

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-499

PHARMACOLOGY REVIEW(S)

NDA 22-499
NDA 22-500

PHARMACOLOGY REVIEW OF ORIGINAL 505(b)(2) APPLICATIONS

SUBMISSION DATE: 3 February 2009
CENTER RECEIPT DATE: 3 February 2009
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REVIEWER: C.A. Resnick, Ph.D.
Supervisory Pharmacologist
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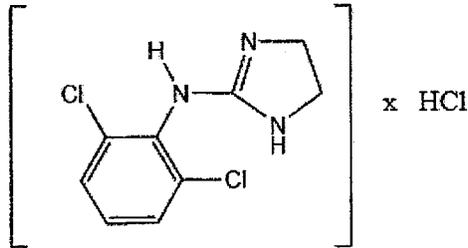
SPONSOR: Tris Pharma Inc.
Monmouth Junction, NJ 08852

DRUG PRODUCTS: NDA 22-499: Clonidine — ER Oral Suspension **b(4)**
NDA 22-500: Clonidine — ER Oral Tablets

REFERENCED LISTED DRUG PRODUCTS:

Primary: Boehringer Ingelheim NDA 17407 for Catapres® Tablets (for both applications)
Secondary: Boehringer Ingelheim NDA 18891 for Catapres-TTS® (for both applications)

DRUG SUBSTANCE: Clonidine HCl



$C_9H_9Cl_2N_3 \cdot HCl$ Mol. Wt. 266.56
centrally acting alpha adrenergic receptor agonist

PROPOSED INDICATION: Hypertension

RELATED APPLICATIONS OF SPONSOR:

IND 102108 for Clonidine — ER Oral Suspension **b(4)**
IND 101635 for Clonidine — ER Tablets

FORMULATION AND ROUTE OF ADMINISTRATION: The suspension contains clonidine HCl 0.1 mg/mL ————— Inactive ingredients are citric **b(4)**

acid anhydrous, flavor, glycerin, high fructose corn syrup, methylparabaen, _____
polyvinyl acetate, polysorbate 80, povidone, propylparaben, purified water, sucrose, triacetin and
xanthan gum. The tablets contain 0.2 or 0.3 mg clonidine HCl (0.17 or 0.26 mg free base)

b(4)

Inactive ingredients for the tablets are
crospovidone, dental-type silica, lactose monohydrate, magnesium stearate, microcrystalline
cellulose, polyvinyl acetate, povidone, triacetin, _____ (0.2 mg tablet),
and _____ (0.3 mg tablet).

b(4)

PROPOSED DOSAGE REGIMEN: Initial Dose _____ with increments of 0.1 mg
per day at weekly intervals until the desired response is achieved. Proposed labeling states that

b(4)

NONCLINICAL PHARMACOLOGY/TOXICOLOGY DATA: None. These applications rely
on the Agency's findings of safety for Catapres (NDA 17407) and Catapres TTS (NDA 18891).

LABELING: Except for changes necessitated by the changes in manufacturer, excipients, and, in
the case of the suspension, dosage form, the information provided by the proposed labels for
these clonidine products 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.)
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 all clonidine labels, irrespective of differences in the maximum recommended human
dose.

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

b(4)

Pregnancy Category C

b(4)

The 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)

The reviewer recommends 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 formulations that are the subject of the Tris Pharma NDAs are intended for the same patient population for which Catapres® is indicated and the maximum recommended dose is no higher than the maximum recommended dose for 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, Tris Pharma may rely on the Agency's findings of safety and efficacy for Catapres® (NDA 17407) in lieu of performing animal safety studies.

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

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/s/

Charles Resnick
6/26/2009 03:51:35 PM
PHARMACOLOGIST