CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210709Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

To: NDA 210709 Administrative File

From: Wendy I. Wilson-Lee, Ph.D.; Acting Branch Chief, OPQ/ONDP/DNDP1/Branch 1

Date: Wednesday, November 08, 2017

Re: NDA 210709 OPQ IQA Correction Memorandum

The purpose of this memorandum is to correct an error in the executive summary of the Office of Pharmaceutical Quality's Integrated Quality Assessment, finalized and archived on Oct 11, 2017, for NDA 210709 Tekturna (aliskiren) Oral Pellets, 37.5 mg from Noden Pharma. On page 4 of the document, Section II.A. Product Quality Overview includes the following statement:

"Adequate stability data were provided for three registration batches and the proposed shelf-life of (b) (4) months is reasonable when drug product blister packs are stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F); protect from moisture."

This statement is incorrect. The original submission included a proposal for (b) (4) months drug product expiry; however, the Quality Amendment – Stability Information dated June 5, 2017 included updated drug product stability data and a proposal for a 36 month shelf-life. Statistical evaluation in accordance with ICH Q1E calculated shelf-lives of the three batches to be 60 months projected stability. Based on this updated stability data and analysis, we grant a 36 month drug product expiry when stored in blisters containing (b) (4) oral pellets in HPMC capsules at or below 25ºC. This is in alignment with the primary drug product review (Pages 36-37 of 87.)

The OPQ IQA document is hereby amended to read the following:

"Adequate stability data were provided for three registration batches and the proposed shelf-life of 36 months is reasonable when drug product blister packs are stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F); protect from moisture."

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Recommendation: APPROVAL

NDA 210709
Review 01

Drug Name/Dosage Form	Tekturna (aliskiren) Oral Pellets
Strength	37.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Noden Pharma, DAC
US agent, if applicable	QuintilesIMS

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment (SD 1088)	15-SEP-2017	DP, Biopharm
Amendment (SD 1087)	31-AUG-2017	DP, Biopharm, Facilities
Amendment (SD 1086)	28-JUL-2017	DP
Amendment (SD 1084)	12-JUL-2017	Process
Amendment (SD 1082)	30-JUN-2017	Process
Amendment (SD 1081)	20-JUN-2017	DP, Biopharm
Amendment (SD 1080)	05-JUN-2017	DP, Biopharm
Amendment (SD 1079)	05-JUN-2017	DP
Original (SD 1078)	05-JUN-2017	All

Quality Review Team

DISCIPLINE	REVIEWER	OFFICE
Drug Substance	Rao Kambhampati/Wendy Wilson-Lee	ONDP
Drug Product		
Labeling		
Environmental Assessment		
Process	Yahong Wang/Peter Guerrieri	OPF
Facility	Wayne Seifert/Ruth Moore	OPF
Biopharmaceutics	Qi Zhang/Ta Chen Wu	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)	Type IV	(b) (4)	(b) (4)	Adequate.	N/A	Sufficient information provided in NDA.
	Type IV		Hypromellose Capsules	Adequate.	N/A	Sufficient information provided in NDA.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21985	Tekturna (aliskiren) Tablets

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210709 for Tekturna (aliskiren) Oral Pellets, 37.5 mg along with the comparability protocol to support a drug product manufacturing site change post-approval.

II. Summary of Quality Assessments

A. Product Quality Overview

Noden Pharma submitted NDA 210709 to support marketing of a pediatric formulation for Tekturna (aliskiren) in response to a FDA pediatric written request. This product was initially submitted as a supplemental NDA but was later reclassified as a new NDA due to the new dosage form classification. The submission was granted priority review with a PDUFA date of November 15, 2017.

Proposed Indication(s) including Intended Patient Population	*Treatment of hypertension in children 6 years and older and adults*
Duration of Treatment	*Chronic*
Maximum Daily Dose	*300 mg*
Alternative Methods of Administration	*None*

The drug substance is aliskiren hemifumarate, the same active ingredient in currently approved Tekturna Tablets (NDA 21985). Aliskiren hemifumarate is a white to slightly yellow, crystalline powder that is freely soluble in water. The pediatric product is formulated as oral pellets that are then encapsulated. The capsule is not intended for administration but is rather considered as a dispensing aid. The proposed administration instructions call for opening of the capsule and mixing of the pellets with either soft foods, liquid, or (b) (4) followed by a sip of water.

Key product quality review issues included confirmation of appropriate dosage form selection and design, assessment of the potential safety risks if patients swallow the capsules (Size 0), adequate labeling to ensure proper administration and reduce medication errors, sufficient taste masking, compatibility of the pellets with soft foods and liquids, and different capsule sizes and blister lid foil used for registration stability versus what is proposed for commercialization. Adequate information was provided in the submission to sufficiently mitigate the potential risks associated with these issues, as described in the product overview and the product quality benefit-risk assessments.

Each capsule contains twelve pellets with each pellet containing 3.125 mg of aliskiren to deliver a total dose of 37.5 mg aliskiren. All excipients used in the drug product are

compendial. (b) (4) butylated methacrylate polymer. Capsules containing pellets are packaged in child resistant/senior friendly unit dose blisters. The proposed blister components are commonly used in the pharmaceutical manufacturing. Both the drug substance and drug product specification contain all the required tests and the proposed acceptance criteria are reasonable. The non-compendial analytical procedures were adequately described and their validation reports are acceptable. Three potential drug product degradation products were identified and included in the drug product specification and they do not have genotoxic potential. HPMC capsules were chosen for this product instead of more commonly used gelatin capsules (b) (4) Adequate stability data were provided for three registration batches and the proposed shelf-life of (b) (4) months is reasonable when drug product blister packs are stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F); protect from moisture.

Adequate batch analysis results were provided and they complied with the proposed specification. The results also showed that the drug product can be manufactured with consistent quality and purity. The proposed commercial drug product manufacturing consists of (b) (4) . The size of the commercial batch is the same as the registration batches. A comparability protocol to support a post-approval drug product manufacturing site change was reviewed and recommended for approval by OPQ review team members (drug product, process, biopharmaceutics, facilities). The Overall Manufacturing Inspection Recommendation is Approval. All proposed commercial manufacturing, testing, and packaging sites have acceptable compliance status.

The Biopharmaceutics review focused on (1) the evaluation of the adequacy of the information/data supporting the proposed dissolution method and acceptance criterion, (2) bridging of formulations throughout product development and (3) providing feedback and recommendation concerning the potential risks associated with direct consumption (i.e. swallowing) of dispensing capsules by young children. For the routine QC testing of the Aliskiren Oral Pellets 37.5 mg for batch release and stability testing, the proposed dissolution method and acceptance criterion are acceptable. The clinical formulation used in the Phase 3 clinical trial is the same as the proposed commercial drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the same as the proposed commercial site. Therefore, bridging the commercial formulation to the clinical formulation is not needed. Based on the available data/information, it is reasonable to expect that swallowing the capsule-containing aliskiren pellets whole will yield significantly lower bioavailability of aliskiren in children. To mitigate the risk of swallowing the whole dispensing capsule, a clear labeling instruction with "do not swallow the capsules" under Dosage and Administration of the labeling is necessary.

