Cross-Discipline Team Leader Review

Date	November 13, 2017
From	Aliza Thompson, MD
Subject	Cross-Discipline Team Leader Review
NDA#	210709
Applicant	Noden Pharma
Date of Submission	May 15, 2017
PDUFA Goal Date	November 15, 2017
Proprietary Name / Established (USAN) names	Tekturna (aliskiren)
Dosage forms / Strength	Oral Pellet in Capsule / 37.5 mg
Proposed Indication(s)	Treatment of hypertension in pediatric patients age 6 to 17 years
Recommended:	Approval for the treatment of hypertension in children 6 years of age and older, to lower blood pressure

This secondary review is based on the following reviews:

Material Reviewed/Consulted	
Quality Assessment (10/11 and 11/8/17)	Rao Kambhampati, Yahong Wang, Peter Guerrieri, Wayne Seifert, Ruth Moore, Qi Zhang, Ta Chen Wu, Grafton Adams, Wendy Wilson-Lee (Application Technical Lead)
Pharmacology Toxicology Review (9/14/17)	G. Jagadeesh, Thomas Papoian
Clinical and Clinical Pharmacology Review (10/12/17)	Christine Garnett, Martina Sahre, Sudharshan Hariharan, Aliza Thompson
Statistical Review (9/22/17)	Fanhui Kong, Hsien Ming Hung
Division of Medication Error Prevention and Analysis Reviews (10/10 and 10/23/17)	Rhiannon Leutner, Alice Tu
Office of Prescription Drug Promotion Review (OPDP) (10/17/17)	Zarna Patel, James Dvorsky
Division of Medical Policy Programs and OPDP Patient Labeling Review (10/18/17)	LaShawn Griffiths, Barbara Fuller, Susan Redwood, Zarna Patel

1. Introduction

On May 15, 2017, Noden submitted NDA 210709 for Tekturna (aliskiren) Oral Pellet in Capsule 37.5 mg for the treatment of hypertension in pediatric patients. The studies upon which the application is based were conducted to address a postmarketing commitment under the Pediatric Research Equity Act and in response to a Written Request under the Best Pharmaceuticals for Children's Act (BPCA).

2. Background

Tekturna® (aliskiren) is an orally active, nonpeptide, renin inhibitor. Tekturna® (aliskiren) 150- and 300-mg tablets were approved in the U.S. in November 2007 for the treatment of hypertension in adults (NDA 021985). Tekturna's approval letter contained a postmarketing study commitment to conduct deferred pediatric studies required under PREA for the treatment of hypertension in pediatric patients ages 6 to 16 years. According to the approval letter, a partial waiver was granted for pediatric studies in patients ages 0 to 6 years "due to too few patients < 6 years to study".

The current NDA contains data intended to support (1) approval of aliskiren oral pellets, a new formulation of aliskiren developed for use in pediatric patients, and (2) approval of aliskiren for the treatment of hypertension in pediatric patients six years of age and older. As previously noted, the application is intended to address commitments under PREA for NDA 021985 and fulfill the requirements of a Written Request.[1] For further information on the regulatory history, see Dr. Garnett's review.

As noted by Dr. Garnett, at this time, there are a handful of drugs approved for the treatment of hypertension in the proposed age group, including other renin-angiotensin-aldosterone system antagonists such as enalapril and valsartan.

3. CMC

OPQ recommends approval of the application from a quality perspective. As discussed in the OPQ and DMEPA reviews, a key issue from a product quality and safety perspective was the use of a capsule as a dispensing aid (i.e., a capsule that could not be swallowed). See "Labeling" for further discussion of this issue.

- *Drug substance:* The active ingredient, aliskiren hemifumarate, is the same as in the approved tablet formulation of aliskiren. It is a white to slightly yellow, crystalline powder that is freely soluble in water.
- *Drug Product:* The drug product consists of pellets for oral administration. Each pellet contains 3.125 mg of aliskiren, equivalent to 3.45 mg of aliskiren hemifumarate. Pellet excipients include basic butylated methacrylate copolymer, colloidal silicon dioxide, crospovidone, dibutyl sebacate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulphate.

