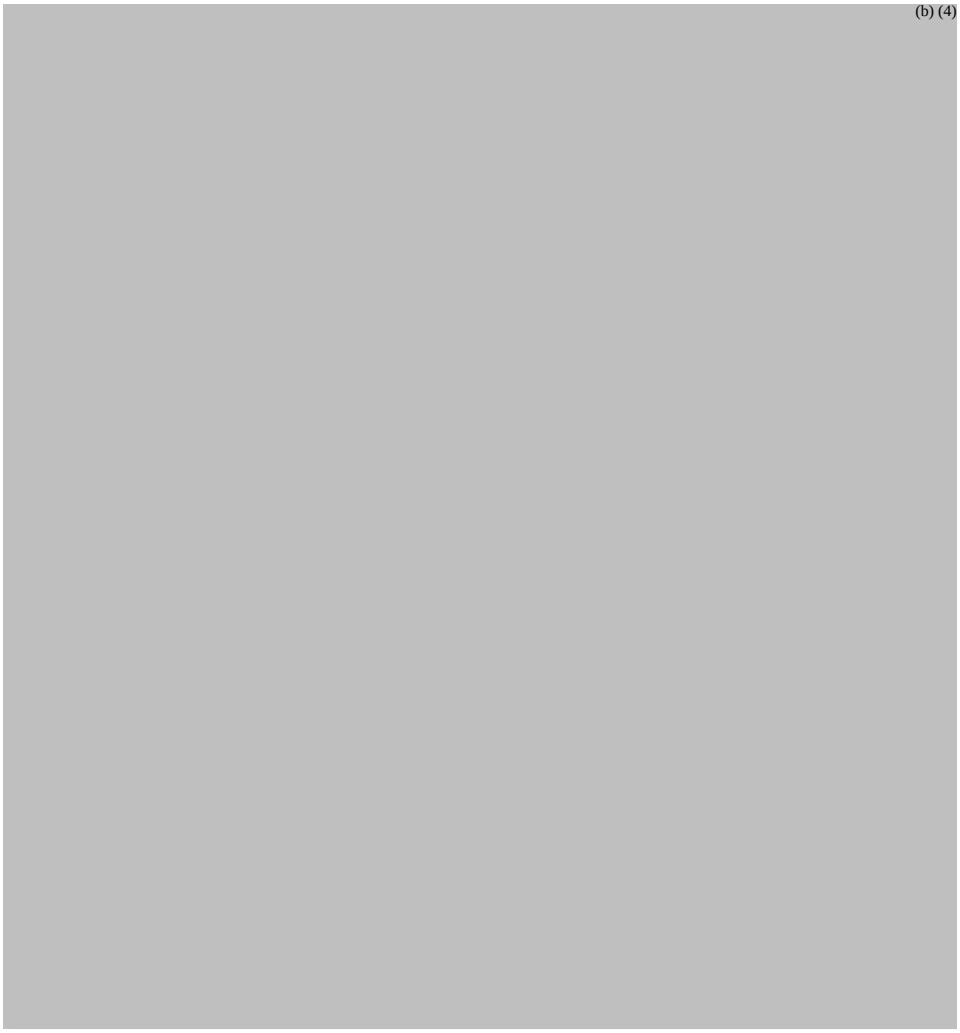
XXX

XX, XX XXXXX

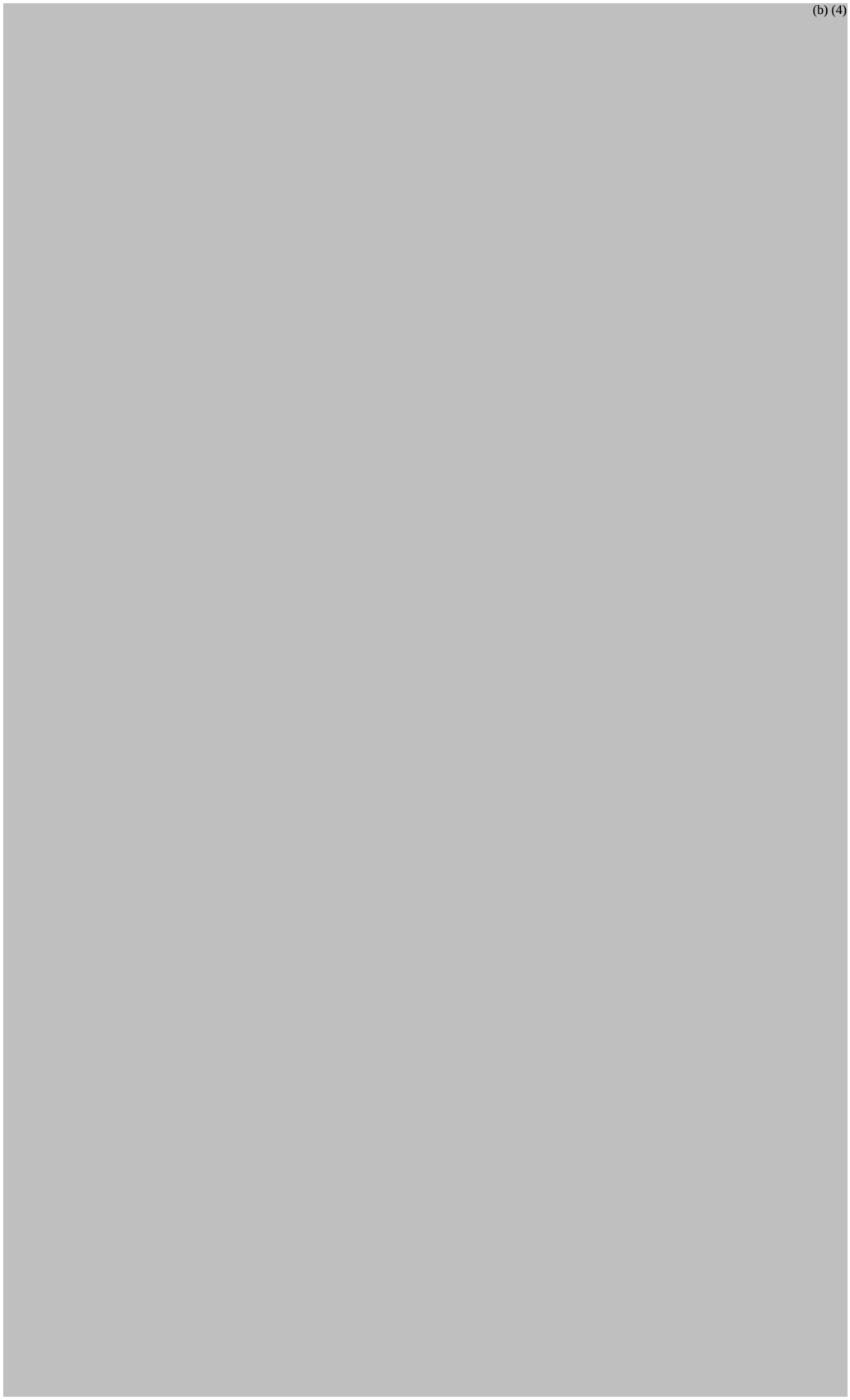
Immediate Container Label

{copy/paste or refer to a representative example of a proposed container label}

(b) (4)



(b) (4)



(b) (4)

Reviewer's Assessment:

1. Recommendation for Container label: Consensi® (amlodipine and celecoxib) tablets, for oral use

   a) (b) (4)

2. Relocate the equivalency statement from the principle display panel to the side panel.

3. Revise storage statement as follows:
   "Store at 20°C to 25°C (68°F to 77°F)"

4. Add to 100 count immediate label-
"This package is child resistant"
"Keep the bottle tightly closed"

{copy/paste or refer to a representative example of the proposed carton label here}

Reviewer's Assessment:

The applicant has not provided a separate copy of the proposed carton label in the NDA submission.