B. Product Quality Benefit-Risk Assessment

Issue #1: Proposed Primary Administration Instructions
The proposed product uses a Size 0 capsule (~ 1 inch length) as a dispensing aid for oral pellets to facilitate mixing with basic pH foods or water. The intended patient population is adults and children 6 years and older. Proposed label includes primary administration instructions to open capsule and mix contents with dosing vehicles (b) (4). Proposed label includes explicit instructions to not swallow whole capsules. Multiple concerns are raised by the proposed labeling from a product quality perspective:

1) Misadministration of the product due to capsule presentation despite labeling instructions to sprinkle
2) Potential for choking if swallowed whole, especially for younger patients
3) Potential impact on bioavailability if swallowed whole
4) Dosage form misalignment with USP dosage form recommendations

Key Evidence/Uncertainties	Assessment/Conclusion	Lifecycle Considerations
Misadministration: Adverse event and patient experience data for products presented as capsules for non-oral routes of administration indicate that the likelihood of patient misuse (i.e. not following labeling instructions, wrong route of administration) is moderate/ high. The potential exists for patients who see a product presented as a capsule to swallow the capsule whole. To mitigate the risk of misadministration, Noden uses several features in dosage form design and labeling. Instructions to "do not swallow" are predominately displayed in the carton/container labels, the prescribing information, and the patient information. The clear capsules are clearly marked with red arrows to indicate that the capsule should be opened. The product is dispensed with instructions for use that provide detailed administration instructions. The administration instructions are based on the administration instructions used during the pivotal clinical studies. Studies A2365 and A2365E1 exposed ~250 patients to aliskiren using the proposed dosage form and administration instructions. In addition to written instructions, pictorial instructions are provided on the labels and in labeling.	**Misadministration:** Clear labeling instructions, written and pictorial, mitigate the risk of misadministration. Instructions to "do not swallow" are predominately displayed in the carton/container labels, the prescribing information, and the patient information. The clear capsules are clearly marked with red arrows to indicate that the capsule should be opened. Clinical experience from studies A2365 and A2365E1 suggests that the proposed labeling was sufficient to ensure proper use. The drug product will be administered chronically for the treatment of hypertension in adults and children (6 years and older). The likelihood of misadministration diminishes after initial dosing once the patient/caregiver is familiar with the dosing instructions. Therefore, the risk of misadministration is considered low from a product quality perspective. Other disciplines will also comment on the misadministration risk (e.g. DMEPA, clinical).	Although clinical evidence suggests that the risk of misadministration is low, adverse event reporting and patient complaints post-approval should be monitored for signals associated with swallowing the intact capsule. If a revision to labeling is required to support swallowing of whole capsules, in vivo data demonstrating comparable bioavailability will most likely be needed.

Choking: The applicant provided a risk assessment of the potential for choking that categorized the risk as low. A search of approved drug products identified several products in either Size 0 or larger Size 00 labeled for use in patients 6 years and older. The majority of these capsules were gelatin-based. The proposed product uses a HPMC(hydroxypropyl methylcellulose) based capsule. HPMC capsules are considered more difficult to swallow compared to gelatin capsules due to the more brittle nature and longer wetting time for the HPMC capsule shell. This longer wetting time results in a capsule shell that is stickier compared to a gelatin capsule shell. Additionally, if the capsule shell is fractured (either during manufacturing or administration), it may result in fragments with sharp edges. The pivotal clinical studies supporting NDA 210709 did not allow the patients to swallow the proposed product whole. **Bioavailability:** *In vitro* dissolution data under acidic conditions indicate a marked reduction in drug release for the intact capsule compared to the pellets alone. At (b) (4)	**Choking:** From a product quality perspective, the risk of choking, if swallowed, is low. The method of administration as outlined in the labeling calls for mixing the oral pellets in food/liquid. Clear labeling instructions indicate "do not swallow". Precedent exists for approving capsules this size or larger for swallowing in this age group (adults and children 6 years and older). Other disciplines will also comment on the choking risk (e.g. DMEPA, clinical, DMPH, etc.). **Bioavailability:** The *in vitro* dissolution results point to a potential issue with *in vivo* bioavailability, if capsules are swallowed whole. Based on this evidence, revisions to the labeling to allow swallowing of intact capsules are not recommended from a product quality perspective. Other disciplines will also comment on the potential impact swallowing whole capsules may have on bioavailability (e.g. OCP).	

USP: In general, USP recognizes swallowing as the primary administration method for oral capsules, with alternative administration methods such as sprinkling or dissolving in liquid as secondary methods. USP recommends that dosage forms intended for sprinkling as the primary administration method be packaged in unit dose containers such as sachets or packets. OPQ informed then sponsor Novartis of concerns regarding development of this dosage form during NDA pre-submission meetings. OPQ recommended reformulation or alternative packaging and noted that acceptance of the proposed dosage form (i.e., pellets in capsules) would be a review issue. Current applicant Noden contends that alternative packaging (such as a sachet) is not technically feasible using the current formulation due to the low product weight (b) (4) on commercial equipment; based on assessments made by equipment vendors.	**USP:** The current challenges: 1) allowing swallowing of the intact capsules (no data to support equivalency to treatment with just pellets) and 2) inability of commercial filling of the low-weight drug product formulation into packets (b) (4) makes aligning this product with USP recommendations difficult. OPQ's pre-submission recommendations to reformulate and/or repackage were not accepted by the applicant. When faced with the choice of having no product available due to requests to align with USP recommendations versus making product available to patients who may benefit despite discrepancies with USP, the need of the patient outweighs the need for alignment with USP recommendations.	

Issue #2: Proposed Dosing Vehicles

The proposed dosing vehicles include vanilla pudding (milk or soy-based), vanilla ice cream (milk or soy-based), (b) (4) Water is proposed for swallowing after dosing of pellets, not for mixing with pellets.

Key Evidence/Uncertainties	Assessment/Conclusion	Lifecycle Considerations
Aliskiren has a bitter taste. The pellets are (b) (4) The number of suitable vehicles is limited be the requirement for neutral to basic pH. Given the age range for use (children 6 – 17 years old and adults), inclusion of (b) (4) is not suggested as it may indicate that use in children younger than 6 is approved. When asked if the pellets could be mixed with small amounts of water or milk, Noden responded that these vehicles were not recommended (b) (4) Milk and most potable water sources have a pH of ~7. This pH is several units away from pH (b) (4) *In vitro* dissolution data in (b) (4) .	Based on the data available, it is unlikely that either milk or potable water will compromise the (b) (4) to such an extent as to cause patient non-compliance due to taste. Instructions to administer the dose immediately after preparation may mitigate this risk. In addition, if non-compliance due to taste after administration with water or milk becomes an issue, alternative administration vehicles are indicated in labeling. Therefore, we support adding milk and water as liquid dosing vehicles in labeling.	Adverse event reporting and patient complaints post-approval should be monitored for a signal associated with non-compliance due to bad taste when administered with the labeled dosing vehicles.