  The pellets are supplied in a capsule, each containing 12 pellets. Each 37.5-mg dose of oral pellets is equivalent to 41.4 mg of aliskiren hemifumarate. The capsule is transparent and is imprinted with "NVR 12" on one side and with red arrows pointing to the top and bottom of the capsule on the other. The capsules are packaged in child-resistant unit-dose blister packages containing 8 strips of 6 capsules.
- *Expiration Date and Storage Conditions:* According to the Quality Assessment, the available stability data support the proposed shelf-life of 36 months in the proposed commercial packaging. The product should be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F) and protected from moisture.

[1] Ownership of Tekturna® (aliskiren; NDA 021985) was transferred from Novartis Pharmaceuticals Corporation to Noden Pharma DAC on October 5, 2016. The IND under which the pediatric studies were conducted remains with Novartis.

- *Facilities review/inspection:* Proposed commercial manufacturing, testing, and packaging sites have acceptable compliance status.
- *Other:* The applicant submitted a comparability protocol supporting a post-approval change in drug product manufacturing site for Tekturna Oral Pellets. Per the OPQ review, the comparability protocol is acceptable.

4. Nonclinical Pharmacology/Toxicology

The application can be approved from a pharmacology-toxicology perspective. Dr. Jagadeesh's review focuses on the findings in juvenile toxicology studies in rats and an in vitro study on the ontogeny of multidrug-resistant protein 1 (MDR1) in human liver and intestine. The juvenile toxicity studies in rats showed increased systemic exposure to aliskiren 85- to 385-fold in 14-day and 8-day old rats respectively, compared with adult rats. Studies of the ontogeny of MDR1 (also known as P-glycoprotein) and organic anion transporting polypeptide 2 mRNA expression in rats suggested that the increased exposure was likely explained by the time course for maturation of drug transporters involved in aliskiren absorption and disposition.

In his review, Dr. Jagadeesh notes that the finding in these studies raise considerable concern for safety in neonates and infants and recommends against administration of aliskiren to children younger than 2 years of age, citing the risk of increased exposure resulting from lack of maturation of the P-glycoprotein drug transporter system and drug metabolizing enzymes. Based on these findings, I agree that use of aliskiren in pediatric patients less than 2 years of age should be contraindicated.

In follow-up discussions about safety in patients 2 to 6 years of age, Drs. Jagadeesh and Papoian emphasized that the concern for safety is greatest in children less than 2 years of age. However, given the available data, they believe it would also be prudent to avoid use in patients 2 to 6 years of age. In support of this position, they cited the severity of the findings in animals, lack of information on the cause(s) of mortality in the animals, and potential risk of increased exposure in this age group (tied to the uncertainty about the time course for maturation of transporters that might affect exposure in humans). Given the available information, I agree that labeling should indicate that use is not recommended in patients 2 to 6 years of age. Of note, this approach (i.e., to include a contraindication against use in children < 2 years of age and recommend against use in the 2 to 6 year age group) is consistent with the approach proposed by the applicant.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology (OCP) recommends approval of the application from a clinical pharmacology perspective. Dr. Sahre's review focuses on the results of Study A2109, a relative bioavailability study that also assessed food effects and Study A2256, a pharmacokinetic and pharmacodynamic study of aliskiren in children 6 to 17 years of age. The review also contains analyses to support dosing recommendations.

Relative bioavailability and food effects: As discussed in Dr. Sahre's review, Study A2109 compared the 300-mg aliskiren mini-tablets to 300 mg-aliskiren tablets (i.e., the marketed formulation) administered after an overnight fast. The study demonstrated that the 300-mg aliskiren mini-tablets are bioequivalent to the marketed 300-mg tablet (i.e., the point estimates for

Cmax and AUC were similar and the 90% confidence intervals for Cmax and AUC fell within the 80 to 125% limits for establishing bioequivalence). The study also showed that administration of the mini-tablets with a high fat, high calorie breakfast results in a marked reduction in AUC and Cmax (an 85% and 95% reduction, respectively), which is similar to the reduction seen with aliskiren tablets.

PK and PD in Study A2256: Study A2256 evaluated the pharmacokinetics and pharmacodynamics (plasma renin activity and blood pressure) of aliskiren (3.125 mg oral pellets) in 39 hypertensive patients 6 to 17 years of age following a single dose and daily administration for 8 days. The doses that were studied (2 mg/kg and 6 mg/kg) were based on weight-based matching to adult doses, and corresponded to the "low" and "high" doses approved for use in adults (150 and 300 mg, respectively).

