

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210709Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	210709	SDN	0000
Applicant	Noden Pharma DAC	Submission Date	5/15/2017
Generic Name	Aliskiren (IND 62976, NDA 21,985)	Brand Name	Tekturna
Drug Class	Direct renin inhibitor		
Indication	Hypertension		
Dosage Regimen	Pediatrics: ≥20 kg to <50 kg: Starting dose <span style="background-color: #cccccc;">(b) (4)</span> 75 mg once daily when greater reduction of blood pressure is needed. Maximum dose is 150 mg. ≥50 kg: Starting dose 150 mg, maximum dose 300 mg once daily Adults: starting dose 150 mg (routine pattern with meals), maximum dose 300 mg once daily		
Dosage Form	SPP100 37.5 mg Oral pellets (made of 12 x SPP100 3.125 mg oral pellets) in one HPMC capsule	Route of Administration	Per os
Review Classification	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority (based on Written Request) <input type="checkbox"/> Expedited		
Filing Date	7/14/2017	74-Day Letter Date	7/28/2017
Review Due Date	9/15/2017	PDUFA Goal Date	11/15/2017
OCP Division	DCPI	OND Division	Cardiovascular and renal products
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Martina Sahre, PhD	Sudharshan Hariharan, PhD	
Pharmacometrics	-	-	
Genomics	-	-	

### Application Fileability

Is the Clinical Pharmacology section of the application fileable?

Yes       No

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

Yes       No: A comment to submit the full study report and appendices for study 2365 to this NDA was sent and the applicant fulfilled this request prior to the filing date. An IR was sent to the applicant to clarify the formulations used in the submitted studies. The sponsor responded 6/19/2017, and the response was acceptable for filing purposes.

Is there a need for clinical trial(s) inspection?

Yes       No

### Clinical Pharmacology Package

Tabular Listing of All Human Studies     Yes     No     
 Clinical Pharmacology Summary             Yes     No  
 Bioanalytical and Analytical Methods     Yes     No     
 Labeling     Yes     No

### Clinical Pharmacology Studies

Study Type	Count	Comment(s)
<b>In Vitro Studies</b>		
<input type="checkbox"/> Metabolism Characterization		
<input type="checkbox"/> Transporter Characterization		
<input type="checkbox"/> Distribution		

<input type="checkbox"/> Drug-Drug Interaction			
<b>In Vivo Studies</b>			
<b>Biopharmaceutics</b>			
<input type="checkbox"/> Absolute Bioavailability			
<input checked="" type="checkbox"/> Relative Bioavailability	2	Study A2109 – 300 mg mini-tablets vs 300 mg tablet (marketed form) Study 2108 – Comparison of multiple mini-tablet formulations, report only	
<input type="checkbox"/> Bioequivalence			
<input checked="" type="checkbox"/> Food Effect	(1)	See Study A2109 – includes food effect arm	
<input type="checkbox"/> Other			
<b>Human Pharmacokinetics</b>			
Healthy Subjects	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
<b>Intrinsic Factors</b>			
<input type="checkbox"/> Race			
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input type="checkbox"/> Renal Impairment			
<input type="checkbox"/> Genetics			
<b>Extrinsic Factors</b>			
<input type="checkbox"/> Effects on Primary Drug			
<input type="checkbox"/> Effects of Primary Drug			
<b>Pharmacodynamics</b>			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<b>Pharmacokinetics/Pharmacodynamics</b>			
<input type="checkbox"/> Healthy Subjects			
<input checked="" type="checkbox"/> Patients	3	Studies A2256 (open-label), A2365 (randomized), A2365E1 (safety extension for study A2365)	
<input type="checkbox"/> QT			
<b>Pharmacometrics</b>			
<input type="checkbox"/> Population Pharmacokinetics			
<input type="checkbox"/> Exposure-Efficacy			
<input type="checkbox"/> Exposure-Safety			
<b>Total Number of Studies</b>		<b>In Vitro</b>	<b>In Vivo</b>
<b>Total Number of Studies to be Reviewed</b>			5 4

<b>Criteria for Refusal to File (RTF)</b>		
<b>RTF Parameter</b>	<b>Assessment</b>	<b>Comments</b>
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	This is a response to a pediatric WR, metabolism and DDI information is known from the originator submission.
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Studies assessing PK/PD in pediatrics were submitted
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Not a 505(b)(2).
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Only summary-clin-pharm
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
<b>Complete Application</b> 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist</b>		
<b>Data</b>		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
<b>Studies and Analysis</b>		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
<b>General</b>		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUDHARSHAN HARIHARAN

07/13/2017

(On behalf of primary reviewer Dr. Martina Sahre)