Overall Benefit-Risk Assessment: Based on my assessment of the information available, I consider the challenges and risks as presented in the above table associated with revising labeling to allow for swallowing of the capsules to be greater than those presented by retaining the proposed labeling with "do not swallow" instructions. Therefore, I recommend that OPQ approve the product with the proposed labeling "do not swallow."

Aliskiren is indicated for the treatment of hypertension in adults and children. Childhood hypertension has a reported 3.3% prevalence rate – approximately 2.2 million children and adolescents – and is associated with long-term cardiovascular risk, including numerous adverse cardiovascular outcomes in adulthood (Hill KD and Li JS. Childhood Hypertension: An Underappreciated Epidemic?. *Pediatrics*. 2016; 138(6):e20162857). The product was developed in response to the agency's pediatric written request.

Aliskiren is not a first-line therapy for the treatment of hypertension in adults and children. The expected use population for this product is limited; however, the availability of this drug product could meet an unmet medical need for those patients, including pediatrics, that cannot use the currently approved aliskiren tablet. Therefore, it is important to consider regulatory flexibility as part of the overall benefit-risk assessment. Labeling changes proposed by the clinical division may further limit the use population. The maximum daily dose will be limited to 300 mg and the maximum pediatric patient weight will be limited to 50 kg. Patients requiring higher doses or weighing more will be indicated for the approved tablet formulation. The applicant notes that it is not technically feasible at this time to develop sachet/packet packaging to better align the product with USP recommendations. Given the potential limited use population, development of a new dosage form is highly unlikely by the applicant. Requiring reformulation or repackaging or an adverse action may result in lack of a viable treatment option for patients who will benefit from this product. In addition, currently there are numerous US commercially approved capsules which are labeled for swallowing or administration by opening the capsule and the contents sprinkled on food for ingestion; the difference here is that the whole capsules will be labeled "do not swallow" and only the opening capsules and the contents sprinkled on food/liquid and then ingesting will be listed in instructions.

The risk of misadministration is mitigated by clear administration instructions – both written and pictorial – in the carton/container labels, the prescribing information, the patient information, and the instructions for use. These instructions are based on the administration instructions used during pivotal clinical studies. No additional training was provided to patients, caretakers, or health care providers in those clinical trials. There were no reported problems with administration difficulties or misadministration. These outcomes provide some assurance that the administration instructions are clear and appropriate to support safe use of the drug product. In addition, the clear capsules are also clearly marked with red arrows to indicate that the capsule should be opened. Further, not using "capsule" in the established name offers another feature that indicates a different method of administration other than swallowing. The use of "Oral Pellets" in the name fits with how the product will be prepared in food/liquid and there is a precedent/history of having oral pellets administered to children via food/liquids. If patients did swallow the capsules, the evidence suggests that risk to patient safety is low with respect to choking; however, the risk to efficacy cannot be fully characterized as the clinical studies supporting approval were not conducted with patients swallowing intact capsules

The *in vitro* dissolution data show a marked reduction in drug release with administration of intact capsules compared to pellets alone. I believe these results foreshadow a reduction in bioavailability in vivo if the capsules are swallowed intact. Even if absorption takes place in the upper or lower gastrointestinal tract, it is highly likely that there will be little drug available for adsorption due to the crosslinking of the HPMC capsule in the stomach which results in the formation of a hydrogel, leading to diffusion-dependent drug release. I agree with the Biopharmaceutics Review Team that the *in vitro* dissolution results do not support a revision in labeling to allow swallowing of intact capsules. I recommend that the labeling be revised to indicate that clinical studies did not evaluate the safety or efficacy of whole capsules.

For the reasons noted above, the OPQ recommendation is approval for Tekturna (aliskiren) Oral Pellets as the challenges and risks associated with revising labeling to allow for swallowing to align with USP recommendations are greater than those presented by retaining the current labeling.

C. Special Product Quality Labeling Recommendations

OPQ recommends the following revisions to the labeling to ensure appropriate administration of the drug product:

1. Add instructions to not chew or crush pellets
2. (b) (4)
3. Add water and milk as liquid vehicles for administration
4. Instruct to administer immediately after preparation

D. Final Risk Assessment (see Attachment)

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ATTACHMENT I: Final Risk Assessment

A. Drug Product Final Risk Assessment – NDA 210709 Tekturna (aliskiren) Oral Pellets, 37.5 mg

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	Formulation Container Closure Raw Materials Process/Scale/Equipment Site	Low		Low	
Solid State		Low		Low	
Content Uniformity		Low		Low	
Microbial Limits		Low		Low	
Pellet Size		Low		Low	
Dissolution		Low		Low	
Palatability		Medium	(b) (4)	Low	
Compatibility with dosing vehicles		Medium	Labeling identifies soft foods/liquids considered compatible with formulation Development studies support the labeled dosing vehicles	Low	
Resuspendability		Low			
Capsule Dimension/Size	Formulation Raw Materials	Low	Sufficient evidence provided to demonstrate that if swallowed, choking hazard is minimal Labeled administration	Low	

			instructions indicate do not swallow		
Pellet disintegration	Formulation Container Closure Raw Materials Process/Scale/Equipment Site	Low		Low	
Moisture content		Medium	Used HPMC capsule (b) (4) Labeled dosing instructions call for swallowing immediately after mixing/drinking water or high water content vehicles	Low	

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LABELING

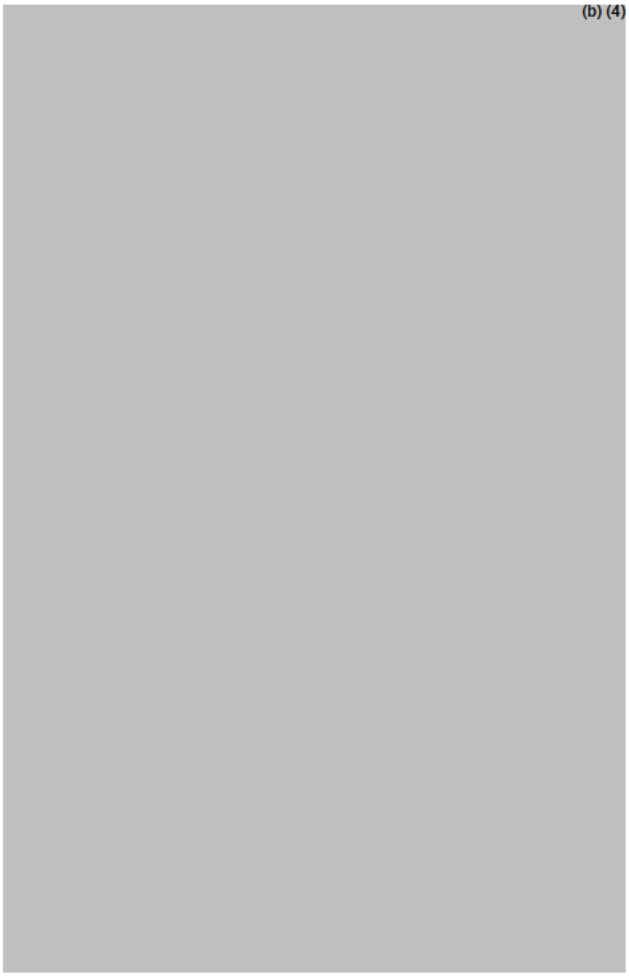
IQA Review Guide Reference

R Regional Information
1.14 Labeling

Immediate Container Label

Unit dose blister label is provided below:

(b) (4)



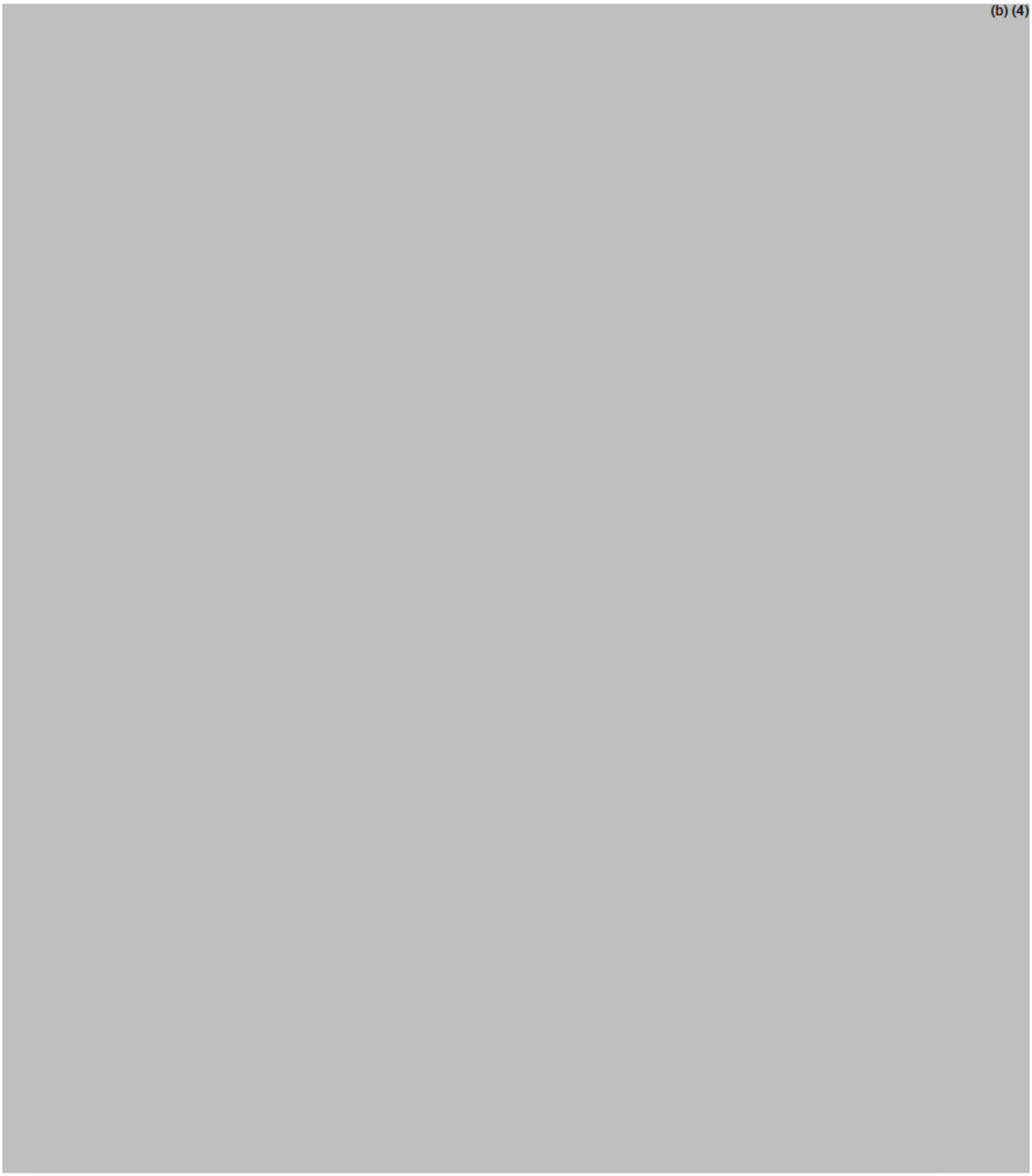
Reviewer's Assessment: Acceptable with the following modifications.
Since the unit dose blister size is small, the applicant tried to include as much information as possible. The following modifications and additions are recommended:

1) **Increase the prominence of "(aliskiren)" to at least 50% of the tradename.**

2) **Include equivalency statement such as "Each capsule contains 37.5 mg of aliskiren as aliskiren hemifumarate 41.4 mg".**
3) **Do not swallow the capsule.**

Carton Labeling

(b) (4)



Reviewer's Assessment: Acceptable.
From CMC perspective the label complies with all the regulations.

List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 10/4/2017

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

Wendy Wilson-Lee, Ph.D. 10/4/2017

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BIOPHARMACEUTICS

NDA: 210709
Drug Product Name/Strength: Tekturna®(Aliskiren) Oral Pellets, 37.5 mg pellets in capsules
Dosage Form: Immediate Release Oral Pellets
Route of Administration: Oral
Applicant Name: Noden Pharma DAC
Intention: Treatment of hypertension in adults and children 6 years of age and older.
Submission Type: 505(b)(1) (Type 3-New Dosage Form)

Review Summary:

The Applicant submitted NDA 210709 to support marketing of a pediatric formulation for Tekturna® (Aliskiren) Tablets (NDA 21985; approved in 2007). Tekturna is a renin inhibitor (RI) indicated for the treatment of hypertension to lower blood pressure in adults and children 6 years of age and older. The proposed pediatric drug product is formulated as (b) (4) oral pellets that are encapsulated in dispensing capsule which is not intended by the Applicant for oral administration. The clinical program in support of this NDA for treatment of hypertension in children patients 6-17 years of age includes Includes an open-label Phase 2 study (A2256), a randomized Phase 3 trial (A2365) and its safety extension study (A2365E1), and interim results of an ongoing long-term growth and development study (A2365E2) which is an observational extension for Study A2365.

The Biopharmaceutics review was focused on (1) the evaluation of the adequacy of the information/data supporting the proposed dissolution method and acceptance criterion, (2) bridging of formulations throughout product development and (3) providing feedback and recommendation concerning the potential risks associated with direct consumption (i.e. swallowing) of dispensing capsules by young children.

Dissolution Method and Acceptance Criterion: For the routine QC testing of the Aliskiren Oral Pellets 37.5 mg for batch release and stability testing, the proposed dissolution method and acceptance criterion, shown in the table below, are acceptable.

