

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-499

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

DIVISION OF CLINICAL PHARMACOLOGY - I
Addendum to Clinical Pharmacology Review

Date: November 24, 2009

NDA: 22-499/ 22-500
_____ (suspension/tablets) **b(4)**
TRIS Pharmaceuticals

Submitted: January 13, 2009

Goal Date: December 03, 2009

Reviewer: Rajanikanth Madabushi, Ph.D.
Team Leader
Division of Clinical Pharmacology I

Through: Mehul Mehta Ph.D.
Director
Division of Clinical Pharmacology I

To: The File

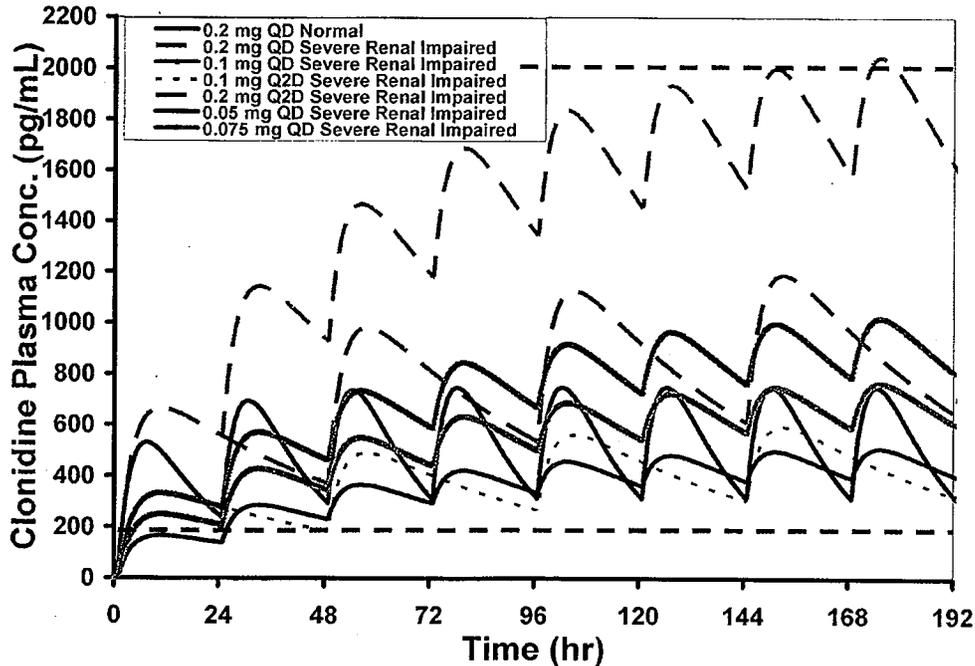
This addendum is aimed to address the two questions raised by the Medical Reviewer Dr. Nancy Xu and forms the basis for the associated labeling recommendations. The two questions raised by Dr. Xu are as follows:

1. What dose of Clonidine _____ ER Tablets or Oral Suspension in renal impaired patients provides comparable exposure to that in patients with normal renal function? **b(4)**
2. What is a reasonable switching regimen for switching patients at steady-state on extended release formulation to Catapres-TTS transdermal system?

1. **What dose of Clonidine _____ ER Tablets or Oral Suspension in renal impaired patients provides comparable exposure to that in patients with normal renal function?** **b(4)**

The current package insert for Catapres (clonidine hydrochloride) states that the half-life in patients with severe renal impairment increases upto 41 hours. The mean half-life of clonidine in subjects with normal renal function is ~12 hrs (see Clinical Pharmacology Reviewer by Dr. Robert O. Kumi dated: 09/09/2009; page 52 – highlights of Modeling Results; $k_{10} = 0.06$, $t_{1/2} = 0.693/k_{10}$). Based on the one-compartment model with lag time (see DARRTS review by Dr. Kumi for model details) developed to describe the concentration-time course of clonidine following administration of extended release formulation, the time-course in severe renal impaired patients (corresponding to 3.5-fold increased half-life as compared to normal subjects) were simulated. Clonidine concentration-time courses with various dosing schemes as shown in Figure 1 were simulated to identify a dosing regimen that will provide comparable steady-state exposures to that of 0.2 mg QD.

Figure 1: A dose of 0.075 mg QD in severe renal impaired subjects provides comparable exposure to that of 0.2 mg QD in subjects with normal renal function.



The key results of the simulations are:

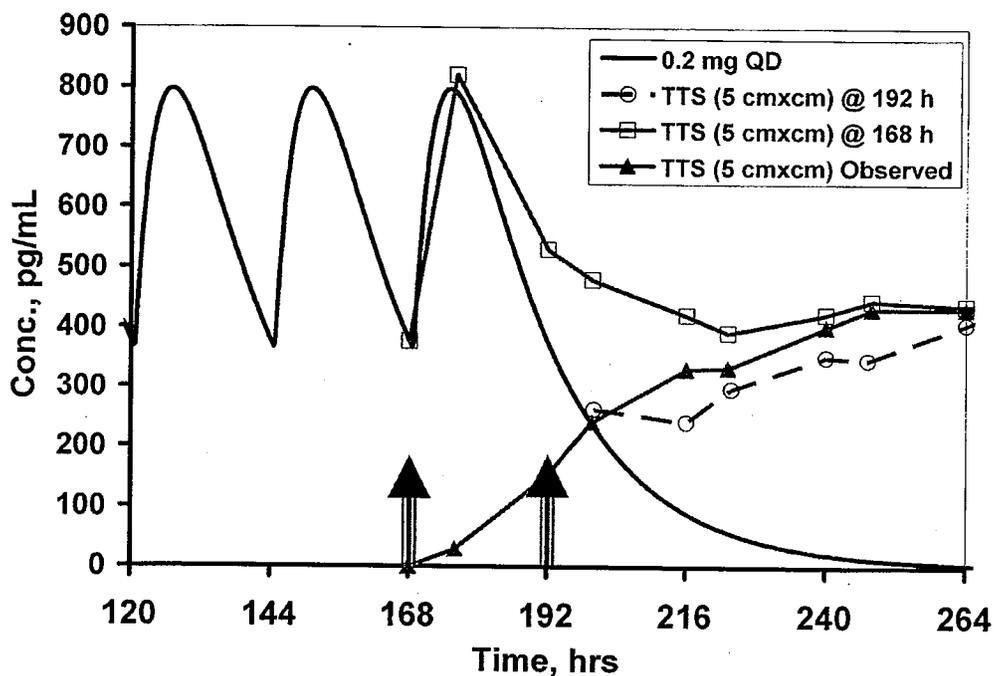
- A dose of 0.2 mg QD in severe renal impaired subjects will result in 2-3 fold increase in clonidine exposure.
- A lower dose of 0.075 mg QD results in exposures comparable to that 0.2 mg QD in subjects with normal renal function. This dose is possible with suspension formulation only. With the tablet dosage form a dose of 0.1 mg QD may be reasonable. It should be noted that 0.1 mg QD provides slightly higher exposure.
- Prolonging the inter-dosing interval (Q2Days) without dose adjustment also results in increase exposure.
- Reducing the dose along with prolonging the inter-dosing interval results in periods with lower exposure of clonidine (especially 24 – 48 hrs).

2. What is a reasonable switching regimen for switching patients at steady-state on extended release formulation to Catapres-TTS transdermal system?

The mean concentration-time course following administration of Catapres-TTS (5 cm² – 2x2.5 cm²) was reported with the Summary Basis of Approval for NDA 18-891. These exposures along with simulation with 0.2 mg QD extended release formulation to steady-state were used to simulate different switching schemes using the principle of superposition. Following the application of the transdermal patch, the steady-state plasma clonidine concentrations are reached in approximately 3 days. The concentrations

at steady-state on an average are reported to range between 400 – 480 pg/mL (~80% of the average steady-state exposure with 0.1 mg BID clonidine hydrochloride immediate release). The goal of the timing of switch from clonidine extended release formulation to the transdermal patch was to ensure that the clonidine exposures are maintained around the steady-state trough. The results of the simulations are shown in Figure 2.

Figure 2: Applying the equivalent dose of Catapres-TTS on the last day of dosing with clonidine extended release ensures average clonidine plasma exposures above the steady-state trough.



The key results of the simulations are:

- Delaying the application of patch till 24 hrs following the last dose results in plasma clonidine concentrations below the steady-state trough for at least 3 days.
- Application of the Catapres-TTS with the last dose of the extended release formulation ensures maintenance of the clonidine plasma concentration above the steady-state trough at all times.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name	
NDA-22499	ORIG-1	TRIS PHARMA INC	CLONIDINE ER ORAL SUSPENSION	b(4)
NDA-22500	ORIG-1	TRIS PHARMA INC	CLONIDINE ER ORAL TABLETS	b(4)

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/s/

RAJANIKANTH MADABUSHI

11/24/2009

Addendum to Clinical Pharmacology Review addressing the labeling recommendations for severe renal impairment and switching from ER to TTS

MEHUL U MEHTA

11/24/2009

DIVISION OF CLINICAL PHARMACOLOGY - I
Team Leader Memo

Date: September 16, 2009

NDA: 22-499/ 22-500
_____ (suspension/tablets) **b(4)**
TRIS Pharmaceuticals

Submitted: January 13, 2009

Goal Date: December 03, 2009

Reviewer: Rajanikanth Madabushi, Ph.D.
Team Leader
Division of Clinical Pharmacology I

Through: Mehul Mehta Ph.D.
Director
Division of Clinical Pharmacology I

To: The File

This memo is aimed to document my views on the interaction potential of alcohol with clonidine hydrochloride extended release formulations and the associated labeling recommendations. The memo is based in part on the primary review of Clinical Pharmacology and Biopharmaceutics by Robert O. Kumi Ph.D., (DARRTS date 09/09/2009).