Analyses of the trial data showed the following:

- PK: Similar pharmacokinetics in pediatric patients 6 years of age and older and adults. Whereas age and gender did not appear to have a significant effect on aliskiren systemic exposure, exposure decreased with increase in body weight.
- PD: At both doses, reductions from baseline in plasma renin activity (76% and 87% for the low and high dose respectively) were within the range observed in adults (50-80%). There did not appear to be an obvious dose-response relationship for blood pressure—a finding that was attributed to the small sample size.

Dosing recommendations: OCP is recommending a starting dose of 37.5 or 75 mg once daily in patients 6 to 17 years of age who weigh between 20 and 50 kg and a maximum dose of 150 once daily in this population. For patients in this age range who weigh greater than 50 kg, the recommended dosage is the same as in adults (i.e., 150 mg once daily, increased to 300 mg as needed). These dosing recommendations are based on the data from the 8-week efficacy and safety study in pediatric patients, a 52-week extension study, and population PK/PD modelling of the blood pressure lowering effect. As shown in Figure 17 of the Clinical Pharmacology Review, the maximum recommended dose in pediatric patients provides trough concentrations reasonably similar to those seen at the maximum approved dose in adults. Achieving higher concentrations does not appear to result in a clinically relevant increase in blood pressure reduction.

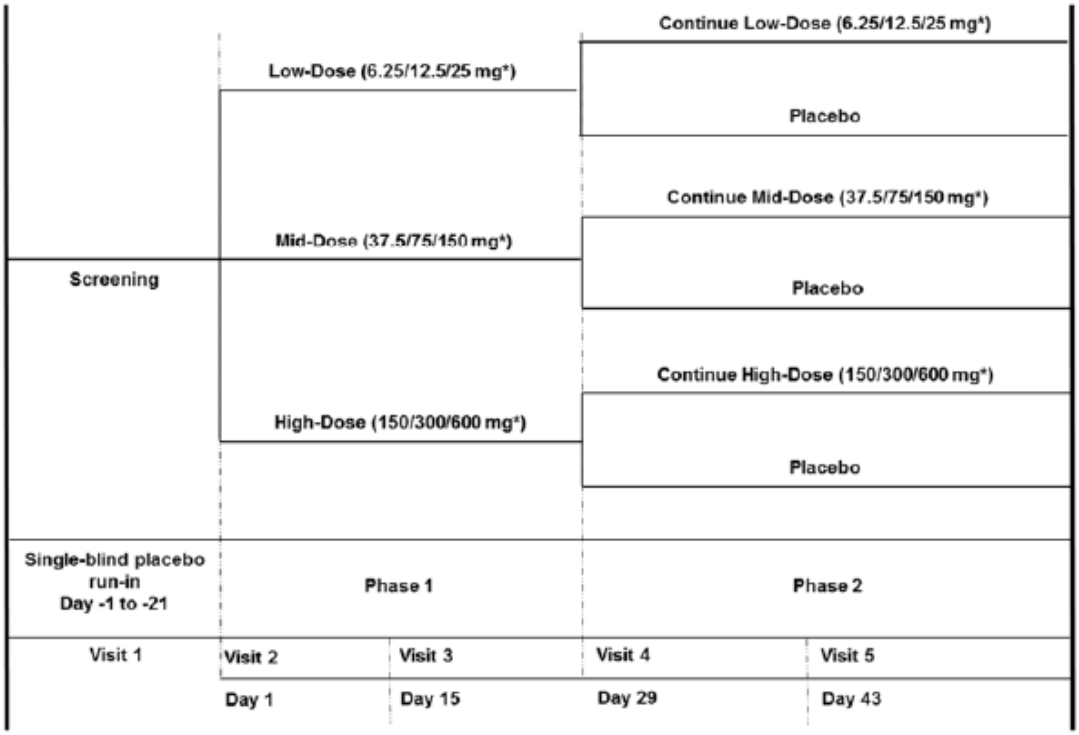
6. Clinical/Statistical- Efficacy

In support of aliskren's efficacy, the applicant submitted the results of an 8-week randomized, double-blind trial in hypertensive patients 6 to 17 years of age and a 52-week extension trial providing data on the efficacy of aliskiren relative to enalapril, which is approved for the treatment of hypertension in pediatric patients.

