CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

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Subject: NDA 209279

Related Applications: NDA-021290, IND-58317, IND-(b) (4), IND-(b) (4)

Actelion, the sponsor for Tracleer (bosentan), an endothelin receptor antagonist approved for treatment of pulmonary arterial hypertension in adults, submitted an application (NDA 20279) for pediatric use in this same disease. To support this indication, the sponsor performed a juvenile toxicity study in rats. This study was reviewed under IND 58317 by this reviewer. The study review was archived in DARRTs on 07/30/2015.

The executive summary from that IND review is provided below.

Brief Discussion of Nonclinical Findings

Bosentan was evaluated in a juvenile toxicity study in rats, with oral dosing by gavage started on postpartum day 4, and continued thru postpartum day 69, or thru mating on postpartum day 84. Dosages evaluated in this study were 0, 15, 45, 135 mg/kg/day, with dosages based on a dose- range finding study in rats. General toxicology was evaluated – mortality, body weight, organ weights and histopathology - along with behavior and learning, and reproduction (fertility, resorptions, corpora lutea, live and dead embryos).

The main juvenile toxicity study findings are summarized below.

- No effects on mortality, behavior, learning and auditory function.
- No histopathology findings, including myocardial.

- A dose-related decrease in body weight at mid and high dosage levels in both males and females.
- Reproductive function (fertility, corpora lutea, resorptions, pre and post implantation loss, live and dead embryos) was not affected.
- A decrease in sperm counts was observed in the epididymides (high dosage group), and a decrease in epididymides weights was noted at all dosage levels. The effect on epididymides weights was not dosage related.
- Testes weights were reduced at the high dosage level.
- Heart weights (absolute and/or relative to body weight) were increased at the high dosage level in males and females. There is less robust evidence that heart weights were increased in low and mid dose levels, since findings in these dosage groups were sporadic.
- Toxicokinetic analysis showed exposure to be dose-related but not dose-proportional.
- Exposure was up to 10-fold less at postpartum day 69 vs postpartum day 20. This finding suggests that the rate of metabolic degradation increased markedly throughout the study, perhaps thru development of metabolism as the animals matured or thru auto-induction with chronic drug administration.

The NOAEL is considered to be 15 mg/kg/day.

The following table was taken from the sponsor's briefing document, D-15-045, dated 17 June 2015, with the NOAEL considered to be 15 mg/kg/day. Animal exposure is taken as a mean of male and female values at postpartum days 20 and 69. The 7-8 fold exposure multiples (animal vs pediatric clinical exposures) seem reasonable.

Table 6 Safety margin calculation

Age of the children	Mean AUC_{0-24} in children at 2 mg/kg bid [a] (ng·h/mL)	Safety margins based on the AUC_{0-24} at the NOEL of 15 mg/kg/day in juvenile rats 65,500 ng·h/mL [b]
< 2 years	7,879	8
> 2 years	8,820	7

a - Study AC-052-373 (Future 3) b - Study T-10.407, average of males and females on days 20 and 69.

AUC_{0-24} = Area under the plasma concentration time curve over a period of 24h; b.i.d. = twice daily; NOEL = no observed area of effect

Also in that IND review, plasma drug exposures in juvenile rats were discussed as shown below. Exposure was dependent on dosage and exposure duration, with substantial decreases observed on day 69 vs day 4, consistent with induction of metabolism seen in animals in rats and dogs in the general toxicology studies reviewed in the original application (NDA-021290).

Table 2 Toxicokinetic parameters and dose dependence of bosentan exposure after oral administration of bosentan to juvenile rats

Dose (mg/kg)	Post-partum Day	Sex	Tmax (h)	Cmax (ng/mL)	AUC0-24h (h*ng/mL)	Cmax/D (ng/mL)/(mg/kg)	AUC0-24h/D (h*ng/mL)/(mg/kg)
0	4	f	3	8.17#	33.1#	NA	NA
0	4	m	3	7.98#	NA	NA	NA
0	20	f	24	71.1	606	NA	NA
0	20	m	2	26.4	230	NA	NA
15	4	f	3	7640#	30600#	510#	2000#
15	4	m	6	10100#	36200#	670#	2400#
15	20	f	4	39500	168000	2600	11000
15	20	m	2	8760	59700	580	4000
15	69	f	1	4550	22500	300	1500
15	69	m	1	3260	11800	220	790
45	4	f	3	36100#	103000#	800#	2300#
45	4	m	6	23500#	57200#	520#	1300#
45	20	f	2	30200	270000	670	6000
45	20	m	2	28500	185000	630	4100
45	69	f	2	15500	53700	340	1200
45	69	m	1	6280	20300	140	450
135	4	f	3	45200#	189000#	330#	1400#
135	4	m	3	34900#	147000#	260#	1100#
135	20	f	2	24800	191000	180	1400
135	20	m	4	36900	282000	270	2100
135	69	f	1	20500	78100	150	580
135	69	m	2	8330	49900	62	370

Cmax and AUC0-6h values on post-partum day 4 should be considered with caution since these were calculated based on only one animal per time point and only three concentration-time points up to 6 hour post-dose.

Proposed labeling

The sponsor proposed the following labeling in their pediatric NDA submission.

"In a juvenile rat toxicity study, rats were treated from Day 4 postpartum to adulthood (day 69 postpartum). Decreased body weights, absolute weights of testes and epididymides, and reduced number of sperm in epididymides were observed after weaning. No effect on testis histology or sperm morphology and function was seen. The NOAEL was (b) (4) times (at Day (b) (4) postpartum) and (b) (4) times (Day 69 postpartum) the human therapeutic exposure, respe ively.

No effects on general development, (b) (4) sensory, cognitive function and reproductive performance were detected at 7 times the therapeutic exposure in children with PAH."

We propose the following revised label.[1]

"In a juvenile rat toxicity study, rats were treated from Day 4 postpartum to adulthood (day 69 postpartum). Decreased body weights, absolute weights of testes and epididymides, and reduced number of sperm in epididymides were observed after weaning. No effect on testis histology or sperm morphology and function was seen. The NOAEL was 4 times (at Day 4 postpartum) and 2 times (Day 69 postpartum) the human therapeutic exposure, respectively.

No effects on general development, sensory, cognitive function and reproductive performance were detected at the highest dose tested in juvenile rats, 7 times the therapeutic exposure in children with PAH."

[1] We revised the safety margins (from the previous IND review and the sponsor's recommended label) to reflect animal exposures on days 4 and 69. We utilized the sponsor's clinical exposure estimate of 8820 ng hr/ml in calculating the safety margins.

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/s/

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03/20/2017

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