

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-331

CROSS DISCIPLINE TEAM LEADER REVIEW



MEMORANDUM
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 11, 2008

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of
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TO: Dr. Norman Stockbridge, M.D., Ph.D., Director, Division of
Cardiovascular and Renal Products, HFD-110.

SUBJECT: Complete Response for NDA 22, 331 (Clonidine HCl, Sympres®,
Addrenex Pharmaceuticals Co., Ltd.)

The following memo constitutes the complete response to NDA 22-331 (clonidine hydrochloride tablets; Addrenex Pharmaceutical Co. Ltd). The proposed formulation is a single strength (0.1 mg) dose. Still unresolved are the issues related to the manufacture and control of this formulation. EER evaluations are still pending. Also pending is a study on the effect of an ethanol medium on the dissolution characteristics of Sympres®.

No pediatric studies have yet been submitted and the sponsor's rationale for not conducting such studies is summarized at the end of the review. I do not find the sponsor's arguments as sufficient to preclude pediatric studies. The sponsor should be held to fulfill PREA requirements.

The Trade Name Sympres® was found acceptable by DMETS.

Since the clinical development program for this formulation of clonidine was modest, at best, no superiority claims or suggestions of superiority should be included in the package insert. Despite not exploring an extension of the dose range in excess of that already approved for an immediate release Clonidine formulation, the effect size demonstrated by steady state ambulatory measurements for the dose-range that was studied is more than adequate to reflect a reasonable treatment effect. Although the sponsor supplied modeled data for maximum concentration or AUC of clonidine and blood pressure effect neither the clinical pharmacology reviewer nor I considered the model as definitive or accurate.

The following reviews were consulted in the generation of this memo.

- Office of New Drug Quality Assessment (Chemistry) Review by Dr. Amit K. Mitra, Ph.D., dated November 12, 2008 and an information request letter dated September 23, 2008.

- Office of Surveillance and Epidemiology Memo by Diane C. Smith, PharmD., dated June 20, 2008 and October 24, 2008.
- Office of Clinical Pharmacology Review by Dr. Divya Menon-Anderson, Ph.D., dated November 7, 2008.
- Clinical Review by Dr. A. O. Williams, M.D., dated September 22, 2008.
- Pharmacology Review by Dr. C.A. Resnick, Ph.D., dated August 29, 2008.®

Clonidine is a previously approved antihypertensive therapy (approved in 1974). Formulations of clonidine are currently marketed either as tablet or as a transdermal patch. This proposed clonidine formulation differs from the immediate release listed formulation, , in that the proposed formulation contains [REDACTED]

as excipients and consequently has a different release pattern of clonidine compared to the reference listed drug. The current application relies on the Agency's finding of safety and efficacy to support the approval of this current formulation under 505(b) (2). The sponsor supplies patent certification and asserts that there are no unexpired exclusivity for the listed reference drug Catapres®.

b(4)

There seems to be inadequate information with regards to the CMC for this new product. The Quality Assessment team transmitted an information request letter to the sponsor dated September 23, 2008. The still-required pieces of information are additional specifications for drug substance, drug product, excipients and quality control steps of the formulation process. The sponsor has not yet responded to this request for information. EERs are also still pending, and their completion is partially delayed by the inadequate specifications of the manufacturing process as noted above.

No preclinical studies were performed and the Pharmacology reviewer considered the current labeling for currently approved products as adequate for this new formulation.

Sympres® will be marketed as a single dose-strength (0.1 mg) formulation. Delayed release is accomplished by [REDACTED]

The sponsor proposed a dosing recommendation for Sympres® which is equivalent to that of the immediate release formulation. The different kinetic profile relative to the listed clonidine formulation makes Sympres® ineligible for approval under CFR 505(j).

b(4)

Based on the results of both a single dose study (CLON-101) and a multi-dose study (CLON-201), this dose-strength appears well behaved, with an acceptable intra-subject reproducibility profile and a reasonable serum concentration profile compared to the IR formulation. Peak concentrations of clonidine from Sympres® after single doses are less than those of the IR formulation with the concentrations at the 12-hour time point equivalent to that of the IR (Catapres) formulation.

Study CLON-101 was a single center study assessing the pharmacokinetic profiles of single doses of Sympres® (0.1 mg) fasted, Sympres® (0.1 mg) fed and Catapres (0.1 mg)

fasted, in a three period cross-over design. Data for 14-15 subjects per treatment were available. The pharmacokinetic profile of the three test doses is shown below.