***In vitro* Dissolution Study**

The sponsor performed an *in vitro* dissolution study to evaluate the effect of 0, 5, 10, and 20% alcohol at pH 1.2 on the clonidine release for Clonidine _____ ER Tablets (0.2 mg and 0.3 mg) and Oral Suspension. The study was performed to assess the potential for alcohol-induced dose dumping. Dose dumping is generally referred to as "unintended, rapid release in a short period of time the entire amount or a significant fraction of the drug contained in a modified release dosage form"¹. It must be noted that the 5% alcohol *in vitro* represents binge drinking associated with a standard drink of beer (4.5%). A 20% alcohol *in vitro* is equivalent to consuming 1 standard drink of 80 proof distilled spirits (21%). A 40% alcohol *in vitro* represents a binge drinking scenario associated with 7 standard drinks of the 80 proof distilled spirits (35%).²

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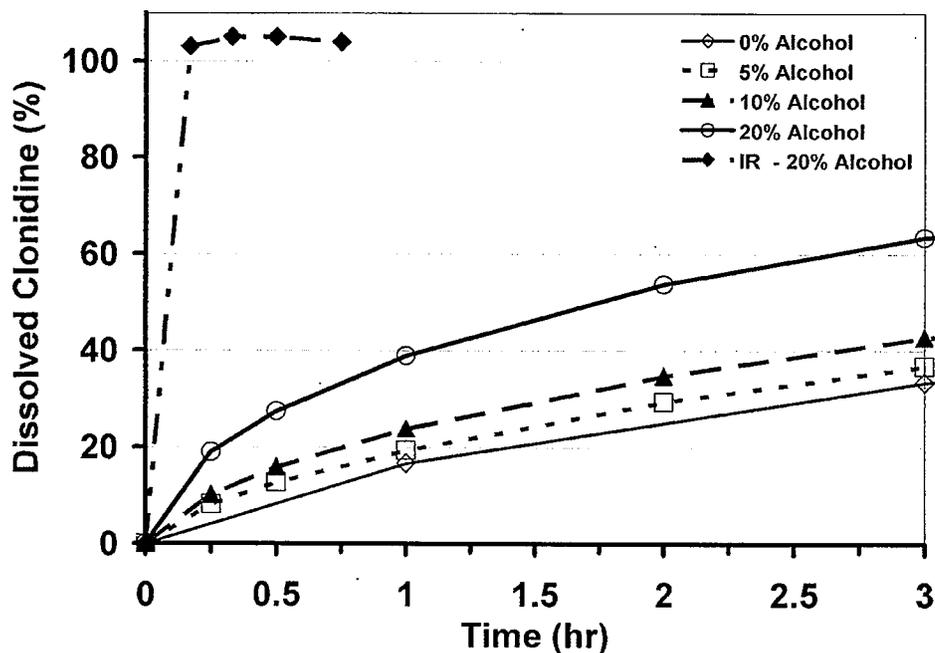
¹ Robert J. Meyers and Ajaz S. Hussain. Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms. FDA's ACPS Meeting, October 2005. http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4187B1_01_08-Alcohol-Induced.pdf

² Evaluation of the potential for alcohol induced dose dumping for oral modified release drug products
Draft MaPP: July 27, 2008

The key findings of the in vitro dissolution study are:

- The amount of clonidine dissolved increases numerically with increasing alcohol percentage for the extended release formulations as seen in Figure 1.
- Both 5 % and 10 % alcohol media had similar dissolution profiles relative to the reference for the first 3 hrs based on similarity factor testing. The dissolution at 20 % alcohol is different from that without alcohol (0 %).
- A medium containing 20 % alcohol at pH 1.2, results in an approximately 40 % increase of dissolution compared to medium without any alcohol at pH 1.2 over a 3 hour period. The amount released is not significant enough to suggest that unacceptable dose dumping occurs as seen in Figure 1.
- Under similar conditions, ~100% dissolution is achieved in 10 min for Catapres, the IR formulation.

Figure 1: No expectation of extended release clonidine formulation to revert back to an immediate release profile in the presence of alcohol. It should be noted that the extended release characteristics are altered. (Note: IR dissolution conducted till 45 min only)



- Further, 100% clonidine was not released even after 24 hrs in contact with alcohol (see appendix). This shows that the ER characteristics of the formulation are reasonably robust and are unlikely to result in dose-dumping.
- The extended release characteristics are achieved by _____
 _____ Hence the effect of alcohol

b(4)

will be evident only on the fraction of the _____ that are in substantial contact with alcohol.

b(4)

In vivo Simulations:

The potential effect of alcohol was further explored utilizing a modeling and simulation approach based on the *in vivo* pharmacokinetics data of the ER and IR formulations. The purpose of the simulations was to explore the changes on an average expected in clonidine exposure and time-course when the input rates were perturbed simulating a potential alcohol effect. This would provide further justifications for appropriate labeling and/or need for more studies.

Mean clonidine plasma concentration-time data following single dose administration of 0.2 mg ER formulation and 0.1 mg IR formulation were modeled to generate a reasonable pharmacokinetic model. This model was used to simulate plasma concentration-time course for different alcohol-effect scenarios. Based on the *in vitro* studies, a 40% and 100% increase in absorption rate constant (Ka) represent a reasonable representation of likely worst-case scenarios. The 40% increase in Ka would be extrapolation from the *in vitro* study with 20% alcohol, while the 100% increase in Ka will likely represent the effect with 40% alcohol *in vitro*.

The key findings of the modeling are:

- A robust model describing the pharmacokinetics of plasma clonidine was developed. A one-compartment open model with a lag-time in absorption was found to best fit the concentration-time course following the administration of the ER formulation. For the IR formulation, a model without lag-time was found to be a good fit. The models were able to reasonably predict the mean steady-state plasma time-course of clonidine (Figure 4 in Appendix). It should be noted that the simulations under-predict the observed steady-state C_{min} by 14% and 16% for the ER and IR formulations respectively. The C_{max} is over predicted by 7% and 14% for the first and second IR doses.

Assumptions for simulation:

- The simulations assume that the absorption rate constant is changed forever in contact with alcohol rather than a temporary modification (2 hr effect).
- The simulations assume concomitant alcohol effect with every dose till steady-state is achieved.
- The 40% and 100% increase in Ka assume linear extrapolation from *in vitro* data.

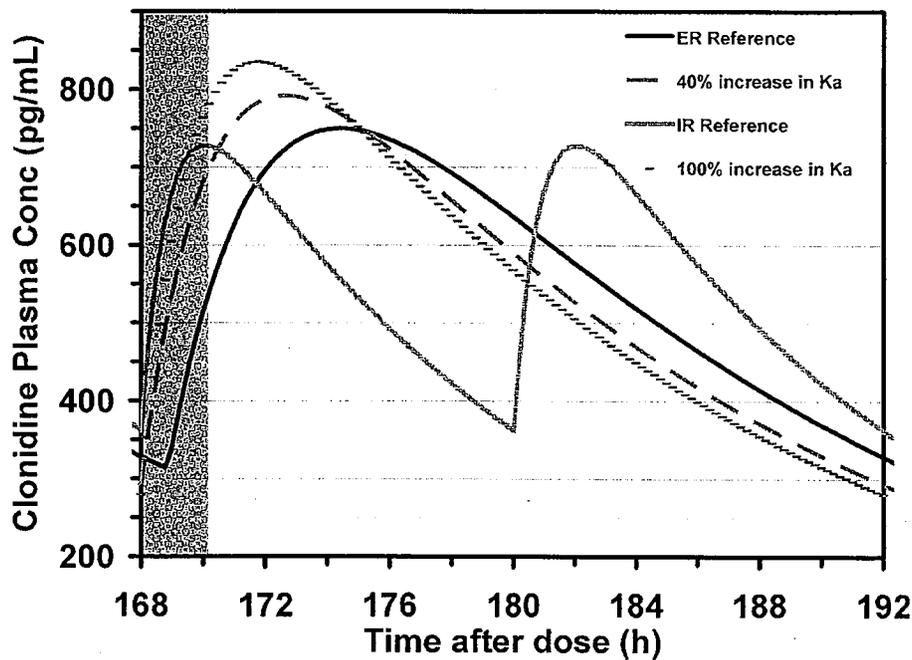
The above assumptions are reasonable and are conservative in nature. The key findings of the simulations are:

- The C_{max} can be expected to increase by 10 - 15% (see Table 1 in Appendix) compared to immediate release clonidine in the absence of alcohol as shown in Figure 2. This translates into an increase 1 - 2 mm Hg of maximal reduction in Mean Arterial Pressure (MAP)³ compared to the immediate release clonidine as expected based on the log-linear relationship. The maximum effective dose of clonidine

³ Change from baseline MAP calculated based on the log-linear relationship reported by Frisk - Holmberg M et al in Br J Clin Pharmacology 1978;6:227 - 232
Change in MAP = 35.35 . log(Plasma Clonidine Conc (ng/mL)) + 24.14
This log-linear relationship is applicable over the range of 0.2 to 2 ng/mL

- indicated in the label is 2.4 mg. Given the huge margin, these small increases in C_{max} are unlikely to be of clinical significance. Further the most common side effect associated with clonidine is drowsiness. One can expect a potentiation of this effect with clonidine, however, this is not selective to the ER formulation. This concern is already addressed in the current label for clonidine under Warnings and Precautions and Drug Interactions.
- The C_{min} on the other hand is expected to decrease by 20 – 23% (see Table 1 in Appendix) compared to immediate release clonidine (Figure 2). Given the between subject variability at C_{min} of 40 -50% and the intra-subject variability of 31% for the IR formulation (*source Table 11.4.3.13 of report tablet-steady-state-1003317-1.pdf*), the potential alcohol effect for the ER formulation is not likely to be significant. Further the mean decrease in the C_{min} translates into a 3 – 4 mm Hg of maximal reduction in MAP. This small occasional decrease in the blood-pressure effect is unlikely to result in rebound exacerbation of symptoms.

Figure 2: The potential effect of alcohol on the pharmacokinetics of clonidine ER formulation is not significant



Conclusion:

- The release characteristics of clonidine ER tablets/suspension will be altered in the presence of alcohol. The effects are comparatively more pronounced with 20% alcohol. This information should be included in the label for clonidine ER under the Drug Interactions of the Clinical Pharmacology section.
- Dose-Dumping does not occur in the presence of alcohol as high as 20%.
- Worst-case scenario simulations do not result in drastic changes in exposures.
- The potential effect of alcohol on the release characteristics of clonidine ER formulations at steady-state is not likely to be significant. Hence, no new language under Warnings and Precautions in addition to the current language is warranted.

Recommendation:

The key labeling recommendations are listed below:

12 Clinical Pharmacology

12.3 Pharmacokinetics

Drug Interactions

Alcohol: Based on in vitro studies, concomitant administration of _____ with alcohol may affect the extended release properties of _____ potentially resulting in a faster rate of release and higher than expected peak and lower than expected trough plasma concentrations of clonidine.

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Appendix:

Figure 3: Release profile at pH 1.2 with and without alcohol for a clonidine hydrochloride ER tablets (0.3 mg) and Catapres Tablets (0.3 mg)

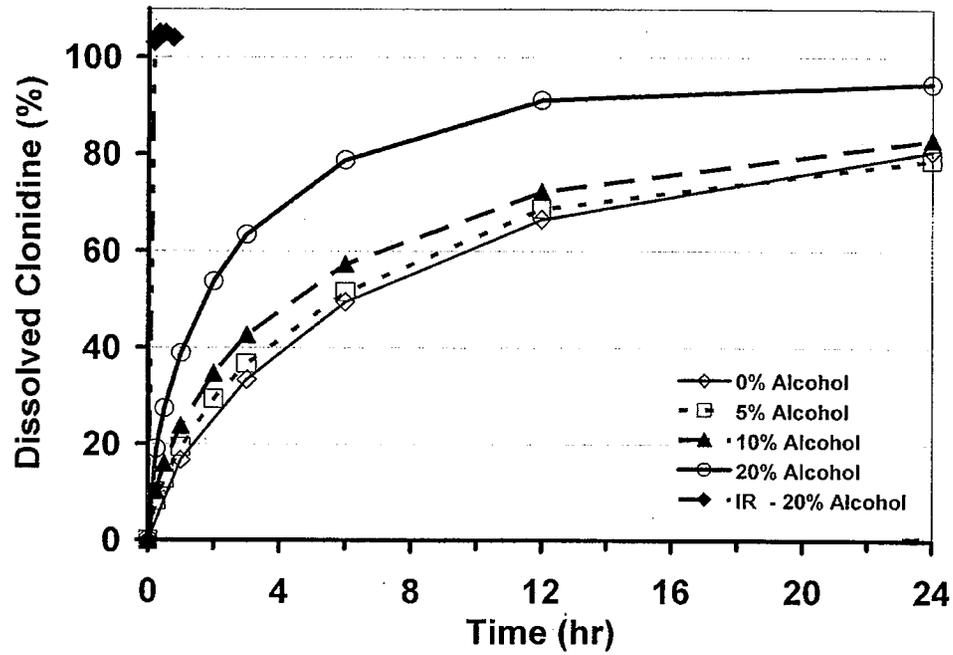


Figure 4: The pharmacokinetic model reasonably predicts the steady-state time course for ER and IR formulations

