CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-500

PHARMACOLOGY REVIEW(S)

Date: July 7, 2009

To: Amit Mitra, PhD Charles Resnick, PhD

From: Donald Nick Jensen, DVM

Subject: NDA 22500, Tris Pharma, Inc., Clonidine [redacted] ER Tablets (safety of proposed levels of polystyrene sulfonate sodium) b(4)

The FDA chemistry reviewer for this NDA, Dr. Amit Mitra, has asked whether the sponsor's proposed levels of one inactive ingredient, polystyrene sulfonate sodium (a cation exchange resin that is also used as an active drug for treatment of hyperkalemia), are safe and appropriate.

Polystyrene sulfonate sodium is an ion exchange resin that adsorbs potassium (and, to a lesser extent, other cations) by exchanging it for sodium. The sponsor indicates that the resin used in their product contains [redacted] by weight. b(4)

For the sponsor's proposed drug product formulation, the total daily dose of polystyrene sulfonate sodium would be [redacted] for typical clonidine doses of 0.2 – 0.6 mg/day. For the maximum effective clonidine dose of 2.4 mg/day (per current labeling of approved clonidine products), the total daily dose of polystyrene sulfonate sodium would be [redacted] b(4)

The highest dose of [redacted] used as an inactive ingredient in an approved product appears to be the [redacted] mg that is used in 30 mg Roxicodone SR tablets (oxycodone sustained release tablets, NDA 20-932). The typical dose for 30 mg oxycodone tablets is one per 4 hours, giving a total daily [redacted] dose of [redacted] b(4) b(4)

Polystyrene sulfonate sodium is also used as an active drug ingredient (Kionex®, Kayexalate®, etc.) for treatment of hyperkalemia by adsorption of potassium from the GI tract. Typical doses for this indication are 15 - 60 g/day. Adverse effects include hypokalemia, hypocalcemia, hypomagnesemia (Calcium and magnesium are also adsorbed by this ion exchange resin.), excess sodium retention (This resin functions by exchanging sodium for other cations, primarily potassium.), GI irritation (including diarrhea, ulcers and necrosis), and GI impaction.

The sponsor briefly summarizes various toxicology studies of polystyrene sulfonate sodium (all either unpublished or otherwise unavailable), including a repeat-dose toxicity study in rats that evaluated doses up to 8 mg/kg for 180 days. (The human equivalent dose, calculated on a mg/m^2 basis, is 77 g/day in a 60 kg subject, i.e., similar to the doses used to treat hyperkalemia.) The sponsor indicates that the results of this repeat-dose study were unremarkable, as were results of shorter-term repeat-dose studies, genotoxicity studies and reproductive toxicity studies. The sponsor does not provide copies of the study reports for these studies.

As noted above, the total daily dose of polystyrene sulfonate sodium in patients treated with typical doses of the proposed drug product would [redacted] i.e., similar to the total daily dose of this ingredient [redacted] b(4)

I did not find any published evidence that the use of polystyrene sulfonate sodium or in other products has caused side effects. The highest recommended dose of the sponsor's product (2.4 mg/day of clonidine, which is probably very rarely used due to clonidine side effects) would deliver of polystyrene sulfonate sodium, i.e., a higher daily dose than is delivered by any approved product that uses this compound as an active ingredient. As is noted above, polystyrene sulfonate sodium is used as an active ingredient at much higher doses but these higher doses can be associated with significant side effects, including electrolyte imbalances and GI ulceration or necrosis. b(4) b(4) b(4)

Given the information above, it is reasonable to suspect that the sponsor's proposed levels of polystyrene sulfonate sodium will not produce adverse effects, particularly if the Medical Officer assigned to this file determines that total daily doses of clonidine will rarely exceed 0.6 mg (which would deliver a maximum of of polystyrene sulfonate sodium) and not the highest recommended dose of clonidine (2.4 mg/day, which would deliver of polystyrene sulfonate sodium). On the other hand, if even a small risk of side effects is considered inappropriate, then the sponsor could be asked to reduce the levels of this inactive ingredient such that the maximum daily dose will not exceed the daily dose delivered by approved products that also use this inactive ingredient. As a note, given that a low sodium diet is typically defined as a daily sodium intake of 2 g or less, release of even the total sodium load contained in the highest recommended dose (approximately of of this inactive ingredient) would not appreciably increase sodium intake. b(4) b(4) b(4)

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/s/

Donald Jensen
7/7/2009 04:02:02 PM
PHARMACOLOGIST

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7/7/2009 04:36:08 PM
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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
REVIEW COMPLETION DATE: 26 June 2009

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

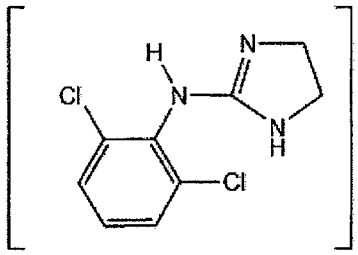
SPONSOR: Tris Pharma Inc.
Monmouth Junction, NJ 08852

DRUG PRODUCTS: NDA 22-499: Clonidine [redacted] ER Oral Suspension b(4)
NDA 22-500: Clonidine [redacted] 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



x 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 [redacted] ER Oral Suspension b(4)
IND 101635 for Clonidine [redacted] ER Tablets

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

acid anhydrous, flavor, glycerin, high fructose corn syrup, methylparabaen, modified food starch, 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) [redacted] Inactive ingredients for the tablets are crospovidone, dental-type silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl acetate, povidone, triacetin, [redacted] (0.2 mg tablet), and [redacted] (0.3 mg tablet). b(4) b(4) b(4)

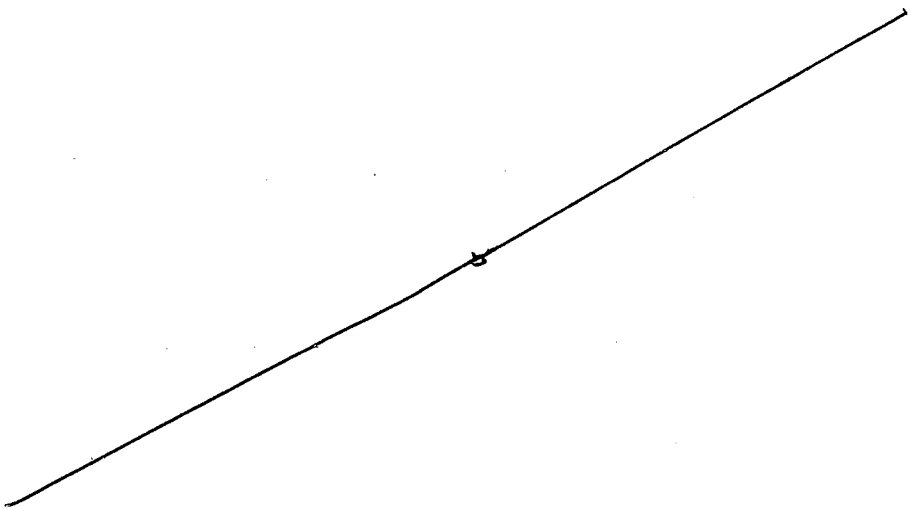
PROPOSED DOSAGE REGIMEN: Initial Dose [redacted] with increments of 0.1 mg per day at weekly intervals until the desired response is achieved. Proposed labeling states that [redacted] b(4)

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:

Pregnancy Category C



b(4)

b(4)

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