Figure 1: Kinetic profiles of Sympres®, fasted, fed and Catapres fasted all at a 0.1 mg single dose.

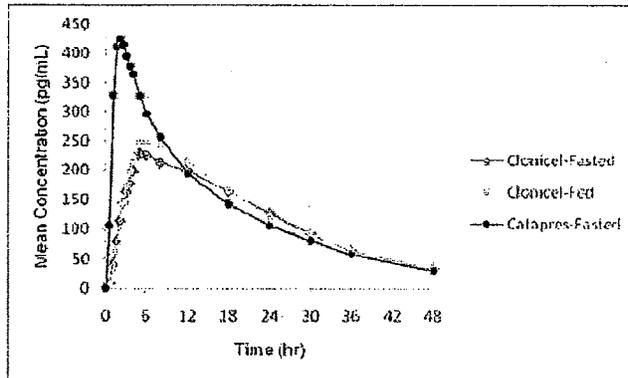


Figure 1: Plot of average plasma clonidine concentration versus time following administration of Sympres 0.1 mg fasted (A), Sympres 0.1 mg fed (B), and Catapres 0.1 mg fasted (C).

Below are tabulated the pharmacokinetic parameters comparing the three treatments.

Table 1: Pharmacokinetic constants for Sympres® fasted, fed and Catapres fasted after a 0.1 mg dose, fasted

Parameter	Treatment: Sympres® - fasted			Treatment: Sympres® - fed			Treatment Catapres-fasted		
	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%
C_{max} pg/mL	235	35	15	258	33	13	443	60	13
T_{max} hr	6.8	3.6	53	6.5	1.2	19	2.1	0.5	13
AUC_{0-48} hr*pg/mL	6505	1728	27	6729	1650	25	7313	1812	25
$T_{1/2}$ (hr)	12.7	3.8	30	12.7	3.6	28	12.5	3.1	25

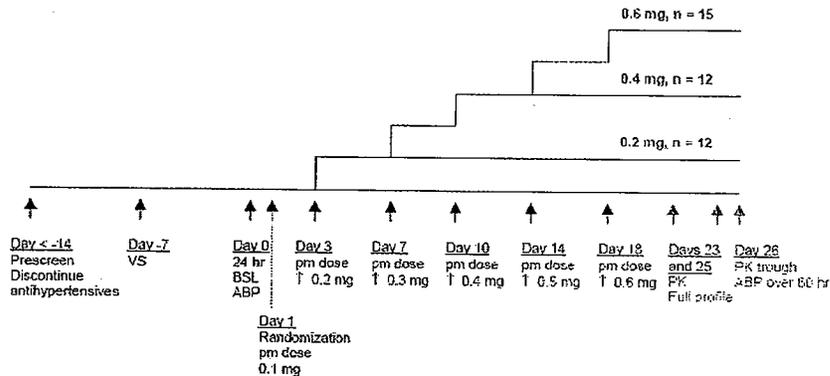
There were minimal differences between Sympres® fed and Sympres® fasted. The T_{max} for Sympres® relative to IR Catapres® is delayed and the C_{max} is decreased; the AUC is also modestly diminished. The concentrations of clonidine at the 12-hour inter-dosing interval are similar.

The performance characteristics of Sympres®, as judged by the intra-subject variability, are acceptable based on steady state measurements. No single-dose data were submitted to assess intra-subject reproducibility. Study CLON-201 was a three-center, dose-ranging, randomized, pharmacokinetic and pharmacodynamic (ABPM) study in 42 subjects with mild to moderate hypertension. All subjects were started at 0.2 mg/day of Sympres® divided BID with titration at 0.1 mg daily dosing increments at 3 day intervals until their randomized dose was achieved. At that point the dose remained constant through day 26. Following day 26 subjects were withdrawn from their randomized dose. Ambulatory measurements of vital signs were performed at baseline and at day 26 after

the last dose of medication and for an additional 60 hours. Pharmacokinetic profiles were derived from serum levels on days 23 and 25 of therapy.