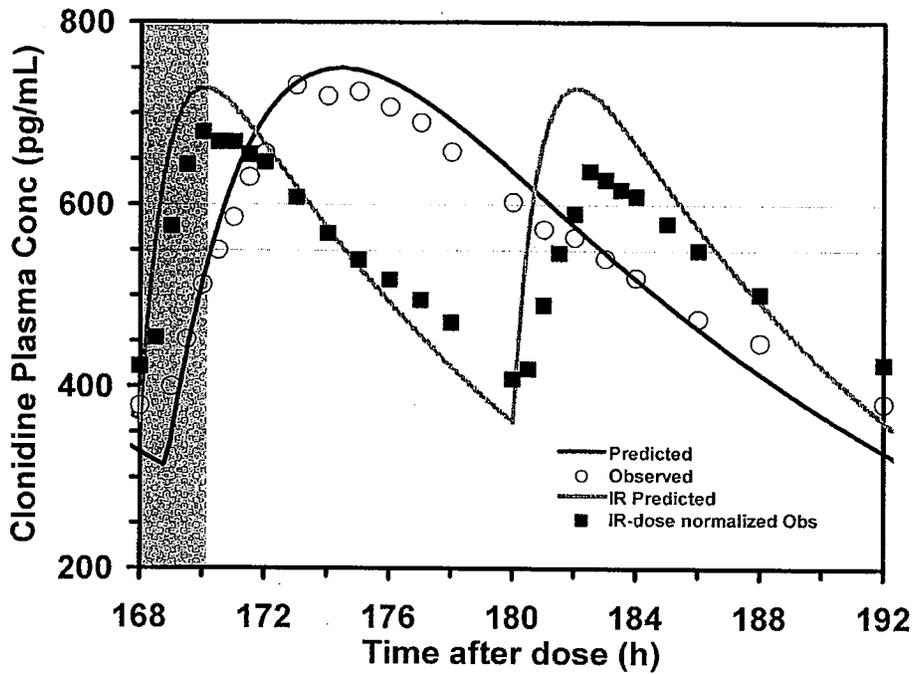


Table 1: Summary of steady-state PK characteristics for various simulation scenarios. (The numbers in the parenthesis represent % change from the corresponding IR reference)

	IR	ER	ER _{SIM40}	ER _{SIM100}
C _{max} (pg/mL)	727 (-)	758 (4%)	792 (9%)	834 (15%)
C _{min} (pg/mL)	362 (-)	328 (-9%)	293 (-19%)	279 (-23%)
T _{max} (hr)	2	6.5	4.5	3

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22499	ORIG-1	TRIS PHARMA INC	CLONIDINE ER ORAL SUSPENSION
NDA-22500	ORIG-1	TRIS PHARMA INC	CLONIDINE ER ORAL TABLETS

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/s/

RAJANIKANTH MADABUSHI
09/17/2009

MEHUL U MEHTA
09/17/2009

Clinical Pharmacology and Biopharmaceutics Review

NDA	22-499 (Clonidine ER suspension) 22-500 (Clonidine ER tablet)
INDs	102,108 (suspension) 101,635 (tablet)
Generic Name	Clonidine Hydrochloride, USP
Proposed Brand Name	
Strength and Dosage Forms	0.1 mg/mL extended release suspension and 0.2 mg and 0.3 mg extended release tablets
Indication	Treatment of hypertension
Applicant	TRIS Pharmaceuticals
Submission Type	Original NDA 505 (b)(2))
Submission Date	January 13, 2009
OCP Division	DCP1
OND Division	Division of Cardiovascular Drug Products
Reviewer	Robert O. Kumi, Ph.D.
Team Leader	Rajanikanth Madabushi, Ph.D.

b(4)

b(4)

Briefing Date: August 31, 2009

Briefing Attendees: R. Madabushi, S. Doddapaneni, I. Zdrojewski, D Menon-Andersen, I. R. Younis, M. Mehta, T. E. Ong, J. Lazor, R. Uppoor, K. Reynolds, N. Stockbridge, N. Gallaher, K. VanDerslice, A. Rahman, D. Bashaw, N. Xu, S. Targum, and R. Kumi (presenter)

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4.2.2 A 3-period, 3-treatment, 3-way crossover bioavailability study of clonidine _____ extended release oral suspension 0.1 mg/mL (2 mL) under fed and fasted conditions (Protocol 1003390) 36

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 22-499 and 22-500 and finds the information acceptable. OCP supports approval of both clonidine extended release products (ER): 0.1 mg/mL suspension and 0.2 and 0.3 mg tablets.

Comments

- 1) The application met the bioavailability criteria for extended release (ER) products as specified in the CFR and Bioavailability Guidance
 - Meets the extended release claims (decreases dosing frequency)
 - Dose dumping does not occur in the presence of food (high fat meal).
 - The steady state performance, evaluated by the area under the plasma concentration-time curve (AUC), of ER tablets was equivalent to that of the Catapres® tablets; additionally, the plasma clonidine concentrations were within the range of 0.2 and 2.0 ng/mL that is achieved with other clonidine products.
 - The ER tablet formulation provides consistent pharmacokinetic (PK) performance between individual dosage units
 - Systemic exposure (suspension and tablet) to clonidine (AUC) was equivalent to the reference approved immediate release product, Catapres®, after single dose administration under fasted conditions.
- 2) The Applicant has requested a biowaiver for evaluating steady state performance of ER suspension. This waiver request is acceptable from a clinical pharmacology perspective based on the in vivo PK information. The suspension and tablet utilize identical _____ technology and exhibit similar single dose PK characteristics. Thus, the steady state performance of the suspension is expected to be similar to that of the tablets. Further, the extended release characteristics are unlikely to be affected following administration of split scored ER tablets. b(4)
- 3) Alcohol consumption, associated with binge drinking, may modify the drug release characteristics of clonidine ER products; this conclusion is based on the in vitro dissolution results with 20 % alcohol. Pharmacokinetic simulations that required a number of assumptions suggested that relative to the immediate release reference listed product, ER formulations would have a similar T_{max} (2 – 4 hrs), higher C_{max} (~ 29 %) and lower C_{trough} (~ 25 %). In essence, alcohol may change the drug releasing characteristics of the ER to that of the IR product and make it subject to the limitations of an immediate release product. The main side effect associated with IR that occurs about an hour after the dose is transient sedation that may lead to a patient falling asleep. Additionally, rebound exacerbation of symptoms occurs at trough levels. The impact of these potential concentration changes for a patient who is stable on a titrated clonidine ER dosage has not been evaluated clinically. It is noted that current clonidine label states that clonidine may potentiate CNS-depressive effects of alcohol (Drug Interactions) and the sedative effect of clonidine may be increased by

concomitant use of alcohol (Warnings and Precautions). Bearing in mind the principal of "Safety First", the existing labeling language and the potential to modify the drug release characteristics of ER products, this reviewer recommends that the product labeling should include language to avoid alcohol consumption during therapy with clonidine ER formulations.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Regulatory Background: NDA 22-499 (oral suspension) and NDA 22-500 (oral tablet) were filed as a 505 (b)(2) applications. These NDAs were submitted for the treatment of hypertension, which is the same indication approved for the reference product, Catapres®, clonidine hydrochloride immediate release (IR) tablets.

Proposed Dosage Regimen: The clonidine ER formulations will have the identical daily dosage and titration schedule as Catapres-IR.

- Initial Dose: _____ **b(4)**
- Maintenance Dose: Further increments of 0.1 mg per day may be made at weekly intervals if necessary until the desired response is achieved.

Relative Bioavailability (Exposure Comparisons): ER formulations vs. IR tablet

- *Single Dose*

Following a total daily dose of 0.2 mg clonidine the relative bioavailability of the ER suspension and ER tablet was comparable to that of IR clonidine. The following table contains the statistical analysis for the single dose relative BA between clonidine ER formulations (TRIS) and clonidine IR (Boehringer Ingelheim)

Table 1: Statistical comparison of clonidine ER tablets and oral suspension to IR tablets in fasted state (Relative BA)

PK Measure	Study 1003390 (Oral Suspension)		Study 1003391 (Oral Tablet)	
	T/R Ratio (%)	90% CI	T/R Ratio (%)	90% CI
Cmax*	90.2	86.1 - 94.6	97.5	93.5 - 101.6
AUCt	90.9	87.3 - 94.6	94.6	91.1 - 98.2

Test = Oral Tablet is Clonidine IR (1 x 0.2 mg) tablet or Oral suspension is 2 mL of an ER oral suspension containing 0.1 mg/mL clonidine (Tris) for a total of 0.2 mg administered given after an overnight fast and given as a single dose.
Reference = 0.1 mg Catapres tablet administered at 0 and 12 hours (for a total of 0.2 mg) after an overnight fast.
Cmax* comparison is based on Cmax of ER vs. second peak of IR

b(4)

- *Multiple Dose*

Steady state AUC of clonidine is comparable after daily (8 days) administration of 0.6 mg clonidine: 0.2 mg x 3 QD clonidine ER tablets and 0.3 mg q12 hr clonidine IR. The Cmax,ss and Cmin,ss were also comparable for the two formulations. The following table contains the statistical analysis after administration of multiple doses of clonidine ER and IR.

Table 2: Statistical comparison of ER tablets (2 x 0.3 mg QD-Test) to IR tablets (0.3 mg q12 h-Reference/Catapres) at steady state (Study 1003317)

Measure	T/R Ratio (%)	90% CI
Cavg	92.71	88.78 - 96.82
Cmin	88.15	83.07 - 93.53
Cmax*	91.13	86.96 - 95.50
AUC ₀₋₂₄	94.81	90.93 - 98.87

Cmax* comparison is based on Cmax of ER vs. second peak of IR

Dose Proportionality

Clonidine exposure was dose proportional over the 0.2 to 0.6 mg daily dose range at steady state.

Pharmacokinetic Performance between Individual Dosage Units

The relatively low pharmacokinetic (PK) intrasubject variability (ISV) estimates (ISV < 10 % for all exposure measures: AUC, Cmax and Cmin) and comparability of plasma concentration-time profiles for two consecutive days in the same individual suggest that the ER tablet formulation provides consistent PK performance between individual dosage units.

Dosage Form and Strengths

- ER Oral Suspension is available in 0.1 mg/mL strength
- ER Oral Tablet is available in 0.2 mg and 0.3 mg strengths; each tablet is scored.

No in vivo data were provided for scored tablets; in addition, no in vivo comparison was made between ER oral suspension and ER oral tablets. However, the tablets are designed to disintegrate rapidly upon administration; furthermore the relative bioavailability studies demonstrated that the PK characteristics of the ER tablets and suspension are similar (see Table 1, Table 28 and Table 32); these findings suggest that the extended release characteristics are unlikely to be affected following administration of split ER tablet.