5. You have provided only the immediate (primary) label, please provide sample copies of any secondary packaging labels.

Add to 100 ct carton-

"The enclosed bottle is child resistant"

DMEPA concurs for the the salt equivalency statement should be on principal display panel. The draft 2018 Product title guidance recommends as part of title the route of administration.

Amendment (April 25, 2018)

1. *Recommendation for Container label: Consensi® (amlodipine and celecoxib)*
   a. (b) (4)

Kitov agrees with FDA's recommendation. The draft container labels have been updated (b) (4) in the principal display panel to "Consensi® (amlodipine and celecoxib)".

The following revised draft Container Labels are provided in Module 1.14.1.1:

- Draft Container Label for Low Strength 100 Count, April 2018 revision
- Draft Container Label for Low Strength 500 Count, April 2018 revision
- Draft Container Label for Mid Strength 100 Count, April 2018 revision
- Draft Container Label for Mid Strength 500 Count, April 2018 revision
- Draft Container Label for High Strength 100 Count, April 2018 revision
- Draft Container Label for High Strength 500 Count, April 2018 revision

2. *Relocate the equivalency statement from the principle display panel to the side panel.*

Kitov agrees with FDA's recommendation. The draft container labels have been updated to move the equivalency statement from the principal display panel to the right side panel. The revised draft Container Labels are provided in Module 1.14.1.1.

3. *Revise storage statement as follows:*
"Store at 20°C to 25°C (68°F to 77°F)"

Kitov agrees with FDA's recommendation. The draft container labels have been updated to revise the storage statement regarding temperature to "Store at 20°C to 25°C (68°F to 77°F)". The revised draft Container Labels are provided in Module 1.14.1.1.

4. *Add to 100 count immediate label- "This package is child resistant" "Keep the bottle tightly closed"*

Kitov agrees with FDA's recommendation. The draft labels for the 100 count containers have been updated to add "This package is child resistant" and "Keep the bottle tightly closed" in the left side panel. On review of the 100 count container labels, Kitov realized that a statement (b) (4) The revised draft Container Labels are provided in Module 1.14.1.1.

5. *You have provided only the immediate (primary) label, please provide sample copies of any secondary packaging labels.*

There is no planned secondary packaging at this time, and therefore, there are no sample copies of carton labels to provide.

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment of Response: Adequate

The applicant amendment responses are acceptable for each of the above comments. Kitov provided copies of each the updated revised immediate label (see examples of the 100ct and 500ct for the 10mg/200 mg strength) as indicated in comment response#1 above. The immediate labels comply with our recommendations and are acceptable. DMEPA may provide further comment on the container closure label in a subsequent review.

List of Deficiencies:

None

Primary Labeling Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
4/25/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Wendy Wilson-Lee, PhD
Branch Chief
OPQ/ONDP/Div1/Branch II

Milton Sloan

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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 4/24/2018 12:07:18PM
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BIOPHARMACEUTICS	
NDA	NDA 210045
Drug Product Name	Amlodipine Besylate and Celecoxib Tablets
Strength	2.5 mg/200 mg, 5 mg/200 mg, 10 mg/200 mg
Route of Administration	Oral
Applicant Name	Kitov Pharmaceuticals, Ltd.

Review Summary

In NDA 210045, the Applicant seeks approval of Amlodipine Besylate and Celecoxib Tablets, 2.5 mg/200 mg, 5 mg/200 mg and 10 mg/200 mg, under the 505(b)(2) pathway. The proposed fixed-dose combination (FDC) drug product is indicated to treat patient population who are administered celecoxib capsules as well as amlodipine besylate tablets individually for the (b) (4) treatment of osteoarthritis and hypertension, respectively. This 505(b)(2) application relies on FDA's previous finding of safety and effectiveness of the individual reference listed drugs (RLDs): NDA 020998 for Celebrex® (celecoxib) capsules held by G.D. Searle, LLC and NDA 019787 for Norvasc® (amlodipine besylate) tablets) held by Pfizer Inc. NDA 210045 is supported by bioequivalence (BE) studies and one pivotal clinical efficacy, safety, and pharmacokinetic drug-drug interaction study.

