

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**209964Orig1s000**

**NON-CLINICAL REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 209964  
Supporting document/s: S0014/eCTD 0012  
Applicant's letter date: 10/25/2018  
CDER stamp date: 10/25/2018  
Product: Corlanor® (Ivabradine)  
Indication: Heart failure in pediatric patients with dilated  
cardiomyopathy  
Applicant: Amgen  
Review Division: DCRP  
Reviewer: John Koerner, Ph.D.,  
Supervisor/Team Leader: Jean Wu, M.D., Ph.D.  
Division Director: Norman Stockbridge, M.D., Ph.D.  
Project Manager: Alexis T. Childers, RAC

Background and Evaluation

A juvenile toxicity study in rats was reviewed previously under NDA 206143 by Jean Wu, MD., Ph.D. (review date 11/25/2014). This data was summarized in the attached labeling review. No new pharmacology/toxicology data was provided in this NDA.

See attached labeling review.

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**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

**Labeling Review**

Juvenile Toxicity Study in Rats and Changes to the Approved Label

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Project Manager: Alexis T. Childers, RAC

## Background

A juvenile toxicity study in rats was reviewed previously under NDA 206143 by Jean Wu, MD., Ph.D. (review date 11/25/2014). This review is summarized below.

Ivabradine was administered orally by gavage to juvenile rats at daily doses of 0, 7.5, 15 and 30 mg/kg from postnatal day (PND) 7 to at least PND 77, followed by a 3-week drug-free recovery period to determine reversibility of any test article related effects.

Observations included neurobehavioral development, motor activity, learning and memory, sexual maturation, estrous cycling, reproductive capacity (fertility), and reproductive performance.

There was no effect on the postnatal (pre-weaning) development and reproductive performance (post-weaning development) at doses up to 30 mg/kg/day.

Key drug-related findings are as follows.

- Significantly decreased white blood cell count related to decreased lymphocyte and large unstained cells count at the end of the treatment period was observed at 30 mg/kg/day with partial recovery at the end of the 3-week recovery period.
- Dose-dependent significant decrease in heart rate for all treated animals is considered an expected pharmacologic effect.
- Increased heart weight of the females given 30 mg/kg/day were observed without correlated histopathologic changes.
- Cardiac histopathology findings were observed, consistent with the those observed in adult rat toxicity studies.
  - Slightly increased incidence of minimal to slight interstitial mononuclear cell aggregates (most in minimal severity) in the heart of males treated at 15 or 30 mg/kg/day,
  - marginally increased incidence of minimal degenerative cardiomyocytes in all treated male groups without dose-dependency.

The NOAEL was identified as 7.5 mg/kg/day. At this dose, exposures (AUC<sub>24h</sub>) in males and female rats on PND77 were 696 and 1883 ng.h/mL, respectively, which are approximately 5 and 13-times the mean clinical exposure at steady state at the highest doses across age groups in pediatric patients, based on modeled AUCs.

The following table shows modeled AUC values at steady state for the highest dose across age groups in pediatric patients.<sup>1</sup>

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<sup>1</sup> These modeled pediatric exposures were kindly provided by Sudharshan Hariharan in an email dated March 19, 2019.

| PARAMETERS                             | MEAN  | SD    | CV    | GEOMEAN | GEOCV | MEDIAN | QT5 | LIQR | UIQR  | QT95  | MIN | MAX   |
|----------------------------------------|-------|-------|-------|---------|-------|--------|-----|------|-------|-------|-----|-------|
| AUC<br>at steady state<br>(ng/mL * hr) | 147.1 | 156.3 | 106.2 | 78.1    | 198.1 | 101.2  | 9.0 | 31.4 | 206.3 | 465.4 | 3.5 | 734.6 |

### Labeling Review

Propose to add the following animal data under Section 8.4 Pediatric Use

#### Animal Data

Ivabradine given orally to juvenile rats from postnatal day (PND) 7 until PND 77 at 7.5, 15 and 30 mg/kg/day did not affect postnatal (pre-weaning) development and reproductive performance (post-weaning development). Similar to adult animals, ivabradine decreased heart rate dose-dependently, and increased heart weights at the highest dose administered. Ivabradine decreased white blood cell counts (lymphocytes) at the highest dose administered. The decrease in white blood cell counts partially reversed within a 3-week recovery period. Exposures in male and female rats at the NOAEL of 7.5 mg/kg/day are approximately (b) (4)-times, respectively, (b) (4) steady state at the highest doses across age groups in pediatric patients, based on modeled AUCs.

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