The study design is shown below:

Figure 2 Schematic for study CLON-201



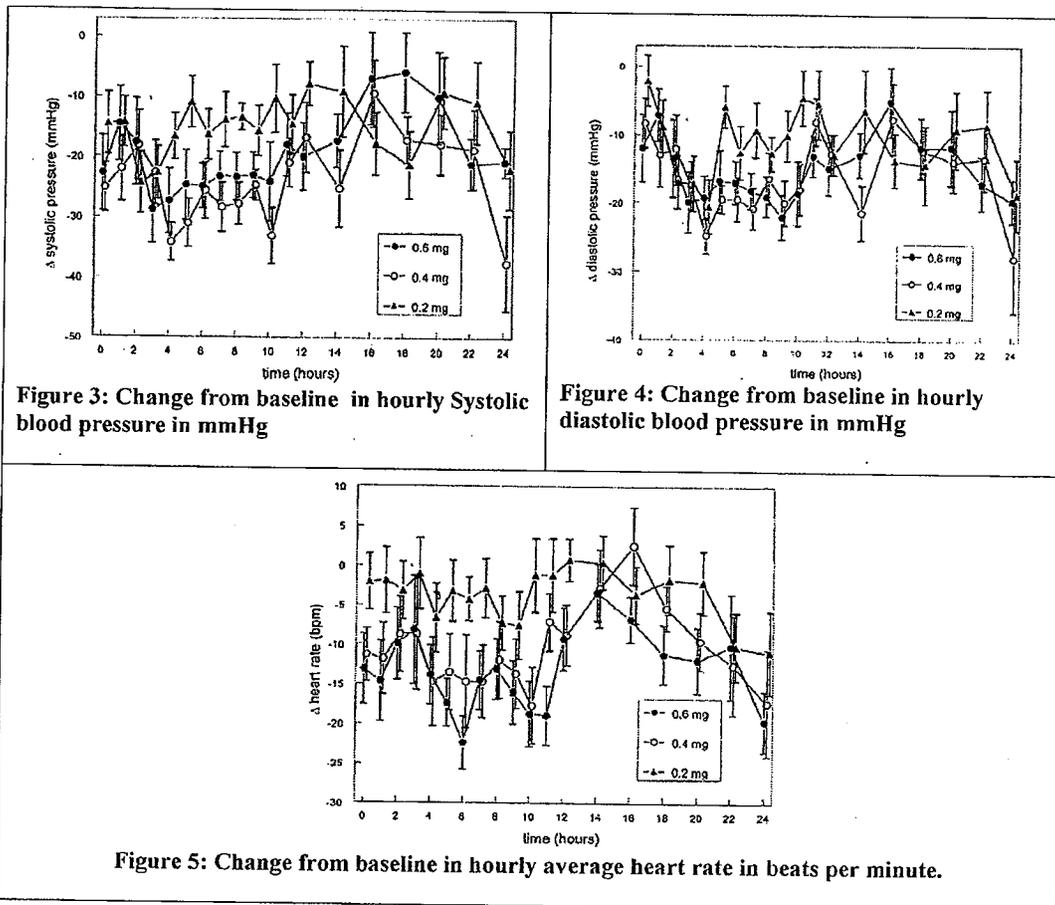
Pharmacokinetic profile parameters at steady state for the three randomized treatments are shown below:

Table 2: Pharmacokinetic profile for steady state clonidine levels after treatment with either 0.2, 0.4 or 0.6 mg Sympres® divided BID

	0.1 mg BID		0.2 mg BID		0.3 mg BID	
	Day 23	Day 5	Day 23	Day 5	Day 23	Day 5
C_{max} pg/ml	333 ± 157	360 ± 183	1060 ± 291	986 ± 173	1980 ± 839	1870 ± 636
C_{min} pg/ml	407 ± 138	375 ± 119	762 ± 241	709 ± 147	1380 ± 568	1320 ± 451
$AUC_{0-\tau}$ pg*hr/ml	5867 ± 1735	5627 ± 1594	11050 ± 3196	10410 ± 2007	20130 ± 8207	19310 ± 6561
T_{max} hr	5.0 ± 2.1	4.3 ± 1.7	4.4 ± 1.2	4.7 ± 1.2	4.5 ± 1.8	5.0 ± 1.5

The two lowest doses appear to be proportional based on the AUC values. The highest dose seems in excess of proportional for this parameter as well as for C_{max} . C_{min} appear approximately dose proportional. Given the fairly large standard deviations, it is likely but not definite that there is a more than proportionate increase in exposure as the dose increased. The biopharmaceutic reviewer noted that the intra-subject variability (based on 5 trough measurements) was an acceptable 12%,

With respect to the effect of treatment on vital signs, the changes from baseline at the various time points are shown below.