Study A2365

Study Design

As shown in the figure below, Study A2365 included a 4-week randomized, double-blind, dose-response phase and a randomized double-blind placebo-controlled withdrawal phase of up to 4 weeks. In the 4-week, dose-response phase (Phase 1), subjects were randomized to weight-based low, mid and high dosing groups. At the end of this period, subjects entered a 4-week randomized-withdrawal phase (Phase 2) in which they were randomized to continue the same dose of aliskiren or take placebo.



*Patients were stratified by weight; patients weighing ≥ 20kg to < 50 kg received the lower dose indicated in each treatment arm, patients weighing ≥ 50 kg to < 80 kg received the mid dose indicated in each treatment arm, patients weighing ≥ 80 kg to ≤ 150 kg received the high dose indicated in each treatment arm.

Figure 1: Design of Study A2365
Source: Clinical Study Report for Study A2365, Figure 9-1

The doses for the trial (see table below) were based on data in adults and modeling and simulation of interim data from Study A2256. Dose selection assumed reasonably similar responses in pediatric patients and adults. Because of possible differences in response in pediatric patients and adults, a wider range of doses than approved in adults was used. Based on modeling and simulation, the mean reduction in SBP (absolute; not adjusted for placebo) in the low, mid and dose groups was expected to be 7.3 mmHg, 10.2 mmHg and 13.6 mmHg, respectively. Relative to placebo, the mid dose was predicted to produce a 3-mmHg reduction in SBP.

Table 1: Dosing Groups in Phase 1

	Dosing Groups		
Weight Category	**Low Dose**	**Mid Dose**	**High Dose**
≥20 to <50 kg	6.25 mg o.d (0.13 – 0.31 mg/kg)	37.5 mg o.d (0.75 – 1.88 mg/kg)	150 mg o.d (3.0 – 7.5 mg/kg)
≥50 to <80 kg	12.5 mg o.d (0.16 – 0.25 mg/kg)	75 mg o.d (0.94 – 1.5 mg/kg)	300 mg o.d (3.75 – 6.0 mg/kg)
≥ 80 to ≤ 150 kg	25 mg o.d (0.17 – 0.31 mg/kg)	150 mg o.d (1.0 – 1.88 mg/kg)	600 mg o.d (4.0 – 7.5 mg/kg)

Source: Clinical Study Report for Study A2365, Table 9-1

The prespecified primary endpoint in Phase 1 was the change in mean sitting SBP (msSBP) from baseline to the end of 4-week period, as measured by office blood pressure. The prespecified primary endpoint in Phase 2 was the change in msSBP from end of Phase 1 to the end of Phase 2, as measured by office blood pressure. According to the SAP, the primary dose-response relationship was to be evaluated by testing the slope of the dose-response curve for the change from baseline in msSBP at the end of Phase 1. The primary efficacy analysis of Phase 2 was to compare the changes in msSBP from the end of Phase 1 to the end of Phase 2 in the pooled aliskiren mid/high dose group and the corresponding placebo groups.

As discussed, in the Statistical Review the power calculation for each phase of the trial assumed a treatment difference in mean sitting SBP of 5.5 mmHg (i.e., a 5.5 mmHg reduction in SBP from low dose to high dose in Phase 1 and a 5.5 mmHg treatment difference from end of Phase 1 to end of Phase 2). The power calculation for Phase 2 was somewhat optimistic given the predicted treatment effect of the mid-dose. As noted in the Statistical Review, it was also inconsistent with the Written Request which stated that the study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary endpoint and that to satisfy the Written Request, a clinically meaningful treatment benefit was considered to be a 3-mmHg effect. However as also noted in the Statistical Review, according to the sponsor's calculation, 907 subjects would need to be randomized to satisfy such a requirement.

Study Results:

According to the Clinical and Statistical Reviews:

- The trial appeared to be adequately conducted. Of the 268 subjects randomized in Phase 1, 260 subjects (97%) completed Phase 1 and 255 subjects (98%) completed Phase 2. Although protocol violations were reported in a significant proportion of the study population, most of these violations were minor in nature.
- Demographic characteristics were, as a whole, well-matched across the arms and were reasonably representative of the target population. Approximately 82% of subjects had primary hypertension and 59% had a BMI $\geq 95^{th}$ percentile. Mean age was 11.8 years, with a similar proportion of subjects in the 6 to 11 and 12 to 17 age groups. Eleven percent of subjects were Black and 74% were Caucasian. Around 20% of subjects had an estimated GFR between 60 and 90 mL/min/1.73m^2; few subjects (< 2%) had an estimated GFR < 60 mL/min/1.73m^2.