USP Apparatus	Speed	Medium	Volume/Temp	Sampling Times	Acceptance Criterion
I (Basket)	100 RPM	0.01 M HCl	900 mL/37 ± 0.5°C	5, 10, 15, 30, 45 min	Q = (b) (4)% at 15 min

Bridging of Formulations: The clinical formulation used in the Phase 3 clinical trial is the same as the proposed commercial drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the same as the proposed commercial site. Therefore, bridging the commercial formulation to the clinical

formulation is not needed.

Effects of Swallowing Capsule-Containing Aliskiren Pellets: Aliskiren oral pellets are rapidly dissolving in acidic environment. However, there were marked decreases in dissolution with the dispensing HPMC capsule at acidic pH 2 (i.e., decreased to approximately 1/20 and 1/5 of drug release at 30 min and 60 min, respectively), compared to pellets only. The decreases in drug release from the capsule-containing pellets can be attributed, at least in part, to the cross-linking potential of the HPMC capsules. In addition, the in vitro dissolution was shown to positively correlate with the in vivo absorption or bioavailability. The formulation variants with slower dissolution of aliskiren resulted in marked decreases in drug exposure (Cmax and AUC0-inf) in humans. Based on the available data/information, it is reasonable to expect that swallowing the capsule-containing aliskiren pellets whole will yield significantly lower bioavailability of aliskiren in children. To mitigate the risk of swallowing the whole dispensing capsule, a clear labeling instruction with "do not swallow the capsules" under Dosage and Administration of the labeling is necessary.

Recommendation:

From a Biopharmaceutics perspective, NDA 210709 for Tekturna®(Aliskiren) Oral Pellets, 37.5 mg pellets in capsules, is recommended for **APPROVAL**.

List of Submissions being reviewed:

eCTD # (SDN #)	Received date	Document
0000 (1078)	6/5/2017	Original submission
0009 (1087)	8/31/2017	Quality/Response to information request

Highlight Key Outstanding Issues from Last Cycle: Not Applicable. This is the 1st review cycle.

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: *Not Applicable.*

No BCS designation request was submitted. Based on the physiochemical properties and bioavailability data, the Applicant reported Aliskiren as a BCS Class III drug with high solubility and low permeability.

Solubility: The drug substance aliskiren hemifumarate is a white to slightly yellowish crystalline powder with a molecular weight of 609.8 (free base- 551.8). The aqueous solubility of aliskiren hemifumarate at 23 °C is displayed in **Table 1**.

Table 1: Solubility of Aliskiren Drug Substance in Aqueous Media

Solvent	Temperature (°C)	Solubility
Water (b) (4)	23 °C	> 350 g/l
0.1N HCl	23 °C	> 350 g/l
Phosphate buffer USP, pH = 7.6	23 °C	> 350 g/l
Phthalate Buffer USP, pH = 4.5	23°C	> 350 g/l

Permeability: The absolute bioavailability of aliskiren in adults is reported approximately 2.6%.

Dissolution: At least (b) (4)% drug release in 15 minutes from the proposed aliskiren oral pellets using the proposed QC dissolution method is reported. Refer to the section "Dissolution Method and Acceptance Criterion" below.

Dissolution Method and Acceptance Criterion

Reviewer's Assessment: ***Adequate***

Proposed Dissolution Method and Acceptance Criterion: The dissolution method and dissolution acceptance criterion proposed by the Applicant for the proposed drug product are presented below.

USP Apparatus	Speed	Medium	Volume/Temp	Sampling Times	Acceptance Criterion
I (Basket)	100 RPM	0.01 M HCl	900 mL/37 ± 0.5°C	5, 10, 15, 30, 45 min	Q = (b) (4)% at 15 min

Dissolution Method Development:

(b) (4)

(b) (4)

(b) (4)

Discriminating Capability of the Dissolution Method:

The proposed dissolution method was capable of discriminating critical formulation changes with regards to the (b) (4) oral pellet cores (**Figure 2** and **Table 3**). The batches X052 0108 (variant B – (b) (4) and X392 1107 (variant C (b) (4) failed the proposed dissolution acceptance criterion of Q (b) (4) % at 15 minutes for the finished drug product.

Figure 2: Dissolution profile of three oral pellet variants

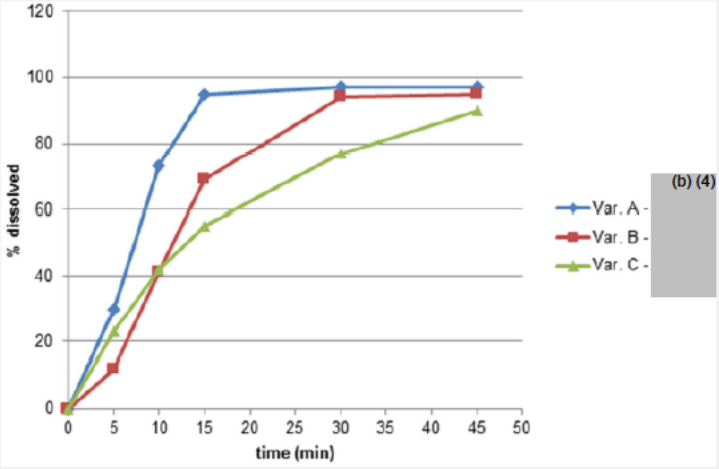


Table 3: Dissolution profile of three oral pellet variants, mean percentage dissolved (min, max, stddev), n = 12

Variant	Batch #	5 min	10 min	15 min	30 min	45 min
A – (b) (4)	X388 1107	30 (20, 32, 3.3)	73 (60, 75, 3.9)	95 (91, 96, 1.4)	97 (96, 98, 0.6)	97 (96, 98, 0.6)
B –	X052 0108	12 (11, 13, 0.4)	41 (36, 44, 2.0)	69 (63, 71, 2.0)	94 (93, 96, 0.8)	95 (95, 97, 0.6)
C -	X392 1107	23 (22, 24, 0.6)	42 (41, 43, 0.6)	55 (54, 55, 0.5)	77 (77, 78, 0.6)	90 (89, 91, 0.6)

(b) (4)

These three variants were further studied for the relative bioavailability comparison in humans (**Table 4**). Study CSPP100A2108A is an open-label, randomized, single-dose, multiple treatment periods, crossover study to determine the relative bioavailability of three SPP100 pediatric oral pellet variants relative to the 300 mg SPP100 Final Market Image (FMI) tablet. It is noted that, based on results presented in **Figure 2** and **Tables 3** and **4**, the decrease in in-vivo drug exposure or bioavailability (as reflected by Cmax and $AUC_{0\text{-inf}}$ values) appears to correspond to the decrease in in-vitro drug release rate.