Effect of Food on the Pharmacokinetics of Clonidine after Administration of Clonidine ER

Administration of food does not lead to dose dumping of ER formulations. Food does not affect the clonidine exposure following concomitant administration of the ER formulations and a high fat meal. The statistical analysis for the food effect is summarized in the following table.

Table 3: Food Effect Information for ER formulations following administration of single 0.2 mg dose

Dependent Variable	Ratio (%) ^a	90% CI ^b	
	(Test/Ref)	Lower	Upper
	ER oral suspension		
ln(C _{max})	90.23	86.08	94.59
ln(AUC _{last})	90.88	87.34	94.56
ln(AUC _{inf})	91.95	88.72	95.30
	ER oral tablet		
ln(C _{max})	94.90	91.72	98.19
ln(AUC _{last})	95.13	90.90	99.56
ln(AUC _{inf})	94.91	90.74	99.26

^a Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref)

^b 90% Confidence Interval

Potential Effect of Alcohol on Clonidine Release Characteristics after Administration of Clonidine ER

In vitro data generated in a dissolution medium containing 20 % alcohol (associated with binge drinking) and pH 1.2 (representative of stomach) indicated that clonidine release from ER dosage forms would be 30 to 40 % greater, relative to when alcohol is not present in the stomach. The mechanism by which alcohol increases clonidine release from ER has not been determined: potentially it can be due to interaction with the _____ (polyvinyl acetate _____) or the _____ (sodium polystyrene sulfonate).

b(4)

The definitive clinical impact of the in vitro alcohol finding is unknown in the absence of in vivo information. Pharmacokinetic simulations of the plasma concentration-time profiles suggested that alcohol could have the following effects on an ER formulation: relative to the immediate release reference listed product, ER formulations would have a similar T_{max} (2 – 4 hrs), higher C_{max} (~ 29 %) and lower C_{trough} (~ 25 %).

2 Question Based Review (QBR)

An abridged version of the "question based review" (QBR) was used for NDA 22-499 (ER oral suspension) and NDA 22-500 (ER tablet). Both formulations use the same extended release technology, but are formulated differently. Please refer to the NDA for clonidine hydrochloride for additional background information on clonidine

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The two listed applications were filed as 505 (b)(2) NDAs. The reference listed drug (RLD) is Catapres® Tablets manufactured by Boehringer Ingelheim. In addition, the applications make reference to Catapres-TTS®, an approved clonidine transdermal delivery system as a secondary RLD.

One pilot and three pivotal bioavailability (BA) studies were sponsored by Tris Pharma Inc. in support of the NDA submissions. The pivotal study designs and regulatory pathway were discussed briefly in a pre-ND meeting held on April 4, 2008. The application does not include a safety and efficacy study of clonidine ER formulations, but relies on demonstration of maintenance of plasma concentrations (pharmacokinetic/BA studies) within the range obtained with approved clonidine products. In addition a biowaiver was requested for evaluating the pharmacokinetics of the suspension at steady state.

Tris has requested a

b(4)

b(4)

2.1.2. What is the proposed therapeutic indication for clonidine extended release formulations?

Clonidine, a centrally acting alpha agonist, is indicated for the treatment of hypertension. Clonidine _____ ER tablet or suspension may be employed alone or concomitantly with other antihypertensive agents.

b(4)

2.1.3. What are the proposed dosage and route of administration?

The ER dosage forms are to be given orally and at the same daily dosage as the currently approved clonidine products, Catapres (immediate release) and Catapres TTS. Clonidine is titrated to effect during antihypertensive therapy; consequently, the dosage must be adjusted according to the patient's individual blood pressure response. The following is a general guide to clonidine administration in adults, per proposed ER labels.

- Initial Dose: _____
- Maintenance Dose: Further increments of 0.1 mg per day may be made at weekly intervals if necessary until the desired response is achieved.

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The therapeutic doses most commonly employed have ranged from 0.2 mg to 0.6 mg per day

b(4)

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the pivotal studies used to support dosing or claims?

The three pivotal studies comprised two single dose trials and one repeat (multiple) dose trial. The single dose study was an open-label, randomized and three-way crossover study performed under fasting and fed conditions, where the following two comparisons were made:

- ER dosage form under fasted conditions vs. ER dosage form under fed conditions (food effect evaluation)
- ER dosage form under fasted conditions vs. IR dosage form under fasted conditions (relative bioavailability evaluation)

The total daily dose was 0.2 mg: a single 0.2 mg dose for ER formulations and 0.1 mg q 12 hr for reference IR formulation; there was a 7-day washout period between each treatment.

In the repeat dose trial, an open label, partially randomized, two-way cross over study design was employed at the 0.2 and 0.6 mg daily dose level. The primary comparison in this study was ER tablet vs. IR tablet at steady state (exposure comparison). There was an up titration and down titration phase, but no washout period between phases.

2.2.2. Are the active moieties in the plasma (or biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the active moieties in the plasma have been adequately identified and measured (Please refer to section 2.6 on Analytical Methods)

2.2.3 Exposure-Response

The application does not include an exposure-response study or clinical safety/efficacy study, but includes pharmacokinetic studies and literature references* to support the existence of an exposure (concentration) - response relationship for clonidine. The most relevant findings related to this relationship are:

- A log-linear relationship exists between clonidine concentrations (AUC) and response (blood pressure lowering) from 0.2 to 2 ng/mL
- Clonidine concentrations above 2 ng/mL result in an attenuated response, where there is a less than proportional blood pressure reduction with increasing concentration
- Concentrations above 4 ng/mL do not lead to any additional benefit

The IR formulation achieves concentrations in this range: 0.1 mg → ~ 0.2 ng/mL and 0.6 mg → ~ 2 ng/mL. The cited literature and the observed data for IR were pivotal in the development of Catapres-TTS; the TTS was engineered such that one 3.5 cm² patch would approximate the AUC obtained with 0.1 mg/day or oral IR clonidine. In general, transdermally delivered clonidine gives steady-state plasma concentrations similar to oral therapy without the peak and trough effect. Steady state concentrations are achieved

approximately three days after application of the patch. Thus, there is precedent in targeting an exposure for approval of a clonidine formulation with a slower delivery rate than oral IR clonidine.

The approval of the ER formulations relies on the ability of the proposed ER formulations to match the exposure of the IR formulation and to maintain plasma concentrations in the range (~ 0.2 to 2.0 ng/mL) of prior approved clonidine products.

* Selected Literature References: Davies et al., 1977; Frisk-Holmberg M, et al., 1984; Wing LM, et al., 1977; Lowenthal DT, et al., 1988).

^ Summary basis of approval for Catapres-TTS (FDA 1984)

2.2.3.1 Does administration of clonidine ER tablets 0.2 to 0.6 mg/day achieve clonidine concentrations within the range (0.2 to 2 ng/mL) of approved products?

Overall, the proposed ER tablet will have concentrations that fall within those of the prior approved products. This assertion is supported by the following two figures: 0.2 mg QD produces concentrations between 0.35 and 0.8 ng/mL whereas 0.6 mg QD produces concentrations between 1.4 and 2.4 ng/mL.

Figure 1: Mean clonidine plasma concentration-times after administration of clonidine ER 0.2 mg QD (test Treatment A) on Study Day 7 (7) and Study Day 8 (8)

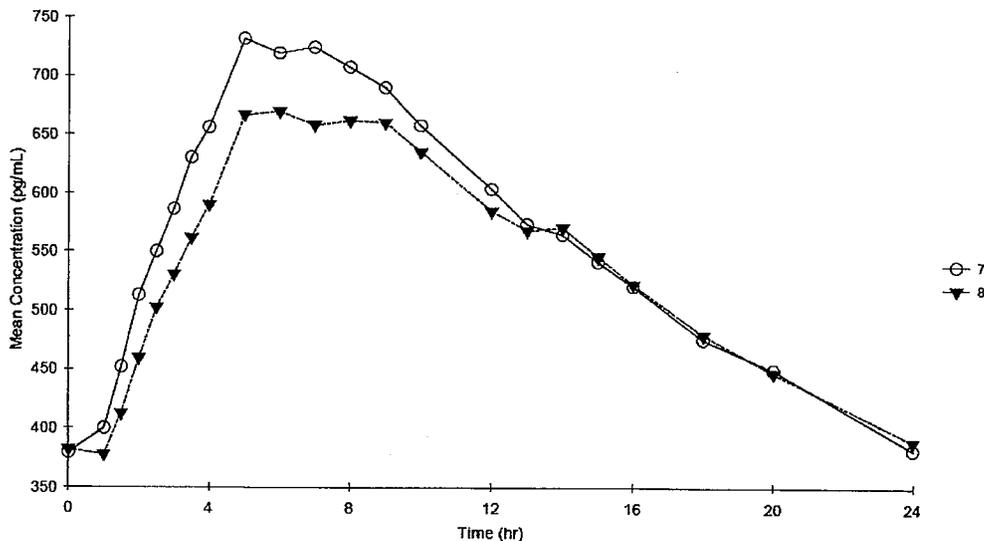
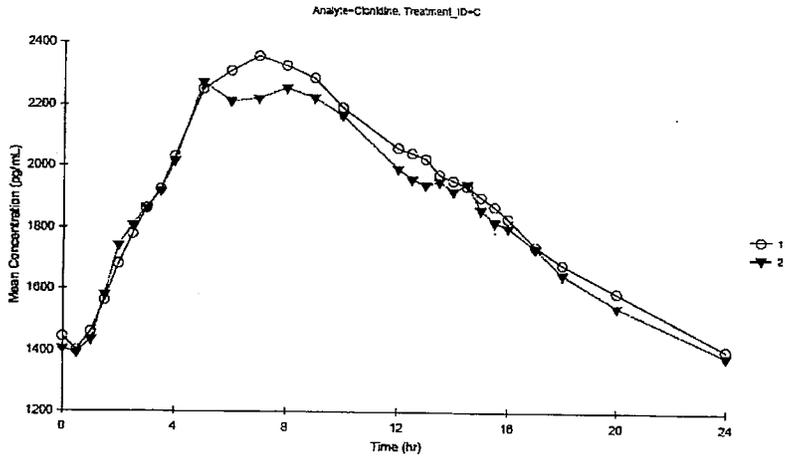


Figure 2: Mean clonidine plasma concentration-times after administration of clonidine ER 2 X 0.3 mg QD (test Treatment C) on Steady State Day 1 (1 = Study Days 21 and 29) Steady State Day 2 (2 = Study Days 22 and 30)



2.2.4 Exposure Comparisons

2.2.4.1 Are the clonidine exposures of ER dosage forms comparable to IR dosage forms after single dose administration (Relative Bioavailability Assessment?)

The AUC₀₋₂₄ of ER suspension and ER tablets under fasted conditions were comparable to that of IR tablet fasted after single dose administration. Similarly, the C_{max} (vs. second peak of IR) were comparable for ER formulation and IR formulations. The Applicant did not provide the basis for choosing the second peak for the comparison.