As discussed in the Statistical Review, the first phase of the trial met its primary endpoint. The slope estimate (-0.17) for the dose-response for the change from baseline to the end of Phase 1 in msSBP was statistically different from zero ($p<0.001$), indicating a dose-response relationship. The LSM change from baseline in the low, mid and high dose groups was -4.5, -6.0 and -8.0

mmHg respectively and the difference in LS mean (-3.5 mmHg) between the high and low dose groups was statistically significant (p< 0001). In contrast, the primary efficacy endpoint was not met in the randomized withdrawal phase of the trial. The LSM change in msSBP from the end of Phase 1 to the end of Phase 2 in the pooled aliskiren mid/high doses was -2.3 mmHg compared to -0.6 mmHg in the placebo subjects pooled from the corresponding arms (p= 0.11).

Despite this finding, both the Clinical and Statistical reviewers believe that the submitted findings provide evidence of effectiveness, albeit, for different reasons.

In her Clinical Review, Dr. Garnett points to other findings in the randomized withdrawal period that she believes provide support for efficacy. In a section that addresses her conclusions on effectiveness, she notes that: "Additional analyses of the Phase 2 data supported the efficacy of the high dose group (150/300/600mg). Specifically, the LSM change was -2.8 mmHg for aliskiren compared to -0.1 mmHg for placebo (p =0.06). At the end of Phase 2, dose-response for msSBP and msDBP were maintained (p <0.01). Furthermore, a dose-response was also observed (p=0.009) for the percentage of patients receiving a positive treatment response in msSBP (defined as an msSBP < 95th percentile (for age, gender and height) or a 7 mmHg decrease in msSBP from the baseline)."

In his Statistical Review, Dr. Kong takes a different approach, focusing instead on language in the protocol and SAP on the role of the randomized withdrawal period in evaluating efficacy. Dr. Kong notes that "According to the protocol and SAP, if the slope is statistically significant at the two-sided significance level of 0.05, then a difference among the doses is identified. Only if the slope test fails to reveal significant differences among the aliskiren doses in Phase 1, the analyses performed in Phase 2 would be used to further identify whether there is an effect on BP due to placebo wash-out. No alpha adjustment is needed for testing these two hypotheses. So according to the predefined analysis procedure, the study provides statistical evidence supporting the effectiveness of aliskiren in the treatment of hypertension in pediatric patients."

Reviewer's comments: As previously noted, the trial was initially designed to detect a 5.5-mmHg treatment effect in the randomized withdrawal phase. Hence, it seems likely that the randomized phase of the trial was underpowered to detect the more modest effect of the pooled mid and high dose groups.

Study A2365E1

The application also contains the results of a multicenter, double-blind, randomized, 52-week extension study evaluating the long-term safety, tolerability and efficacy of aliskiren compared to enalapril in hypertensive patients 6-17 years of age. In this study, 208 subjects from Study A2365 were randomized in a 1:1 ratio (irrespective of whether they were on placebo or aliskiren at the end of the randomized phase of Study A2365) to receive either aliskiren or enalapril for 52 weeks. This extension study included the same three dose levels based on weight with optional dose up-titrations during the study to control blood pressure.

As shown in Figure 12 of the Clinical Review, reductions in blood pressure from baseline to week 52 were similar in patients receiving aliskiren and enalapril (7.6/3.9 mmHg and 7.9/4.9 mmHg, respectively).

7. Safety

A total of 268 subjects were randomized into Study A2365. In her safety analyses, Dr. Garnett focused on the 208 subjects who were treated for up to 52 weeks in Study A2365E1, the double-blind, randomized extension study of Study A2365.

Based on the experience in adults, adverse events of special interest included anaphylactic reactions and head and neck angioedema, impaired renal function, hyperkalemia and hypotension. Dr. Garnett's analyses of adverse event and laboratory data did not indicate that these toxicities occurred in a more severe form or at a marked increase in rate in pediatric patients as compared to adults. Analyses of adverse event and laboratory data also did not reveal any new safety signals in pediatric patients.

The applicant's submission also included a discussion of the postmarketing safety experience in children 6 to 17 years of age. Cases were identified via a search of the Novartis Argus Safety database. At the time the Clinical Review was finalized, the applicant had not yet submitted narratives for the serious cases; narratives for 14 cases were subsequently provided.