The Biopharmaceutics review is focused on the evaluation of data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) the request of biowaiver for 5 mg/200 mg strength. Based on the review of the provided information/data, Division of Biopharmaceutics has the following assessment, conclusions and recommendations:

Dissolution Method: The dissolution method [USP Apparatus 2 (paddle) at 75 rpm; 900 ml of pH 6.8 phosphate buffer with 0.5% sodium lauryl sulfate at 37.0 ± 0.5°C] currently proposed for the proposed fixed-dose combination (FDC) product, Amlodipine Besylate and Celecoxib Tablets, 2.5 mg/200 mg, 5 mg/200 mg, 10 mg/200 mg strengths, under the NDA 210045 is not an optimal method for the evaluation of the dissolution characteristics of each drug component of the proposed FDC product. Therefore, the current dissolution method has been accepted only on an interim basis, and the Applicant has been recommended to develop separate dissolution methods for each drug component of the combination product as a Post-Marketing Commitment (PMC).

Dissolution Acceptance Criteria: The dissolution acceptance criteria of 'not less than (NLT) (b) (4) % (Q) in 20 minutes' for amlodipine, and 'NLT (b) (4) % (Q) in 30 minutes' for celecoxib, revised as per FDA's

recommendation, are acceptable on an interim basis. The Applicant has been recommended (b) (4) new dissolution methods (to be developed as a PMC). The Applicant has been recommended to submit the final report (b) (4)

Biowaiver Request: The Applicant requested biowaiver for the middle strength (5 mg/200 mg) of the proposed product. The proposed product does not have the classical proportionality between the strengths, due to the constant celecoxib dosage of 200 mg across the three strengths. The Applicant adopted the approach of bracketing for the in vivo pharmacokinetic studies and provided data to demonstrate bioequivalence of the highest and the lowest proposed strengths compared to their corresponding listed drug products. The Applicant provided data showing similar dissolution profiles in multi-media (b) (4) between the highest strength (10 mg/200 mg) and the middle strength (5 mg/200 mg) of the proposed product. Also, the Applicant provided data showing similar dissolution of the three strengths of the proposed product in the proposed dissolution medium. Based on the provided data/information, the biowaiver request for Amlodipine Besylate and Celecoxib Tablets, 5 mg/200 mg, is granted.

Conclusion and Recommendations: The following dissolution method and acceptance criteria are acceptable on an interim basis for the quality control of the proposed product:

FDA's Approved Dissolution Method and Acceptance Criteria on an interim basis for Amlodipine Besylate and Celecoxib Tablets 2.5 mg/200 mg, 5 mg/200 mg and 10 mg/200 mg strengths	
Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	75 rpm
Volume	900 ml
Medium	pH 6.8 Phosphate Buffer with 0.5% SLS
Temperature	37.0 ± 0.5 C
Acceptance Criteria	Amlodipine: Not less than (b) (4) % (Q) at 20 minutes Celecoxib: Not less than (b) (4) % (Q) at 30 minutes

From the Biopharmaceutics perspective, NDA 210045 for Amlodipine Besylate and Celecoxib Tablets, 2.5 mg/200 mg, 5 mg/200 mg and 10 mg/200 mg strengths, is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Kaushalkumar Dave, Ph.D. (04/20/2018)
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Reviewer Name and Date:
I concur with Dr. Dave's Biopharmaceutics assessment and recommendation.

