

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-331

PHARMACOLOGY REVIEW(S)

NDA 22-331

PHARMACOLOGY REVIEW OF ORIGINAL 505(B)(2) APPLICATION

SUBMISSION DATE: 15 February 2008

CENTER RECEIPT DATE: 19 February 2008

REVIEW COMPLETION DATE: 28 August 2008

REVIEWER: C.A. Resnick, Ph.D.
Supervisory Pharmacologist
Division of Cardiovascular & Renal Products

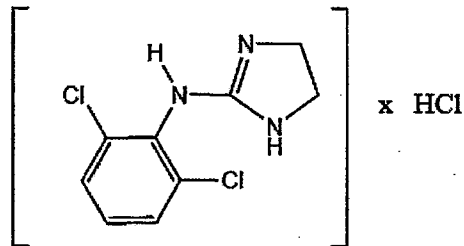
SPONSOR: Addrenex Pharmaceuticals, Inc.
Durham, NC 27703

CONTACT: Paul Ketteridge
Regulatory Consultant
(410) 458-7846

DRUG PRODUCT: CloniBID (clonidine HCl) Sustained Release Tablets

REFERENCED LISTED DRUG PRODUCT: Catapres (clonidine HCl) Tablets
Boehringer Ingelheim NDA 17-407

DRUG SUBSTANCE: clonidine HCl



Molecular Formula: $C_9H_9Cl_2N_3 \cdot HCl$

Molecular Weight: 266.56

CAS No. 4205-91-8

Pharmacologic Category: centrally acting α_2 adrenergic agonist

PROPOSED INDICATION: hypertension

FORMULATION AND ROUTE OF ADMINISTRATION: 0.1 mg tablets (equivalent to 0.087 mg of clonidine free base) for oral administration. Inactive ingredients are sodium lauryl sulfate, lactose monohydrate, hypromellose type 2208, partially pregelatinized starch, colloidal silicon dioxide and magnesium stearate. The formulation is designed to delay the absorption of active drug in order to decrease peak to trough plasma concentration differences.

PROPOSED DOSAGE REGIMEN: According to proposed labeling, dosing should be initiated with one 0.1 mg tablet at bedtime with increments of 0.1 mg/day made at weekly intervals, if

necessary (dosing morning and at bedtime), until the desired response is achieved. Doses above 0.6 mg/day (0.3 mg twice daily) were not evaluated in clinical trials and are not recommended.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY DATA: None provided. Sponsor relies on the previous findings of safety and efficacy for the referenced listed drug product, Catapres (clonidine HCl) Tablets.

LABELING: Except for changes necessitated by the change in manufacturer and excipients, the information provided by the proposed label is, for the most part, identical to that provided by the label for the referenced listed drug product. (Identical wording used to describe the results of animal studies.) However, the labeling for Catapres, the referenced product, indicates a maximum recommended human dose of 1.2 mg b.i.d., whereas the labeling for the Adrenex product indicates a maximum recommended human dose of 0.3 mg b.i.d. This reviewer recommends changes to the animal study descriptions (deletion of human dose multiples and addition of human equivalents of animal doses) that will allow identical text to be used for both labels.

Under **WARNINGS AND PRECAUTIONS, Pregnancy**, the proposed text reads as follows:

Pregnancy Category C

b(4)

This reviewer recommends the text be modified to read as follows:

Pregnancy Category C. Oral administration of clonidine HCl to pregnant rabbits during embryo/fetal organogenesis, at doses up to 80 mcg/kg/day (human equivalent dose 26 mcg/kg/day), produced no evidence of teratogenic or embryotoxic potential. In pregnant rats, however, doses as low as 15 mcg/kg/day (HED 2.4 mcg/kg/day) were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating and throughout gestation. Increased resorptions were not associated with treatment at the same or higher dose levels (up to 150 mcg/kg/day (HED 24 mcg/kg/day)) when treatment of the dams was restricted to gestation days 6-15. Increases in resorptions were observed in both mice and

rats at 500 or more mcg/kg/day (HED 80 mcg/kg/day for rats and 40 mcg/kg/day for mice) when the animals were treated on gestation days 1-14.

Under **NONCLINICAL TOXICOLOGY**, the proposed subsection titled **Carcinogenicity, Mutagenesis and Impairment of Fertility** reads as follows:



b(4)

This reviewer recommends that the subsection (both header and text) be modified to read as follows:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Clonidine HCl was not carcinogenic when administered in the diets of rats (up to 132 weeks of exposure) at doses as high as 1620 mcg/kg/day in males (human equivalent dose: 260 mcg/kg/day) and 2040 mcg/kg/day in females (HED 324 mcg/kg/day) or the diets of mice (up to 78 weeks of exposure) at doses as high as 2500 mcg/kg/day (HED 203 mcg/kg/day). There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity. Fertility of male or female rats was unaffected by clonidine HCl doses as high as 150 mcg/kg/day (HED 24 mcg/kg/day). In a separate experiment, fertility of female rats appeared to be adversely affected at dose levels of 500 and 2000 mcg/kg/day (HED 80 and 324 mcg/kg/day, respectively).