The sponsor conducted an open-label, three-way crossover study; two of the treatment arms were conducted under fasting conditions to assess relative bioavailability. The following table contains the statistical analysis for clonidine after administration of ER clonidine and IR clonidine.

Table 4: Statistical comparison of clonidine ER tablets and suspension to IR tablets in fasted state (Relative BA)

Measures	Study 1003390(Oral Suspension)				Study 1003391(Oral Tablet)			
	Geometric Means		T/R (%)	90% CI	Geometric Means		T/R (%)	90% CI
	Test	RLD			Test	RLD		
C _{max} (pg/mL)	508.7	563.8	90.2	86.1 - 94.6	555.5	569.8	97.5	93.5 - 101.6
AUC _T (pg·hr/mL)	12840	14130	90.9	87.3 - 94.6	13557	14336	94.6	91.1 - 98.2
AUC _{0-∞} (pg·hr/mL)	13411	14585	92.0	88.7 - 95.3	14000	14798	94.6	91.2 - 98.2

Test = Oral Tablet is Clonidine ER (1 × 0.2 mg) tablet or Oral suspension is 2 mL of an ER oral suspension containing 0.1 mg/mL clonidine (Tris) for a total of 0.2 mg administered given after an overnight fast and given as a single dose.

Reference = 0.1 mg Catapres tablet administered at 0 and 12 hours (for a total of 0.2 mg) after an overnight fast.

* The applicant did not provide a basis for selecting the second peak for the comparison

b(4)

2.2.4.2 Are the clonidine exposures of ER dosage forms comparable to IR dosage forms after repeat dose administration?

The exposure (AUC_{0-24}) following a total daily dosage of 0.6 mg Clonidine ER tablets (0.6 mg QD) and Catapres IR (0.3 mg q12 hr) are comparable at steady-state. Clonidine C_{max} (ER C_{max} vs. second peak of IR), C_{avg} and C_{min} were also comparable for the two formulations. The basis for choosing the second peak for the comparison is unclear.

The applicant conducted an open-label, two-way crossover and partially randomized study to compare the exposure of ER tablets and IR at steady state.

The following figure and table demonstrate the comparability in exposure of the IR (Treatment D) and ER (Treatment C) formulations at steady state.

Figure 3: Reviewer generated plasma concentration time profiles for Treatment C (0.6 mg QD via two 0.3 mg ER tablets) and Treatment D (0.3 mg q12hr via 0.3 mg Catapres IR tablet) on last day of dosing

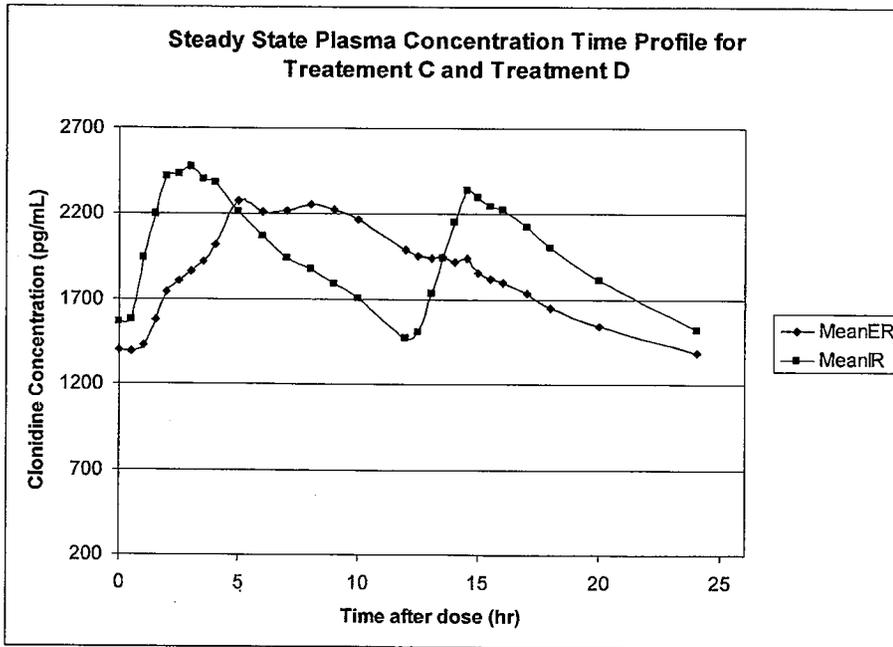


Table 5: Statistical comparison of ER tablets (2 x 0.3 mg QD- Test) to IR tablets (0.3 mg q12 h- Reference/Catapres) at steady state (Study 1003317)

Dependent Variable	GeoMean ^b Test	GeoMean ^b Ref	Ratio (%) ^d (Test/Ref)	90% CI ^e	
				Lower	Upper
$\ln(C_{avg})$	1744.0752	1881.1723	92.71	88.78	96.82
$\ln(C_{min})$	1188.7509	1348.6152	88.15	83.07	93.53
$\ln(C_{max}^*)$	2269.4214	2490.2590	91.13	86.96	95.50
$\ln(AUC_{0-12})$	22968.7459	22574.0678	101.75	97.14	106.57
$\ln(AUC_{0-24})$	41857.8043	44147.0585	94.81	90.93	98.87

* The applicant did not provide a basis for selecting the second peak for the comparison

2.2.5. Are the concentrations of clonidine proportional after administration of Clonidine ER tablets from 0.2 mg to 0.6 mg daily dose?

The results of the assessment of dose proportionality (Reviewer Generated) suggest that clonidine exposure is dose proportional between 0.2 to 0.6 mg daily dose. The applicant did not conduct a dose-proportionality study.

Table 6: Assessment of clonidine dose proportionality of ER tablet at two dose levels

Value	Actual		Dose Normalized		Ratio
	0.2 QD	0.6 QD	0.2 QD	0.6 QD	
AUC ₀₋₂₄	12840	44290	64200	73817	1.15
C _{max}	694	2370	3470	3950	1.14
C _{min}	360	1300	1800	2167	1.20

* 0.2 dose obtained by using one 0.2 mg ER tablet and 0.6 mg dose obtained by using two 0.3 mg tablets

This finding of dose proportionality is consistent with clonidine literature following administration of IR formulations. However, the assessment of dose proportionality (PK linearity) in the current NDA is limited by the fairly narrow dose range and the availability of data from only two dose levels.

2.2.6 Does the ER tablet formulation (0.3 mg strength) provide consistent pharmacokinetic performance between individual dosage units?

The ER tablet appears to provide consistent pharmacokinetic performance between individual dosage units. This conclusion is based on the findings related to intrasubject variability and inspection of plasma concentration time profiles.

Apart from C_{min} for the IR formulation, the ANOVA CV% (a measure of intrasubject variability/ISV) for comparisons of C_{min}, C_{max}, and AUC₀₋₂₄ across study days within treatment (Clonidine ER Tablet 2 x 0.3 mg QD and Catapres 0.3 mg BID) was less than 10%. Overall, the plasma concentration-time profiles of individual subjects for the two consecutive days were comparable. One anticipates that the 0.2 mg tablets and suspension should also have low ISV because they are derived from the same drug substance and utilize the same technology.

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The ISV was estimated by using pharmacokinetic data from Periods 1 and 2 between two consecutive steady state dosing intervals (Day 21/29 vs. Day 22/30), for Clonidine ER Tablet and Catapres separately. The ISV estimates are tabulated below.

b(4)

Table 7: Estimation of intrasubject variability for Treatment C and Treatment D (based on comparison of two consecutive dosing days; steady state Day 1 vs. Day 2)

Dependent Variable	ISV as CV (%)	Comment*
Extended Release Formulation, Treatment C		
Ln C _{min}	9.22	Satisfactory
Ln C _{max}	8.27	Satisfactory
Ln AUC ₀₋₂₄	5.97	Satisfactory
Immediate Release formulation, Treatment D		
Ln C _{min}	31.22	Unsatisfactory
Ln C _{max}	7.96	Satisfactory
Ln AUC ₀₋₂₄	4.75	Satisfactory

2.2.7 When is steady state attained?

Steady state was attained within six days following once daily administration of ER tablet. Similarly the IR formulation achieved steady state within six days on a twice daily schedule.

The attainment of steady state was assessed by comparing trough concentrations over four days (Days 5 to 8) for three daily treatments: 0.2 mg QD of ER tablet (1 x 0.2 mg tablet), 0.6 mg QD for ER tablets (2 x 0.3 mg tablets) and 0.3 mg q12 hr for IR tablets (2 x 0.3 mg tablet). Using Tukey’s test for significance, p was > 0.05 for all pairwise comparisons (Days 5 to Days 8) in all treatments. This finding indicates that trough concentrations were comparable from Days 5 to 8 and that steady state was attained by Day 6.

2.2.8 What is the overall adverse events profile in Phase 1 studies reported by the applicant and what are potential safety and compliance implications?

In the multiple dose study, adverse events with the Clonidine ER Tablet were similar to Catapres. These events are tabulated below and are common for centrally acting alpha antagonists.

b(4)

Table 8 Summary of the Most Common Adverse Effects Seen with Catapres Use^a

System	Adverse Effects Seen
Digestive	Dry mouth (40%)
Central Nervous System	Drowsiness (33%), dizziness (16%), and sedation (10%)
Gastrointestinal	Constipation (10%)

^a Information from Catapres labeling (Boehringer Ingelheim, 2007a;Boehringer Ingelheim, 2007b).

The potential safety advantages of the proposed ER formulations are based on achieving therapeutic concentrations within the range of approved products and improving the following relative to approved clonidine products:

- TTS: Produces a high rate of contact dermatitis. Additionally, there are problems with patch adherence to the skin in humid environments and with active individuals. The patch may need replacement after extended swimming or exertion.
- IR: The main side-effects are dry mouth and drowsiness, which occurs particularly about an hour after the given dose when the patient may become transiently sedated, even falling asleep. Additionally, rebound exacerbation of symptoms occurs at trough levels.

The clonidine ER Tablet and Clonidine ER Oral Suspension will provide more stable serum levels compared to Catapres tablets. Furthermore, these ER formulations may be more convenient or acceptable for the patient than BID dosing (Catapres) or the transdermal patch, therefore may improve patient compliance.

b(4)

2.3 Intrinsic Factors

The role of intrinsic factors on clonidine exposure-response was not evaluated in NDAs 22-499 and 22-500.

2.4 Extrinsic Factors

The role of extrinsic factors on clonidine exposure-response was not evaluated in NDAs 22-499 and 22-500.