Jing Li, Ph.D. (04/26/2018)
Acting Team Lead, Biopharmaceutics Branch-1
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

BIOPHARMACEUTICS ASSSESSMENT

1. LIST OF SUBMISSIONS BEING REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	07/31/2017	Original NDA Submission
0010	02/05/2018	Quality/Response to Information Request
0012	03/27/2018	Multiple Submissions
0013	04/20/2018	PMR/PMC/ Quality - Response to Information Request

2. DRUG PRODUCT

In the current Application, Kitov Pharmaceuticals, Ltd. has requested approval of Amlodipine Besylate and Celecoxib Tablets (KIT-302, a research code name during the product development given by the Applicant), 2.5 mg/200 mg, 5 mg/200 mg and 10 mg/200 mg, as a 505(b)(2) NDA. The proposed drug product, Amlodipine Besylate and Celecoxib Tablets, 200 mg/2.5 mg, 200 mg/5 mg, and 200 mg/10 mg, is a fixed-dose combination (FDC) product developed as a 'convenience reformulation' consisting of celecoxib, a non-steroidal anti-inflammatory drug (NSAID), and amlodipine besylate, a calcium channel blocker antihypertensive agent, co-formulated in a single immediate release tablet. The proposed product is developed to target the patient population who are administered celecoxib capsules as well as amlodipine besylate tablets individually for the (b) (4) treatment of osteoarthritis and hypertension, respectively. To establish the bioequivalence, the Applicant performed pharmacokinetic studies with the proposed combination product, Amlodipine Besylate and Celecoxib Tablets, 2.5 mg/200 mg and 10 mg/200 mg strengths, against the listed drugs (LDs), Celebrex® (celecoxib) 200 mg capsules and Norvasc® (amlodipine besylate) 2.5 mg, and 10 mg tablets administered together.

The proposed product is intended to have an immediate release (IR) profile (b) (4) (b) (4) The compositions of the three strengths of the proposed drug product are listed in Table 1.

Table 1. Composition of the proposed product

Composition (Function)	Celecoxib/Amlodipine Besylate					
	200 mg/2.5 mg		200 mg/5 mg		200 mg/10 mg	
	mg/tab	w/w%	mg/tab	w/w%	mg/tab	w/w%
[redacted]						

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

BCS Class Designation

In the Pharmaceutical Development Report (Module 3.2.P.2.Drug Product), the Applicant noted amlodipine besylate as BCS Class I compound and celecoxib to be a BCS Class II compound; however no permeability data have been provided by the Applicant to support this. No BCS Class has been previously designated by the FDA for amlodipine besylate or celecoxib and no request for BCS designation has been submitted under the current NDA.

4. DISSOLUTION INFORMATION

In the current submission, the applicant provided dissolution data to support the proposed dissolution specifications and bio-waiver request for the intermediate strength of the proposed product, Amlodipine Besylate and Celecoxib Tablets; 5 mg/200 mg. Also, the Applicant used dissolution testing during the stages of formulation and manufacturing development. The Applicant provided a dissolution method development report within the Pharmaceutical Development Report provide in the Module 3.2.P.2.2.3. The Applicant's originally proposed dissolution method and acceptance criteria are as following:

Table 9. Dissolution method and acceptance criteria originally proposed by the Applicant

	(b) (4)
Apparatus	
Paddle Speed	
Volume	
Medium	
Temperature	
Acceptance Criteria	

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(b) (4)

Table 10. Dissolution method and acceptance criteria newly proposed by the Applicant and accepted by the FDA on interim basis

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	**75** rpm
Volume	900 ml
Medium	pH 6.8 Phosphate Buffer with 0.5% Sodium Lauryl Sulfate
Temperature	37.0 ± 0.5°C

Dissolution Acceptance Criteria

The Applicant proposed dissolution acceptance criteria of 'NLT (b) (4)% (Q) in (b) (4) minutes' for celecoxib and 'NLT (b) (4)% (Q) in (b) (4) minutes' for amlodipine. Data provided in Figure 9 and 10 suggest that the following dissolution acceptance criteria are suitable for the proposed product at paddle speed of 75 rpm:

Amlodipine: NLT (b) (4)% (Q) at 20 minutes
Celecoxib: NLT (b) (4)% (Q) at 30 minutes

Via an IR dated 04/11/2018, the Applicant was recommended to implement these dissolution acceptance criteria. Via an IR response dated 04/13/2018, the Applicant accepted the FDA recommendation and revised the dissolution acceptance criteria to 'NLT (b) (4)% (Q) at 20 minutes' for amlodipine, and 'NLT (b) (4)% (Q) at 30 minutes' for celecoxib.