Although there was no intent to explore an expanded dose range relative to the IR formulation of clonidine, the magnitude of blood pressure change is substantial, particularly for the 0.2 mg Bid (0.4 daily) and 0.3 mg BID (0.6 mg) dose group. The effect at the 12-hour time point (actually the average of the 11 and 12 hour time point) appears to retain an acceptable portion of the blood pressure effect compared to the average of the 4 and 5 hour time point (corresponds to approximately C_{max}). There also appears to be a drastic heart rate effect with a mean drop of between 15-20 beats per minute decrease at the two higher doses.

The sponsor performed a modeling exercise with the sparse data from study CLON-201. The modeled data is shown below in Figure 6. The biopharmaceutical reviewer makes clear that the pharmacokinetic-pharmacodynamic model appears to be post-hoc with no apparent pre-defined method for constructing the model. The model also does not adequately characterize the error entailed in the outcome parameters. In addition, I would note that the residuals at or around the steep portion of the curve are surprisingly small compared to the residuals around the flat portion of the modeled data. Furthermore, the rise in effect by the model occurs over a very modest increase in concentrations of clonidine (between 400 and 700 pg/ml), a very narrow range and not

the usual two-log dose range for which the dose-response curve usually is required. In summary I agree that this model does not define the blood pressure-concentration effect of clonidine.

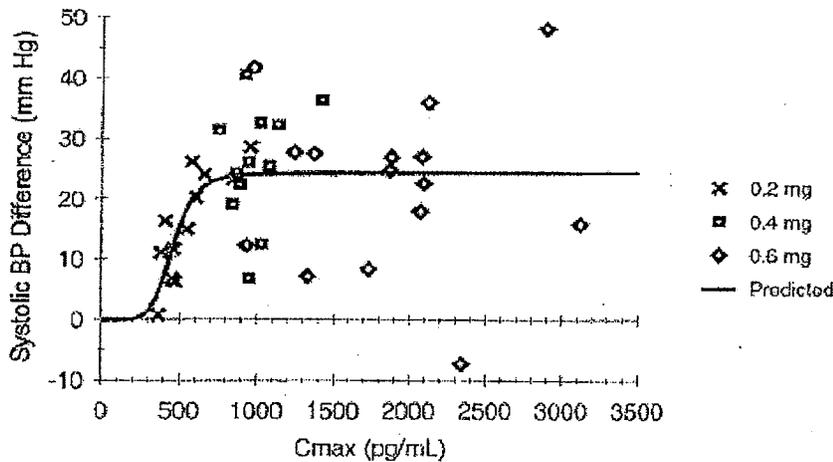


Figure 6: Plot of C_{max} versus blood systolic pressure effect for study CLON-201. Solid lines are modeled predicted effects.

Pediatric Waiver:

The sponsor argues that pediatric studies are not necessary because:

1. The sponsor believes that Sympres® tablets will not represent a meaningful therapeutic benefit over existing therapies for hypertension in pediatric patients, and it is not likely to be used by a substantial number of pediatric patients, as specified in section 505B9q)(4)(D) of the Act.
2. The sponsor also believes that there is evidence suggesting the clonidine may be unsafe when used for hypertension in the pediatric population. This is specified in section 505B(a)(4)(D) of the Act.

In support of the first point, the sponsor notes that in several review articles or practice guidelines which tabulate lists of therapies to treat pediatric hypertension, clonidine is not included as one of the acceptable therapies.

With respect to the concern regarding safety, this concern is related to the potential for withdrawal hypertensive response should pediatric patients be unable to take their medication for some period of time. They argue that pediatric patients are more prone to gastrointestinal ailments and they are therefore more likely to a rebound hypertensive effect.

I find neither argument compelling. The reason for not including clonidine in the list of antihypertensive drugs is not stated, but presumably it is because there is no data on its

use in that population. Consequently, I would conclude that efficacy studies with clonidine are necessary to either define the utility or futility of using this drug in pediatrics.

With respect to the safety argument I don't think that the potential of hypertensive withdrawal effects of clonidine, particularly during bouts of gastroenteritis, is a credible argument for not having adequate data in a pediatric population. Clonidine is routine used in pediatric patients either as an adjunct to ADHD therapies and in patients with Tourette's syndrome to improve motor tics. These groups are similarly vulnerable to drug withdrawal effects during episodes of gastroenteritis. Nevertheless, the potential risks are considered acceptable for the continued off-label use for these indications. In addition, there are trans-dermal formulations available for adults that could (off label also) be used to mitigate any rebound during periods when oral treatments are not feasible. In summary, I don't find the sponsor's arguments as credible and the pediatric studies requirement should not be waived.

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/s/

Abraham Karkowsky
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MEDICAL OFFICER