Table 4: PK parameters of aliskiren following aliskiren single oral doses of 300 mg market tablet and pediatric oral pellets variants to healthy subjects (Study CSPP100A2108A)

Treatment	T_{max} (h) median (min, max)	C_{max} (ng/mL) mean±SD (CV%)	$AUC_{0\text{-inf}}$ (h•ng/mL) mean±SD (CV%)
(Ref) (N=29)	1.0 (0.3, 4.0)	215.2±137.8 (64.0)	1356.5±553.5 (40.8)
(Var A) (N=25)	0.5 (0.3, 4.0)	314.8±133.4 (42.4)	1678.7±763.1 (45.5)
(Var B) (N=20)	0.5 (0.5, 4.0)	231.5±114.2 (49.3)	1608.9±798.7 (49.6)
(Var C) (N=28)	1.5 (0.3, 6.0)	135.0±83.4 (61.8)	1139.8±504.1 (44.2)

The proposed QC dissolution method is expected to be lacking in discriminating power toward particle size of drug substance, small changes in formulation, and manufacturing process parameters such as hardness, due to the very high solubility of the drug substance across the physiologic pH range, small size of oral pellets, as well as the very rapid dissolution of the drug product in the proposed QC dissolution medium.

Validation of Dissolution Method

An HPLC assay method (with UV detection at 210 nm) was used to quantify the drug in the

dissolution samples. The Applicant reported that the HPLC method was validated with regard to specificity, linearity, accuracy, instrument repeatability, intermediate precision, filter validation, solution stability, and manual vs. automated sampling and robustness with respect to dissolution conditions (temperature (36.5-37.5°C) and basket speed (96-104 RPM)). Refer to the Drug Product Review, for the evaluation of the adequacy of the analytical method validation (including the HPLC method used for dissolution testing).

Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is "Q=(b) (4)% of labeled amount at(b) (4) min". Complete in vitro dissolution profile data for the pivotal clinical batches and registration stability batches were not deemed needed because no additional information will be gained by this information request since the drug product dissolves very rapid and complete.

Overall, the proposed dissolution method is fully validated and is considered adequate for quality control purposes.

Bridging of Formulations

Reviewer's Assessment: Adequate

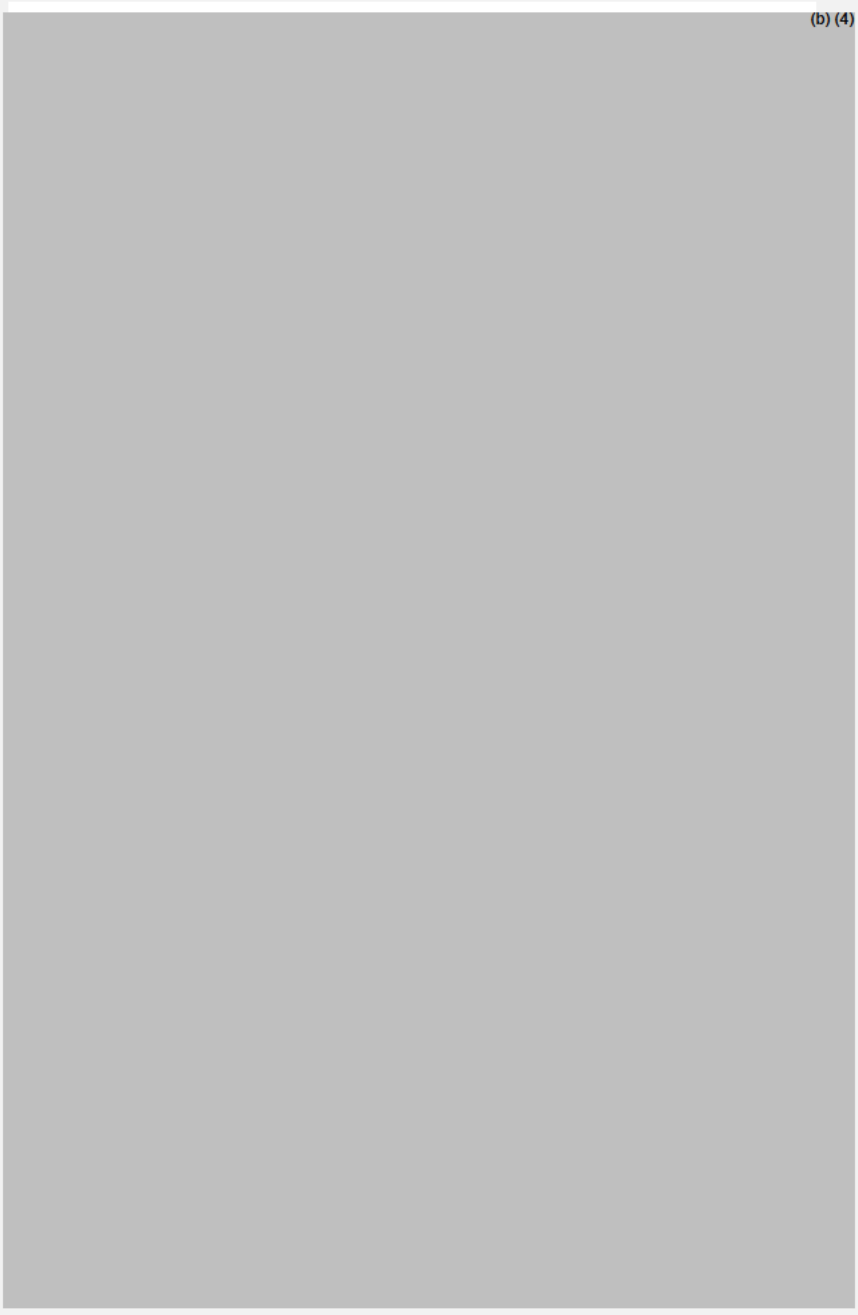
Both market formulation (MF) and final market image (FMI) formulation were used in Phase 3 clinical trial (Study A2365). The only difference between MF and FMI is the presence/absence of (b) (4) colloidal silicon dioxide (b) (4) **(Table 5)**.

Table 5: Composition (mg/pellet) of Aliskiren 3.125 mg oral pellets

Formulation	MF	FMI	Function
Formulation Number			(b) (4)
Components			
(b) (4)			
SPP100 hemifumarate			
Microcrystalline Cellulose			
Povidone			
Crospovidone			
(b) (4)			
Microcrystalline Cellulose			
Colloidal Silicon Dioxide			
Magnesium stearate			
(b) (4)			
Basic butylated methacrylate copolymer			
Magnesium stearate			
Dibutyl sebacate			
Sodium lauryl sulphate			
Colloidal Silicon Dioxide			
Oral pellet			

MF: Market Formulation; FMI: Final Market Image

The manufacturing site of the Phase 3 clinical batches is also the proposed commercial site. Therefore, bridging between the Phase 3 clinical and the proposed commercial drug products was not needed. It is acknowledged that the Applicant provided comparative in vitro dissolution profile to support the formulation bridging between MF and FMI, using USP basket method at 100 rpm in three pH media (0.01 M HCl, and Buffers pH 4.5 and pH 6.8) (**Figure 3**). The dissolution profiles generated demonstrate the similarity in in vitro drug release of these two formulations.