Dissolution of Pivotal Clinical Study Batch and Registration Batches

Dissolution profiles for the pivotal bioequivalence study batch (BY261015A) obtained using the originally proposed dissolution method (b) (4) rpm) are provided in Table 11. Dissolution data for individual units are provided in .xpt format in Module 3.2.P.2.1[1].

Table 11: Dissolution Results for Batch BY261015A (Pivotal Bio Batch)

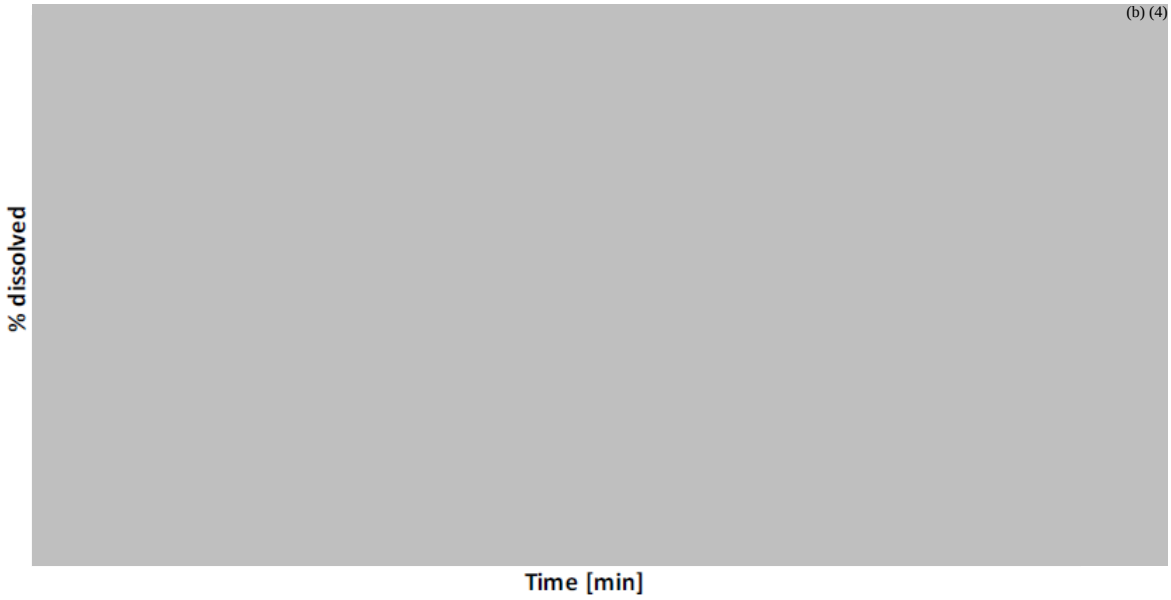
(b) (4)

[1] GlobalSubmit Review Link: Application 210045 - Sequence 0001 - Dissolution Data xpt

Dissolution profiles for the registration batches of each of the strengths are provided in Figure 13 (celecoxib) and Figure 14 (amlodipine).

Figure 13. Dissolution of celecoxib from the registration stability batches

Figure 14. Dissolution of amlodipine from the registration stability batches



It is noted that the above dissolution studies were performed with the originally proposed dissolution method with the paddle speed of (b) (4) rpm; however, the proposed FDC product is expected to show similar dissolution profiles for amlodipine and celecoxib with the newly proposed and agreed to dissolution method with the paddle speed of 75 rpm.