Under **NONCLINICAL TOXICOLOGY**, the **Animal Toxicology and/or Pharmacology** subsection should be retitled **Ocular Toxicity**. The only change recommended to the text of this subsection is that the third paragraph be combined with the first paragraph, as both describe results of animal studies.

EVALUATION: Clonidine HCl is currently approved in the United States as an immediate-release tablet (Boehringer Ingelheim's Catapres[®], NDA 17407), a transdermal patch (Boehringer Ingelheim's Catapres-TTS[®], NDA 18891) and an epidural injection (Xanodyne Pharmaceutical's Duraclon[®], NDA 20615). The oral formulation that is the subject of this NDA is intended for the same patient population for which Catapres[®] is indicated and the maximum recommended dose is no higher than the maximum recommended dose of the approved oral formulation. Under section 505(b)(2) of the FD&C Act, in situations where a sponsor does not have a right of reference to all of the studies supporting approval, approval can be based on the prior approval of a listed drug (i.e., Agency findings of safety and efficacy for the listed drug) with the only additional studies needed being those that address the differences, if any, in the identities of the active ingredients and the way in which the products are used. Therefore, the

sponsor of this NDA may rely on the Agency's finding of safety for Catapres® (NDA 17407) in lieu of performing animal safety studies.

RECOMMENDATIONS: The application is approvable. See our recommendations on labeling, above.

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Information from NDA 17-407 to Facilitate Relabeling of Both the Boehringer Ingelheim and Addrenex Products

Maximum Recommended Human Daily Dose: 0.3 mg b.i.d. for new product (0.01 mg/kg/day)
0.3 mg b.i.d. or 1.2 mg b.i.d. for old product (up to 0.04 mg/kg/day)

Reproductive Toxicity Studies

Rat Dams treated continuously from 2 months prior to mating through 2 complete breeding cycles at doses of 0, 15 & 150 mcg/kg/day.

Rat Dams treated on gestation days 6-15 at doses of 0, 15 & 150 mcg/kg/day.

Rat Dams treated on gestation days 1-14 at doses of 0, 500 & 2000 mcg/kg/day.

Mouse Dams treated on gestation days 1-14 at doses of 0, 500 & 2000 mcg/kg/day.

Rabbit Does treated on gestation days 7-16 at doses of 0, 8 & 80 mcg/kg/day

Carcinogenicity Studies

Mice treated for up to 78 weeks via the diet at doses of up to 2.5 mg/kg/day

Rats treated for up to 132 weeks via the diet at fixed concentrations of up to 20 ppm. Actual intake for high dose group estimated at 1.62 mg/kg/day for males and 2.04 mg/kg/day for females.

Human Equivalent doses for Rat

HED for 15 mcg/kg (0.015 mg/kg) = $0.015/6.2 = 0.0024$ mg/kg or about 0.24 X MRDHD
HED for 150 mcg/kg (0.15 mg/kg) = $0.15/6.2 = 0.024$ mg/kg or about 2.4 x MRDHD
HED for 500 mcg/kg (0.50 mg/kg) = $0.50/6.2 = 0.08$ mg/kg or about 8 x MRDHD
HED for 1600 mcg/kg (1.6 mg/kg) = $1.6/6.2 = 0.26$ mg/kg or about 26 x MRDHD
HED for 2000 mcg/kg (2.0 mg/kg) = $2.0/6.2 = 0.324$ mg/kg or about 32 x MRDHD

Human Equivalent doses for Mouse

HED for 500 mcg/kg (0.50 mg/kg) = $0.50/12.3 = 0.04$ mg/kg or about 4 x MRDHD
HED for 2000 mcg/kg (2.0/mg/kg) = $2.0/12.3 = 0.163$ mg/kg or about 16 x MRDHD
HED for 2500 mcg/kg (2.5 mg/kg) = $2.5/12.3 = 0.203$ mg/kg or about 20 x MRDHD

Human Equivalent doses for Rabbit

HED for 8 mcg/kg (0.008 mg/kg) = $0.008/3.1 = 0.0026$ mg/kg or about 0.26 x MRDHD
HED for 80 mcg/kg (0.08 mg/kg) = $0.08/3.1 = 0.026$ mg/kg or about 2.6 x MRDHD

Above human dose multiples based on the MRDHD in the labeling for the new product (0.3 mg b.i.d.)

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/s/

Charles Resnick
8/29/2008 02:16:49 PM
PHARMACOLOGIST