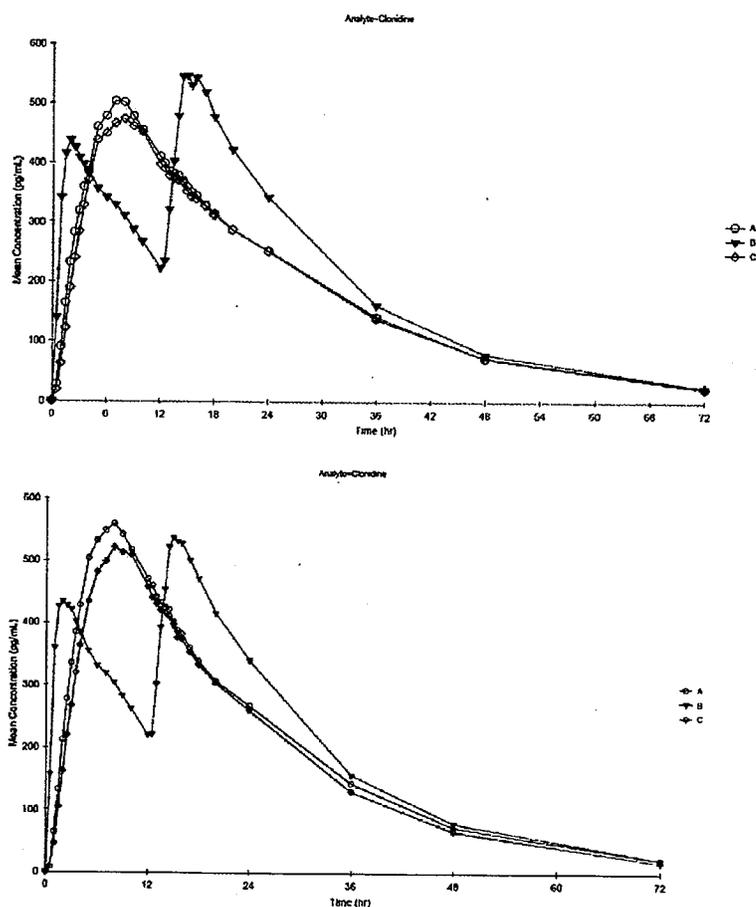
2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the bioavailability of clonidine from ER formulations?

Food did not alter the bioavailability of clonidine from ER oral suspension or ER tablet following concomitant administration of a high-fat/high calorie meal and the respective ER formulations.

Standard food effect studies were conducted with the recommended FDA high-fat meal. The plasma concentration time-profiles in the presence and absence of food are depicted in the following two figures*.

Figure 4: Food Effect Plasma concentration time profiles for suspension (upper panel) and tablet (lower panel) following administration of clonidine ER formulations (0.2 mg single dose) [Treatment A is under fasted conditions and Treatment C is under fed conditions]



* Treatment B is the reference IR formulation

- **Oral Suspension**

The PK measures and statistical comparisons for the ER oral suspension are summarized in the following two tables.

Table 9: Food Effect Information for ER Oral Suspension

Measure	<u>Treatment A (n = 24):</u> Test Formulation (Fasted)		<u>Treatment C (n = 25):</u> Test Formulation (Fed)	
	Mean	SD	Mean	SD
T_{max} (hr)	7.42	0.83	7.80	1.71
C_{max} (pg/mL)	516	85.3	488	89.4
AUC_{inf} (hr*pg/mL)	13640	2627	13370	3393
T_{1/2} (hr)	13.27	2.53	13.69	2.99

Table 10: Food Effect Information for ER Oral Suspension

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b	90% CI ^c	
	Test	Ref	(Test/Ref)	Lower	Upper
ln(C _{max})	508.74	563.81	90.23	86.08	94.59
ln(AUC _{last})	12840.29	14129.59	90.88	87.34	94.56
ln(AUC _{inf})	13411.14	14585.05	91.95	88.72	95.30

^a Geometric Mean for the Test Formulation-Fed (Test) and Test Formulation-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

- **Oral Tablet**

The PK measures and statistical comparisons for the ER oral tablet are summarized in the following two tables.

Table 11: Food Effect Information for ER Oral tablet

Parameter	<u>Treatment A (n = 25):</u> Test Formulation (Fasted)		<u>Treatment C (n = 26):</u> Test Formulation (Fed)	
	Mean	SD	Mean	SD
T_{max} (hr)	7.72	1.24	8.27	1.56
C_{max} (pg/mL)	575	108	539	105
AUC_{inf} (hr*pg/mL)	14560	3352	13560	3389
T_{1/2} (hr)	13.06	2.20	12.38	1.81

Table 12: Statistical comparisons for food effect ER Oral tablet

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c	
	Test	Ref		Lower	Upper
ln(C _{max})	533.58	562.26	94.90	91.72	98.19
ln(AUC _{last})	13007.64	13673.08	95.13	90.90	99.56
ln(AUC _{inf})	13400.51	14119.55	94.91	90.74	99.26

^a Geometric Mean for the Test Formulation-Fed (Test) and Test Formulation-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

In sum food does not lead to dose dumping from the ER formulations; thus clonidine ER formulations can be administered with or without food.

2.5.2 What is the effect of alcohol on the dissolution of clonidine ER formulations (Assessment of alcohol induced dose dumping)?

Consumption of large amounts of alcohol in a relatively short period of time, a situation likely to occur during binge drinking, may lead to an increase in the amount of clonidine released from an ER formulation in the stomach (pH ~ 1.2). This conclusion is based on in vitro dissolution data, where a medium containing 20 % alcohol at pH 1.2, results in an approximately 40 % increase of dissolution compared to medium without any alcohol at pH 1.2 over a 3 hour period. This 40 % delta is maintained over a 24 hour period, although, time points beyond 5 hours are unlikely to bear clinical relevance.

Dissolution data were generated using 12 dosage units each of the test (ER suspension or tablet) and reference product (Catapres IR). The characteristics of the dissolution methodology were as follows:

- Apparatus: USP Type 11 (Paddle)
- Speed: 50 rpm
- Medium: pH1.2 (0.1 N HCl) with alcohol content of 0, 5, 10 and 20 % in a total volume of 900 mL
- Sampling times: ranged from 0 to 24 hrs, but less intensive sampling with 0 % alcohol vs. other alcohol contents

The profiles and f2 calculations that support the conclusion are presented in the following figures and table, respectively.

Reviewer Note on Suitability of 5 % alcohol as a reference medium

In this reviewer's opinion, the comparison of 10 % and 20 % vs. 5 % alcohol over a 3 hr period is the most appropriate one because it provides a reasonable number of time-matched points relative to the zero alcohol medium and has clinical relevance (stomach emptying is complete within 5 hrs vs. 24 hrs). Furthermore, the dissolution in 5 % alcohol and no alcohol were similar over a 24-hour period. The major limitation associated with 5 % alcohol is the fact that it is not an absolute reference for the impact of alcohol

Clinical Impact (Labeling Considerations) of Alcohol Dose Dumping Assessment

The applicant concluded that dissolution increases with increasing alcoholic content, but the increase in dissolution is not great enough to suggest that dose dumping occurs. Consequently, the applicant did not make labeling comments nor consider conducting a follow-up clinical trial. The conclusion that dose-dumping does not occur at 5 and 10 % alcohol concentrations is reasonable, taking the following definitions of dose-dumping into account:

"...premature release of the drug (dose dumping) from the formulation" [Ref: Office of Generic Drugs Guidance: Oral extended (controlled) release dosage forms in vivo bioequivalence and in vitro dissolution testing] or *"the rapid release of a dose of the drug that was meant to be administered over several hours"* [Ref: Modified-Release Drug Delivery Technology, Volume 2, M. Rathbone]

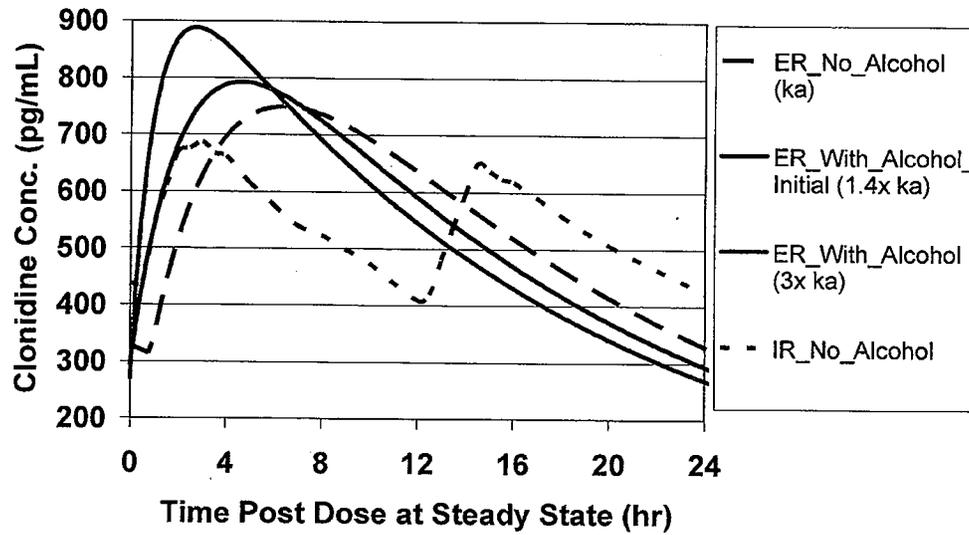
However, alcohol (20 %) clearly modifies the in vitro drug release rate from ER products. Further exploration of the potential alcohol effect was performed based on the in vivo pharmacokinetics data of the ER product. A robust compartment model was developed to describe the time course of plasma clonidine concentrations following single dose administration of the ER tablet. This model was developed and utilized for simulating scenarios that may represent likely alcohol effects. The key findings of the simulations (putative worst-case scenarios, where the absorption rate constant was approximately increased 3-fold and lag time set to zero hours - a scenario in which alcohol and the ER formulation interact for a period greater than six hours) are:

- C_{max} of ER formulation increases from ~ 750 to 900 pg/mL (19% increase) in the presence of alcohol
- C_{min} of ER formulation reduces from 330 to 270 pg/mL (18% decrease) in the presence of alcohol
- Furthermore, relative to IR without alcohol, the C_{max} of ER formulation with alcohol is about ~200 pg/mL greater (29% increase) whereas the C_{min} is about 150 pg/mL lower (25% decrease).

It should be noted that this "worst-case" scenario may not occur as a contact time of 2 to 3 hrs with alcohol is considered to be clinically relevant. Nevertheless, the observed signal with alcohol is significant enough in this reviewer's opinion to warrant a precautionary statement in the label. Consequently, this reviewer recommends that the labeling reflect the fact that (excessive) alcohol consumption may increase the rate of release of clonidine from ER products, thereby modifying the intended slower delivery rate of the product. Thus, alcohol use should be avoided during clonidine therapy with ER formulations.

Figure 6: Plots of observed and simulated data to evaluate the effect of alcohol on clonidine pharmacokinetics

Observed (ER and Dose Normalized IR) and Simulated Plasma Concentration-Time Profiles



2.5.3. *What are the compositions of clonidine ER formulations?*

Both formulations achieve their extended release characteristics via the [redacted] b(4)

In both products the clonidine drug substance is [redacted] b(4)

The clonidine tablet is a [redacted] dosage form that was designed [redacted]

In- active ingredients in the tablet formulation were selected to provide good [redacted] characteristics without [redacted] b(4)

The following two tables provide the quantitative composition of ER clonidine dosage forms.