5. BRIDGING STUDIES

Via an IR (dated 12/29/2017), the Applicant was requested to clarify if there are any changes in drug product composition, its manufacturing process or site, or API suppliers between the pivotal bio-batch and the proposed commercial product. In a response dated 02/05/2018, the Applicant stated that there are no changes in terms of the drug product composition, its manufacturing process or site, or API suppliers between the pivotal clinical study batch and the proposed commercial product. Therefore, no bridging studies are needed.

6. BIOWAIVER REQUEST

The proposed product is an FDC product of amlodipine/celecoxib manufactured at three strengths: 2.5 mg/200 mg, 5 mg/200 mg, and 10 mg/200 mg. following the FDA's recommendation provided at the pre-NDA meeting for IND112830 held in April 11, 2016.

The proposed product does not have classical proportionality between the strengths, due to the constant celecoxib dosage of 200 mg across all strengths (Table 1). (b) (4) The Applicant adopted the approach of bracketing for the in vivo pharmacokinetic studies and provided data to demonstrate bioequivalence between the highest (10 mg/200 mg) and the lowest (2.5 mg/200 mg) proposed strengths and their corresponding listed drug products, to support the biowaiver request for the 5 mg/200 mg (middle) strength tablets.

The provided in vivo data for the highest strength (10 mg/200 mg) and the lowest strength (2.5 mg/200 mg) indicate that these two strengths of the proposed FDC product are bioequivalent to the corresponding strengths of the LDs (refer to the Office of Clinical Pharmacology review for assessment of the BE studies). To support the biowaiver request for the intermediate strength, the Applicant provided comparative dissolution data only with the originally proposed dissolution method (b) (4) rpm), but did not provide multi-media dissolution data. Therefore, via an IR dated 12/29/2017, the Applicant was recommended to provide multi-media dissolution data to support the biowaiver request for the intermediate strength of the proposed product. It was stated in the IR that (b) (4)

In a response dated 02/05/2018, the Applicant provided comparative dissolution data for the 200mg/10 mg and 200 mg/5 mg strengths of the proposed product in three different pH media, each with 0.5% SLS. The dissolution data for celecoxib and amlodipine are summarized in Figure 15 and Figure 16, respectively. (b) (4) The data are summarized in Table 12.

Figure 15: Comparative Dissolution of 200 mg/10 mg and 200 mg/5 mg KIT-302 Tablets – Celecoxib Component