Potential impact on bioavailability of aliskiren associated with direct consumption (i.e. swallowing) of dispensing capsules by young children

Reviewer's Assessment: *The HPMC capsules should not be swallowed whole.*

During the review cycle, issue arose as to whether the dispensing capsules-containing Tekturna (Aliskiren) Oral Pellets) can be swallowed whole and what will be the risk consequence of dosing as such. Note that (1) the Applicant proposed in the labeling not to swallow the capsules-containing Tekturna Oral Pellets, and (2) dissolution data profiles supporting the NDA application were generated exclusively with Tekturna Oral Pellets alone. Given that, a Biopharmaceutics Information Request (dated 8/25/2017) was sent to the Applicant requesting for comparative dissolution profile data between capsules-containing Tekturna Oral Pellets and Tekturna Oral Pellets alone. Data submitted as part of the Applicant's Responses (dated 8/31/2017) showed much slower and incomplete dissolution of aliskiren from the HPMC capsule-containing pellets than from the pellets alone at acidic pH 2.0, i.e., approximately 1/20 and 1/5 of that from the pellets alone at 30 min and 60 min, respectively **(Figure 4)**. The differences in dissolution profile at pH 6.8 were smaller, though still significant. The decreases in drug release from the capsule-containing pellets can be attributed, at least in part, to the cross-linking potential of the HPMC capsules.

Aliskiren oral pellets are rapidly dissolving in acidic environment and the in vitro dissolution was shown to positively correlate with the in vivo absorption or bioavailability. (b) (4)

Since there are marked differences in drug dissolution profiles with and without the dispensing capsule at pH 2, it is reasonable to expect that swallowing the whole dispensing capsule filled with the pellets will result in significantly lower bioavailability of aliskiren. Furthermore, the much slower or delayed in-vitro drug release from the capsule-containing pellets at the same acidic pH 2, compared to variant-C formulation, could translate to further reduction in aliskiren bioavailability as a result of less available drug presented at its absorption sites (**Figures 2 and 4; Tables 6 and 7**).

Based on the above information and data, to mitigate the risk of swallowing the whole HPMC dispensing capsule, a clear labeling instruction with "do not swallow the capsules" under Dosage and Administration of the labeling is necessary. To possibly allow the swallowing the capsule whole without the similar concern, this Reviewer recommends that the Applicant consider developing hard gelatin capsules in place of HPMC capsules as the dispensing capsules.

Figure 4: Dissolution profiles of SPP100 37.5 mg with capsule (Batch: X236 1114) and pellets alone (batch X218KL), mean values (n=12)*

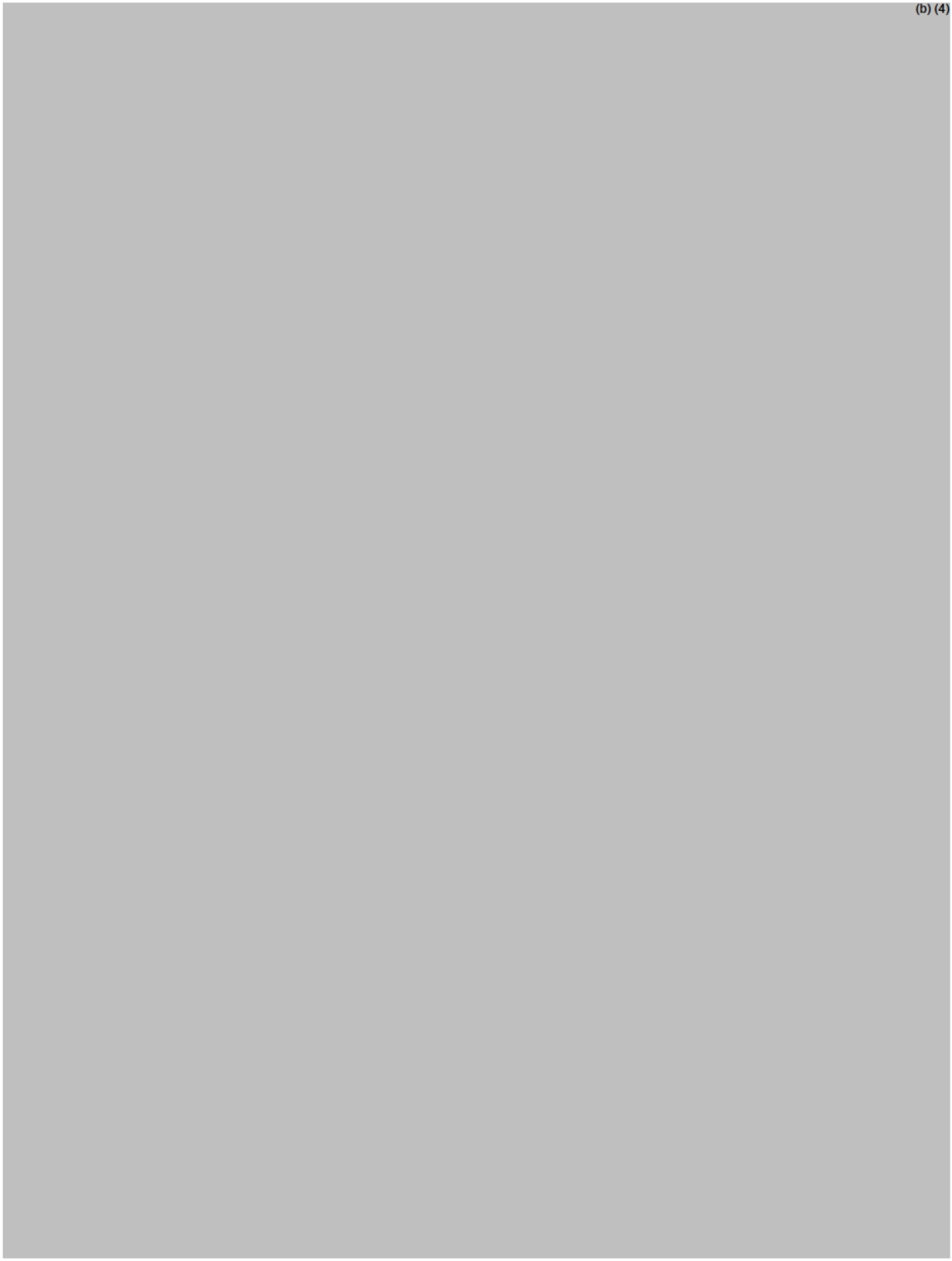


Table 6: Measured and calculated values for AUC0-inf based on dissolution data at (b) (4)

(b) (4)

[redacted]

Biowaiver Request

Reviewer's Assessment: *Not Applicable*

A biowaiver was not requested or required. The proposed to-be-marketed pediatric formulation was used in the Phase 3 clinical study. In addition, the Phase 1 comparative BA study (A2109) was reported to demonstrate the bioequivalence between aliskiren pediatric (b) (4) formulation (3.125 mg/(b) (4)) and the aliskiren market film-coated tablet formulation (300 mg/tablet); refer to the Clinical Pharmacology Review for the final

determination of the adequacy of bridging between the pediatric and adult formulations.