Table 14: Quantitative composition of 0.1 mg/mL Clonidine [redacted] ER Oral Suspension b(4)

Ingredients	Function	Quantity (mg/mL)
Sodium Polystyrene Sulfonate	[redacted]	[redacted]
Clonidine Hydrochloride USP	Active	0.1
Povidone USP	[redacted]	[redacted]
Polyvinyl Acetate	[redacted]	[redacted]
Triacetin USP	[redacted]	[redacted]
Purified Water USP	[redacted]	[redacted]
Citric Acid USP (Anhydrous)	[redacted]	[redacted]
Polysorbate 80 NF	[redacted]	[redacted]
High Fructose Corn Syrup	[redacted]	[redacted]
Sucrose NF	[redacted]	[redacted]
Glycerin USP	[redacted]	[redacted]
Methylparaben NF	[redacted]	[redacted]
Propylparaben NF	[redacted]	[redacted]
Xanthan Gum NF	[redacted]	[redacted]
Strawberry Banana Flavor	[redacted]	[redacted]

b(4)

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1 Sodium Polystyrene Sulfonate USP
 2 Amount represents [redacted]
 3 Amount represents [redacted] basis

Table 15: Quantitative composition of Clonidine ER tablets

Ingredients	Function	Quantity (mg/tablet) 0.2 mg tab	Quantity (mg/tablet) 0.3 mg tab
Sodium Polystyrene Sulfonate			
Clonidine Hydrochloride USP	Active	0.2	0.3
Povidone USP			
Polyvinyl Acetate			
Triacetin USP			
Microcrystalline Cellulose NF			
Lactose Monohydrate NF			
Crospovidone NF			
Dental-Type Silica NF			
Magnesium Stearate NF			
Total			
¹ Sodium Polystyrene			
² Ammonium			

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b(4)

• **Relative bioavailability assessment: ER tablet vs. suspension**

The bioavailability of the ER tablet was not compared to the ER suspension. This information would have been useful for situations where switching from one ER form to the other is necessary; however, the information is not critical as the product is titrated to effect and both products had similar exposure relative to the approved clonidine IR product.

2.6 Analytical Methods

2.6.1 What bioanalytical methods are used to assess concentrations?

In the pivotal pharmacokinetic studies, clonidine concentrations were determined by a validated LC/MS/MS method. Overall, the assay performance was acceptable and had the following characteristics in the validation study and individual pharmacokinetic studies:

- Calibration range 8 to 1500 pg/mL with $R^2 > 0.988$ b(4)
- Lower limit of quantification 8 pg/mL
- Precision (measured as % CV) b(4)
- Accuracy (measured as relative bias)
- Specificity was demonstrated via representative chromatograms

3 Detailed Labeling Recommendations

Overall, the applicant's proposed labeling is acceptable with some minor editorial changes. The key OCP recommendations are listed below.

Warnings and Precautions

Excessive alcohol consumption may cause premature and exaggerated release (dose dumping) of clonidine. Alcohol consumption should be avoided or minimized during therapy with _____

b(4)

Drug Interactions

Potential for Alcohol Induced Dose Dumping

Based on in vitro studies, excessive consumption of alcohol may result in an increased rate of clonidine release from _____ This may lead to the loss of controlled clonidine delivery and increase the occurrence of adverse events. Consequently, alcohol consumption should be avoided during clonidine therapy.

b(4)

4 Detailed Appendices

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ON ORIGINAL**

4.1 Proposed labeling with OCP comments and edits

Please refer to Detailed Labeling Recommendations (Section 3) and the EDR for the applicant's proposed draft labeling (\\CDSESUB1\EVSPROD\NDA022499 and \\CDSESUB1\EVSPROD\NDA022500)

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ON ORIGINAL

4.2 Individual Study Reviews

**APPEARS THIS WAY
ON ORIGINAL**

4.2.1 A study to evaluate the steady-state plasma concentrations of 0.2 mg TRIS clonidine ~~_____~~ extended release tablets and steady state plasma concentrations of TRIS clonidine ~~_____~~ release tablets versus Catapres® at a 0.6 mg daily dose in mild to moderate hypertensive patients [Protocol 1003317]

b(4)

PRINCIPAL INVESTIGATORS	Steven Hinit, M.D., M.P.H., M.P.A and Frederick A. Bieberdorf, M.D., CPI
STUDY SITE	CEDRA, Clinical Research, LLC, Austin, Texas and San Antonio, Texas
STUDY PERIOD	October – December 2008

Objectives (per Applicant)

To evaluate the steady state plasma clonidine concentrations of the 0.2 mg TRIS Clonidine ~~_____~~ Extended Release Tablet formulation and to evaluate steady-state plasma clonidine concentrations of both the 0.6 mg (2 x 0.3 mg) TRIS Clonidine ~~_____~~ Extended Release Tablet and Catapres® formulations.

b(4)

Study Design

This was an open-label, randomized, steady-state, multi-dose study where 32 patients with mild to moderate hypertension, otherwise healthy, received Clonidine ~~_____~~ Extended Release tablets once daily or Catapres® (immediate-release) tablets every 12 hours. Doses were titrated up to a maximum total daily dose of 0.6 mg.

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There were four treatment groups:

- Treatment A: clonidine ~~_____~~ ER, 1 x 0.2 mg tablet, daily morning dose
- Treatment B: clonidine ~~_____~~ ER, 2 x 0.2 mg tablet, daily morning dose
- Treatment C: clonidine ~~_____~~ ER, 2 x 0.3 mg tablet, daily morning dose
- Treatment D: Catapres®, 1 x 0.3 mg tablets, every 12 hours

b(4)

The dosing details and pharmacokinetic assessment days are outlined in the following figure.

Figure 7: Dosing Scheme for Steady State Evaluation

	Daily Dose	Study Days	Patient Randomization
Upward Titration Phase	Treatment A Clonidine  Extended Release Tablet 0.2 mg QD	Days 1 – 8 (steady state PK assessment on Day 7 & 8)	All Patients
	Treatment B Clonidine  Extended Release Tablets 0.4 mg (2 x 0.2 mg) QD	Days 9 – 14	All Patients
0.6 mg Phase	Treatment C Clonidine  Extended Release Tablets 2 x 0.3 mg QD OR Treatment D Catapres® 0.3 mg Q12H	Days 15-22 (steady state PK assessment on Day 21 & 22)	Patients Randomized 1:1 To Treatments
	Treatment C Clonidine  Extended Release Tablets 2 x 0.3 mg QD OR Treatment D Catapres® 0.3 mg Q12H	Days 23-30 (steady state PK assessment on Day 29 & 30)	Patients Cross Over to Receive Alternate Treatment from Days 23-30
Downward Titration Phase	Treatment B Clonidine  Extended Release Tablets 0.4 mg (2 x 0.2 mg) QD	Days 31-33	All Patients
	Treatment A Clonidine  Extended Release Tablet 0.2 mg QD	Days 34-36	All Patients
	Resume any previous antihypertensive medications as prescribed by primary care physician	Day 37	All Patients on Previous Treatment

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Formulation

- Clonidine  ER 0.2 mg tablet; Lot # TB-021A (TRIS)
- Clonidine  ER 0.3 mg tablet; Lot TB-020A (TRIS)
- Catapres ®0.3 mg tablets; Lot #755233 (Boehringer Ingelheim)

b(4)

Blood (pharmacokinetic) sampling schedule

Blood samples were collected for pharmacokinetic purposes during each dosing period according to the following tabulated schedule.

Table 16: Pharmacokinetic sampling schedule

Study Day	Pharmacokinetic Sample Schedule
Day 1	Pre-dose (0-hour)
Day 5	Pre-dose (trough)
Day 6	Pre-dose (trough)
Day 7	Pre-dose (trough), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 18, and 20 hours
Day 8	0 (24-hour Day 7 & pre-dose Day 8), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 18, and 20 hours
Day 9	0 (24-hour Day 8 & pre-dose Day 9)
Day 19	Pre-dose AM (trough)
Day 20	Pre-dose AM (trough)
Day 21	Pre-dose (trough), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 17, 18, and 20 hours
Day 22	0 (24-hour Day 21 & pre-dose Day 22), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 17, 18, and 20 hours
Day 23	0 (24-hour Day 22 and pre-dose Day 23)
Day 27	Pre-dose (trough)
Day 28	Pre-dose (trough)
Day 29	Pre-dose (trough), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 17, 18, and 20 hours
Day 30	0 (24-hour Day 29 & pre-dose Day 30), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 17, 18, and 20 hours
Day 31	0 (24-hour Day 30 and pre-dose Day 31)

Bioanalytical methods

Clonidine concentrations were determined using a validated LC-MS-MS method. The assay performance was acceptable as illustrated in the following table.

Table 17: Performance of clonidine assay in steady state study

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the _____ pg/mL range; $R^2 > 0.991$	Satisfactory
Between day Precision	CV was _____	Satisfactory
Accuracy (percent bias)	QC samples were within _____ of nominal concentration	Satisfactory
LLOQ	8 pg/ml	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

b(4)

b(4)

Pharmacokinetics

Steady-state pharmacokinetics were assessed at the 0.2 and 0.6 mg daily dose levels for TRIS Clonidine Extended Release tablets and at the 0.3 mg q12 hr (0.6 mg/day) dose level daily for Catapres tablets. Data were analyzed by noncompartmental methods in WinNonlin (Version 4.0, Pharsight Corporation). Several clonidine pharmacokinetic measures were estimated including T_{max} , C_{max} , AUC , AUC_{inf} , AUC_{Extrap} , λ_z , $T_{1/2}$, T_{last} , C_{last} , accumulation index, and percent fluctuation. Additionally, time to reach steady-state, relative exposure comparisons and intrasubject variability estimations were made using standard pharmaco-statistical approaches.

b(4)

Results

Clonidine Pharmacokinetics

The mean clonidine plasma concentration-time profiles following administration of clonidine ER and IR tablets are depicted in the following three figures.

Figure 8: Mean clonidine plasma concentration-times after administration of clonidine ER 0.2 mg QD (test Treatment A) on Study Day 7 (7) and Study Day 8 (8)

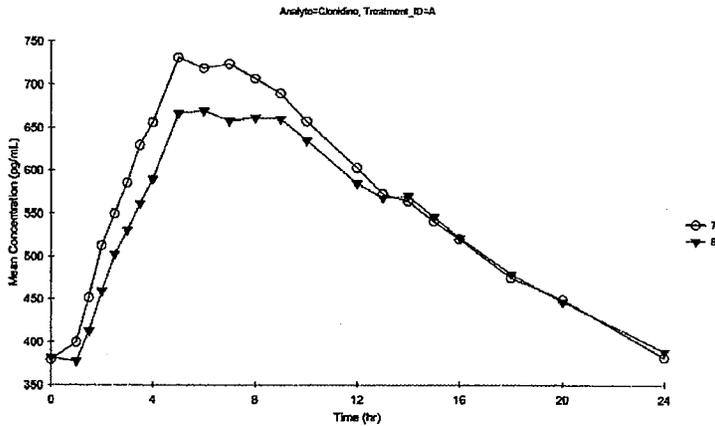


Figure 9: Mean clonidine plasma concentration-times after administration of clonidine ER 2 X 0.3 mg (0.6 mg) QD (test Treatment C) on Steady State Day 1 (1 = Study Days 21 and 29) Steady State Day 2 (2 = Study Days 22 and 30)