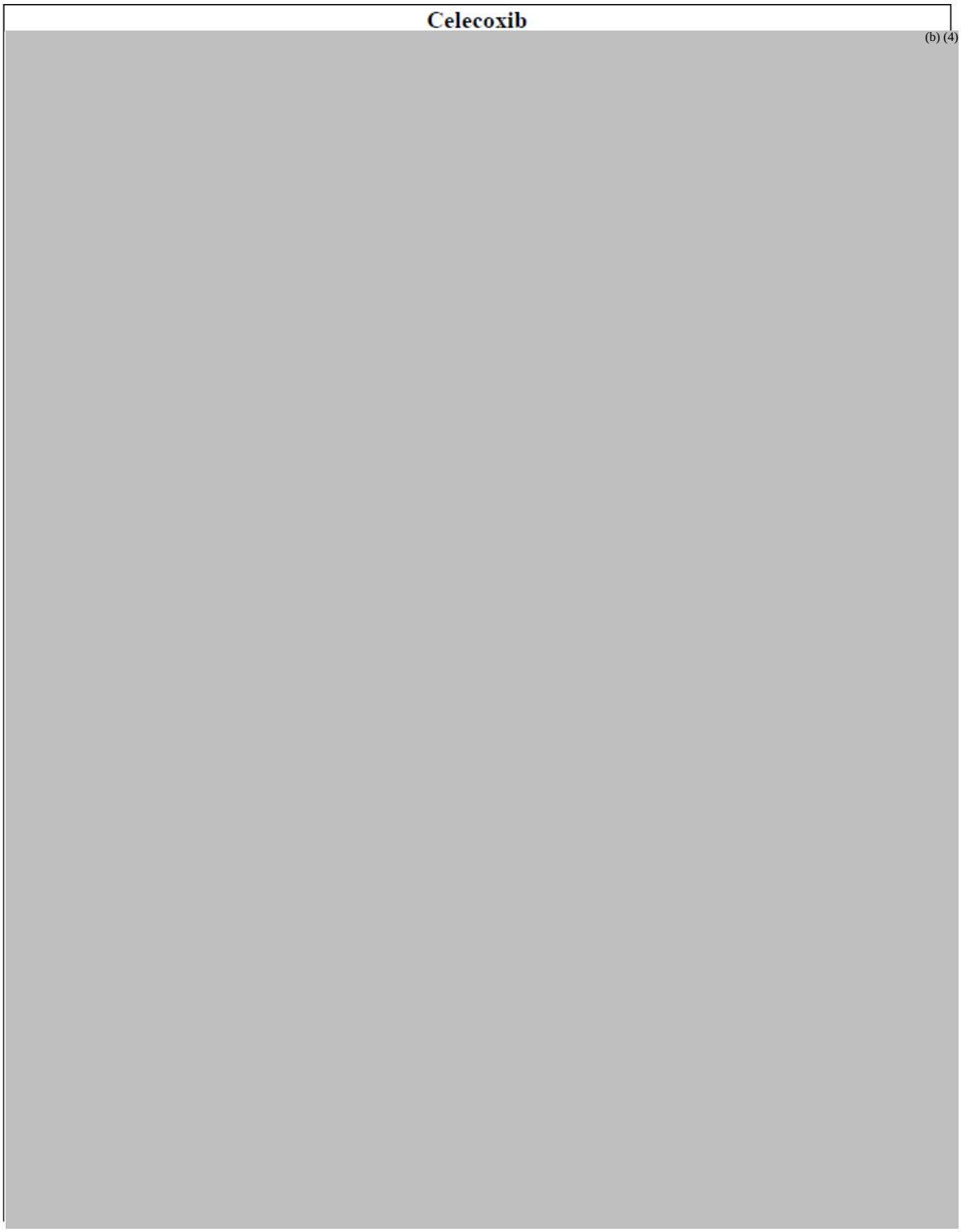


Figure 16: Comparative Dissolution of 200 mg/10 mg and 200 mg/5 mg KIT-302 Tablets – Amlodipine Component

Table 12: Comparative Amlodipine Dissolution Results for High Strength (10 mg/200 mg) KIT 302 Tablets (Lot BY261015A; Pivotal Bio Batch) and Mid Strength (5 mg/200 mg) KIT-302 Tablets (Lot BY291015A)

(b) (4)

The comparative dissolution data provided by the Applicant show similar profiles in multi-media (b) (4) between the highest strength (10 mg/200 mg) and the middle strength (5 mg/200 mg) of the proposed product. Also, the Applicant provided data show similar dissolution across all three strengths of the proposed product in the proposed dissolution medium (Figures 13 and 14).

Overall, the provided data/ information support the Applicant's biowaiver request for the middle strength, Amlodipine Besylate and Celecoxib Tablets, 5 mg/200 mg. Therefore, the Applicants biowaiver request is **granted**.

7. CONCLUSIONS AND RECOMMENDATION

From a Biopharmaceutics perspective, NDA 210045 for Amlodipine Besylate and Celecoxib Tablets, 5 mg/200 mg, 5 mg/200 mg, 10 mg/200 mg, is recommended for **APPROVAL**.

The Applicant has agreed to the following PMC in the response dated 04/13/2018 and has committed to submitting the requested data/information in a final study report (b) (4)

Agreed-Upon Studies to be Performed Under the PMC

(b) (4)

- (b) (4)

  Submit the final report (b) (4)

Kaushalkumar Dave

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Jing Li

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Wendy
Wilson- Lee

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