R Regional Information

Comparability Protocols

Reviewer's Assessment: *Adequate*

The following post-approval changes will be evaluated according to this protocol:

1. Replacement of Novartis Pharma Stein AG by the validation and launch site (b) (4) for the manufacture of pellet (b) (4), two processing operations used in the manufacture of Aliskiren 37.5 mg oral pellets in HPMC Capsules.
2. Potential changes (b) (4) parameters.
3. Change in batch size (down scaling) for (b) (4) operations at (b) (4)
4. Change in (b) (4)

Per the protocol, comparative dissolution profiles using the proposed dissolution method to demonstrate similarity of the drug product manufactured at the current sites under registration and at the proposed sites will be submitted in the transfer supplement in support of this change.

Overall Recommendation

From a Biopharmaceutics perspective, NDA 210709 for Tekturna®(Aliskiren) Oral Pellets, 37.5 mg pellets in capsules, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

10/11/2017
Qi Zhang, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

10/11/2017
Ta-Chen Wu, PhD
Division of Biopharmaceutics
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Qi Zhang

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Ta-Chen Wu

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Date: 10/11/2017 12:50:03PM
GUID: 508da6df000269e151ff37cd8f4e13a1

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: 210709	**Established/Proper Name:** Aliskiren
Applicant: Noden Pharma DAC	**Dosage Form:** Capsule for Oral Suspension
Submission Type: 505(b)(1)	**Strength(s):** 37.5 mg (net contents); 3.125 mg/pellet
Chemical Type: 3 – New Dosage Form	**Cross Referenced Applications:**

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	

B. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS

Noden Pharma submitted NDA 210709 to support marketing of a pediatric formulation for Tekturna (aliskiren) in response to a FDA pediatric written request. This product was initially submitted as a supplemental NDA but was later reclassified as a new NDA due to the new dosage form classification. The submission was granted priority review with a PDUFA date of November 15, 2017.

The pediatric product is formulated as oral pellets that are then encapsulated. The capsule is not intended for administration but is rather considered as a dispensing vehicle. The proposed administration instructions call for opening of the capsule and mixing of the pellets with either soft foods, liquid, or [redacted] (b) (4) followed by a sip of water.

Key product quality review issues include confirmation of appropriate dosage form selection and design, potential safety risks if patients swallow the capsules (Size 0), adequate labeling to ensure proper administration and reduce medication errors, adequacy of the proposed control strategies for both the individual pellets and the filled capsule, sufficient taste masking, compatibility of the pellets with soft foods and liquids, resuspendability of the pellets in the labeled administration vehicles, and different capsule sizes and blister lid foil used for registration stability versus commercialization. In addition, four product quality-related administrative issues that require consideration during the review include reconciliation of release and stability acceptance criteria, appropriate cross referencing to drug substance information, dosage form designation, and labeling of strength (i.e. pellets and/or capsule). The applicant proposes oral pellets as the dosage form, which is not a USP-recognized dosage form.

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			25.31 (b) and 25.15 (d)
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			Will ask for an confirmatory list of sites
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		Cross reference to either sister NDA or DMF needed
	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			
	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?			X	Defer to OCP for the review of BA/BE and PK data.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout	X			The proposed commercial pediatric formulation is the same as the clinical

C. FILING CONSIDERATIONS					
	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)*				formulation ("FMI") used in pivotal Phase III clinical studies. The clinical formulation ("MF") used in the pivotal BA/BE study and phase II study A2256 (b) (4) [redacted] Applicant provided the comparative dissolution profile data of the "FMI" vs "MF". The manufacturing site of the clinical batches is the proposed commercial site.
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.		X		A biowaiver is not requested nor required for this NDA. The Applicant performed the clinical studies for the proposed pediatric formulation. In addition, the Applicant reported that the pivotal clinical BA/BE study A2109 (comparative BA study) demonstrated the bioequivalence between aliskiren pediatric (b) (4) formulation (3.125 mg/ (b) (4)) and the aliskiren market film-coated tablet formulation (300 mg/tablet).
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			X	The proposed drug product is an immediate release dosage form for oral administration.
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?			X	The dosage form is immediate release.
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?			X	Aliskiren drug substance is reported as a BCS class III drug with high solubility and low permeability.
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 compliance with 21 CFR 610.9 and 601.2(a)?			X	

OFFICE OF PHARMACEUTICAL QUALITY

Initial Risk Assessment: NDA 210709 Tekturna (aliskiren) Capsules for Oral Suspension (tentative); 37.5 mg (net contents); Each pellet contains 3.125 mg of active ingredient.

Pediatric formulation for suspension in foods/liquids [redacted] (b) (4) Not a high risk drug; Moderately stable; High drug load

Product Property/Impact of Change/CQAs	Factors Affecting CQA	O	S	D	FMEA RPN	Comment(s)
Assay	Formulation Container closure Raw materials Process/Scale/Equipment Site	3	2	Release: 1 Stability: 3	Release: 6 Stability: 18	Assay of the pellets and of the filled capsule should be assessed
Solid state	Formulation Container closure Raw materials Process/Scale/Equipment Site	4	2	4	32	Highly soluble with low permeability; [redacted] (b) (4) (b) (4)
Content Uniformity	Formulation Container closure Raw materials Process/Scale/Equipment Site	2	2	4	16	Content uniformity of the pellets and of the filled capsule should be assessed
Microbial Limits	Formulation Container closure Raw materials Process/Scale/Equipment Site	1	2	3	6	Hygroscopic drug substance in HPMC capsules
Pellet Size	Formulation Raw materials Process/Scale/Equipment Site	2	3	2	12	Drug substance batches with different flow properties may impact pellet size and assay
Dissolution	Formulation Container closure Raw materials Process/Scale/Equipment Site	3	2	2	12	
Palatability	Formulation Raw materials Process/Scale/Equipment Site	3	3	5	45	Insufficient tastemasking will impact patient compliance
Compatibility with vehicles	Formulation Raw materials	3	3	4	36	Inability to detect incompatibility at point of use increases the risk; likelihood of administration using non-labeled foods/liquids is moderate

OFFICE OF PHARMACEUTICAL QUALITY

Product Property/Impact of Change/CQAs	Factors Affecting CQA	O	S	D	FMEA RPN	Comment(s)
Resuspendability	Formulation Container closure Raw materials Process/Scale/Equipment Site	2	3	Release: 1 Stability: 3	Release: 6 Stability: 18	
Capsule Dimensions/Size	Formulation Raw materials	2	3	1	6	Need to evaluate Size 0 capsule dimensions against potential for choking based on indicated patient population(s); high risk populations include young children and patients with difficulty swallowing
Disintegration of pellets	Formulation Container closure Raw materials Process/Scale/Equipment Site	3	2	Release: 1 Stability: 3	Release: 6 Stability: 18	
Moisture content	Formulation Container closure Raw materials Process/Scale/Equipment Site	3	3	Release: 1 Stability: 3	Release: 9 Stability: 27	Hygroscopic drug substance in HPMC capsules; (b) (4) content may lead to changes in drug product attributes as well as inability to dispense the pellets from the capsule shell as labeled

RPN < 25 is considered low risk; RPN 25 – 60 is considered moderate risk; RPN > 60 is considered high risk