In brief, the submitted cases appear to include spontaneous reports as well as reports of adverse events in subjects who had participated in clinical trials. In a number of the cases, it is not clear aliskiren played a role in the reported event(s) (e.g., a suicide attempt in a patient with a history of depression; a hospitalization for influenza; an episode of appendicitis). It is likely, however, that aliskiren contributed to other reported events, including two cases of hyperkalemia and a case of lip swelling (without respiratory compromise) and urticarial rash. In sum, the submitted narratives do not raise any new or additional safety concerns.

8. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug in the proposed population; hence, no Advisory Committee Meeting was held.

9. Pediatrics

See discussions in other sections of the review.

10. Other Relevant Regulatory Issues

Pediatric Exclusivity: Pediatric Exclusivity has been granted, effective October 3, 2017. As noted during the meeting with the Pediatric Exclusivity Board and in the Statistical Review, the Written Request stated that the study must be powered to detect a 3-mmHg effect on blood pressure. This provision was put in place to ensure that a negative study was interpretable. Because the 8-week study demonstrated a blood pressure lowering effect, the study can be viewed as interpretable. Hence, the Division believes that the submission fairly responds to this aspect and other aspects of the Written Request.

Inspections: Clinical inspections were not conducted. Review of financial disclosure information did not raise concern and study findings were not driven by a single site.

11. Labeling

At this time, agreement has been reached on labeling, including the prescriber information, patient label, IFU, cartoon labels, and container labels.

Key labeling issues
As discussed in the OPQ and DMEPA Reviews, a key issue from a product quality and safety perspective was the proposed use of a capsule as a dispensing aid for the pellets. Specifically, the applicant's proposed labeling included instructions to open the capsule and mix the contents with specified dosing vehicles or (b) (4). Proposed labeling also stated that the capsule should not be swallowed whole. (b) (4)

Early in the review, DMEPA voiced concern that the proposed design could lead to administration errors (i.e., patients might swallow the capsule since many medications are administered as capsules that are intended to be swallowed). In addition to this issue, OPQ noted that the proposed use of the capsule did not appear to be aligned with USP dosage form recommendations." Per the OPQ Review, "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."

The team considered potential risks associated with inadvertently swallowing the capsule, including choking hazard and decreased therapeutic response (because of delayed capsule dissolution resulting in reduced bioavailability). As relates to these risks,

- There were no protocol violations, treatment discontinuations or adverse events related to the dosage form or administration in the clinical trials.
- The capsule size (as well as larger sizes) has been used by other drug products labeled for use in patients 6 years of age and older
- Decreased therapeutic efficacy would likely be detected and, in the short term, would be unlikely to result in harm.

As discussed in the OPQ Review, other packaging options were also considered, but posed challenges.

Given these considerations as well as others[2], the review team concluded that labeling should indicate that the capsule should not be swallowing whole. To mitigate the risk of administration errors, labeling will include prominent statements about appropriate administration in the prescribing information and patient information and on the container and carton labels.

Other
The proposed proprietary name, Tekturna, has been deemed acceptable. Tekturna® (aliskiren) oral pellets will share a common label with Tekturna® (aliskiren) tablets, for oral use.

[2] See OPQ and DMEPA Reviews for further discussion.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval for the treatment of hypertension in children 6 years of age and older, to lower blood pressure.

Risk Benefit Assessment
Tekturna® (aliskiren) is an orally active, nonpeptide, renin inhibitor. Tekturna® (aliskiren) tablets, for oral use are approved in the U.S. for the treatment of hypertension in adults. In the current NDA, the applicant seeks approval of aliskiren oral pellets for the treatment of hypertension in pediatric patients six years of age and older. The submitted data indicate that aliskiren is effective in lowering blood pressure in the proposed pediatric population; these data also support safety and provide adequate instructions for use. As in adults, potential risks in pediatric patients include angioedema, worsening renal function, hyperkalemia, and hypotension. These risks can be mitigated with appropriate labeling and monitoring.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None.

Recommendation for other Postmarketing Requirements and Commitments
None.

Recommended Comments to Applicant
None at this time.

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/s/

ALIZA M THOMPSON
11/13/2017

NORMAN L STOCKBRIDGE
11/14/2017
I concur.