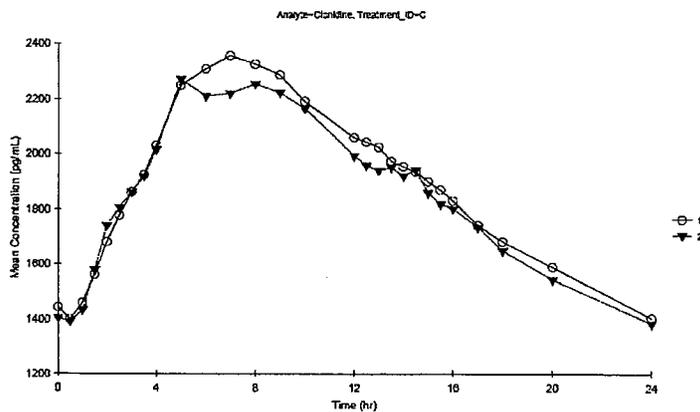
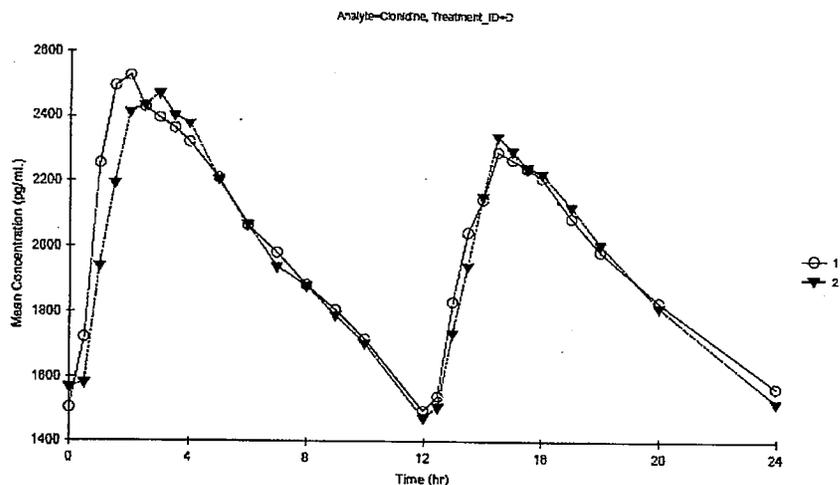


Figure 10: Mean clonidine plasma concentration-times after administration of the reference product 0.3 mg QD q12 h (Treatment D) on Steady State Day 1 and Day 2



The clonidine PK measures obtained with Treatments A, C and D are summarized in the following three tables.

Table 18: Clonidine PK Measures at steady state for Treatment A, 0.2 mg QD

Parameter	Study Day 7				Study Day 8			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	32	6.53	1.90	29.08	32	6.53	1.54	23.60
C _{max} (pg/mL)	32	752	192	25.50	32	694	189	27.21
C _{min} (pg/mL)	32	362	150	41.42	32	360	141	39.24
C _{avg} (pg/mL)	32	555	160	28.81	32	535	165	30.84
AUC ₀₋₇ (hr*pg/mL)	32	13330	3841	28.81	32	12840	3959	30.84
AUC ₀₋₁₂ (hr*pg/mL)	32	7507	1971	26.25	32	7002	1993	28.46
AUC ₀₋₂₄ (hr*pg/mL)	32	13330	3841	28.81	32	12840	3959	30.84
AUC _{last} (hr*pg/mL)	32	13330	3841	28.81	32	12840	3959	30.83
AUC _{inf} (hr*pg/mL)	32	25430	14150	55.64	32	24650	11690	47.41
AUC _{Extrap} (%)	32	42.16	12.22	28.99	32	44.55	8.91	20.00
λ _z (hr ⁻¹)	32	0.0412	0.0147	35.65	32	0.0382	0.0094	24.68
T _{1/2} (hr)	32	19.98	12.29	61.51	32	19.51	6.09	31.20
T _{last} (hr)	32	24.01	0.02	0.09	32	24.00	0.01	0.05
C _{last} (pg/mL)	32	382	148	38.70	32	389	150	38.56
PF (%)	32	73.73	19.27	26.13	32	65.36	14.82	22.67
Accumulation Index	32	1.7816	0.7181	40.31	32	1.7480	0.3489	19.96

Table 19: Clonidine PK measures at steady state for Treatment C, 2 x 0.3 mg QD

Parameter	Steady-State Day 1: (Study Days 21 and 29)				Steady-State Day 2: (Study Days 22 and 30)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	31	7.07	1.21	17.11	31	7.50	1.94	25.88
C _{max} (pg/mL)	31	2450	934	38.17	31	2370	765	32.28
C _{min} (pg/mL)	31	1310	693	52.96	31	1300	584	45.03
C _{avg} (pg/mL)	31	1880	795	42.25	31	1850	674	36.55
AUC _{0-τ} (hr*pg/mL)	31	45180	19090	42.25	31	44290	16190	36.55
AUC ₀₋₁₂ (hr*pg/mL)	31	24600	9755	39.65	31	24140	8399	34.79
AUC ₀₋₂₄ (hr*pg/mL)	31	45180	19090	42.25	31	44290	16190	36.55
AUC _{last} (hr*pg/mL)	31	45190	19090	42.23	31	44300	16190	36.55
AUC _{inf} (hr*pg/mL)	31	90010	45120	50.13	31	91210	47990	52.62
AUC _{Extrap} (%)	31	47.14	9.46	20.07	31	46.60	11.86	25.46
λ _z (hr ⁻¹)	31	0.0357	0.0104	29.27	31	0.0372	0.0133	35.84
T _{1/2} (hr)	31	21.09	6.34	30.05	31	21.32	8.46	39.71
T _{last} (hr)	31	24.01	0.04	0.17	31	24.01	0.03	0.11
C _{last} (pg/mL)	31	1400	665	47.39	31	1380	609	44.02
PF (%)	31	64.83	15.32	23.63	31	61.98	16.51	26.64
Accumulation Index	31	1.8381	0.3624	19.72	31	1.8546	0.4857	26.19

Table 20: Clonidine PK measures at steady state for Treatment D, 0.3 mg q 12h

Parameter	Steady-State Day 1: (Study Days 21 and 29)				Steady-State Day 2: (Study Days 22 and 30)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	32	2.22	1.13	51.02	32	2.77	0.77	27.94
C _{max} (pg/mL)	32	2630	918	34.92	32	2590	720	27.75
C _{min} (pg/mL)	32	1420	695	48.95	32	1460	587	40.30
C _{avg} (pg/mL)	32	2020	741	36.70	32	1980	650	32.77
AUC _{0-τ} (hr*pg/mL)	32	24220	8888	36.70	32	23800	7800	32.77
AUC ₀₋₁₂ (hr*pg/mL)	32	24220	8888	36.70	32	23800	7800	32.77
AUC ₀₋₂₄ (hr*pg/mL)	32	47120	17080	36.25	32	46570	15360	32.98
AUC _{last} (hr*pg/mL)	32	47120	17080	36.25	32	46590	15360	32.98
AUC _{inf} (hr*pg/mL)	32	93950	54800	58.32	32	82370	36630	44.47
AUC _{Extrap} (%)	32	43.91	12.39	28.21	32	40.17	10.46	26.03
λ _z (hr ⁻¹)	32	0.0452	0.0161	35.68	32	0.0516	0.0179	34.64
T _{1/2} (hr)	32	18.57	11.07	59.61	32	15.23	5.78	37.93
T _{last} (hr)	32	24.00	0.01	0.04	32	24.01	0.03	0.13
C _{last} (pg/mL)	32	1570	674	43.04	32	1520	593	38.93
PF (%)	32	63.24	17.70	27.99	32	61.12	18.03	29.49
Accumulation Index	32	2.7772	1.3173	47.43	32	2.3823	0.6784	28.48

Statistical comparisons of Clonidine PK exposure measures

Relative Bioavailability (Exposure Comparisons)

The applicant provided the following tabulated exposure comparison for the relative bioavailability assessment (ER vs. IR at 0.6 mg daily dose).

Table 21: Statistical analysis of log-transformed systemic exposure measures of (0.6 mg daily) clonidine comparing the test formulation (Treatment C) to the reference product (Treatment D) on steady state Day 2 (Day 22 and 30)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	2269.4214	2490.2590	91.13	86.96	95.50	1.0000	10.84
ln(AUC ₀₋₂₄)	41857.8043	44147.0585	94.81	90.93	98.87	1.0000	9.68

^a Geometric Mean for the Test Formulation 2 x 0.3 mg QD (Test) and Reference Product 0.3 mg Q12h (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Reviewer's Comment: The statistical comparisons demonstrate that the exposure (AUC and C_{max}) for ER and IR are comparable at the 0.6 mg daily dose per FDA Bioavailability Guidance to Industry. The AUC comparison is more relevant than that of C_{max} because the IR has two peaks vs. one peak for ER. Nevertheless, the C_{max} findings support the comparable exposure claim. It is noted that the applicant elected to use the second peak in the analysis; the basis for the selection of this peak is unclear.

The comparisons for secondary exposures are tabulated below; the findings from these secondary measures support the findings (comparable clonidine exposure for IR and ER at same daily dose) based on the primary exposure measures.

Table 22: Statistical analysis of log-transformed secondary exposure measures of 0.6 mg daily clonidine comparing the test formulation (Treatment C) to the reference product (Treatment D) on steady state Day 2 (Day 22 and 30)

Exposure Measure	Geometric Mean (Test)	Geometric Mean (Reference)	Ratio (Test/Reference)	90 % CI range
C _{avg}	1744.08	1881.17	92.71	88.78 – 96.82
C _{min}	1188.75	1348.62	88.15	83.07 – 93.53
AUC ₀₋₁₂	22968.75	22574.07	97.14	97.14 – 106.57

Intrasubject Variability

The applicant provided the following estimates for intrasubject variability (ISV).

Table 23: Estimation of intrasubject variability for Treatment C and Treatment D (based on comparison of two consecutive dosing days; steady state Day 1 vs. Day 2)

Dependent Variable	ISV as CV (%)	Comment
Extended Release Formulation, Treatment C		
Ln Cmin	9.22	Satisfactory
Ln Cmax	8.27	Satisfactory
Ln AUC ₀₋₂₄	5.97	Satisfactory
Immediate Release formulation, Treatment D		
Ln Cmin	31.22	Unsatisfactory
Ln Cmax	7.96	Satisfactory
Ln AUC ₀₋₂₄	4.75	Satisfactory

Apart from Cmin for the IR formulation, both formulations had relatively low intrasubject variability. However, it is noted that two subjects had markedly different plasma concentration-time profiles (approximately 2-fold difference in concentrations at several time-matched points) on the two consecutive dosing days; these profiles are included in the appendix to this study. The reason for these large differences is unclear but may be related to clonidine's pharmacokinetic profile (variable absorption, enterohepatic recycling and other factors).

b(4)

Steady State Assessment

Steady state was assessed by comparing trough concentrations over four days (Days 5 to 8) for the three evaluated Treatments (A, C and D). As shown in the following table, the p-values for comparing trough concentrations during the multiple dosing regimens were above 0.05 for at least three consecutive sampling days prior to the last day of a given dosing regimen. This finding indicates that trough concentrations were comparable from Days 5 to 8; thus, steady state conditions were achieved prior to collection of the concentration-time data subjected to pharmacokinetic analysis.

Table 24: Tukey's test for comparing differences in trough concentrations for Treatment A

Study Day	1	5	6	7	8
1	-	<0.0001	<0.0001	<0.0001	<0.0001
5	<0.0001	-	0.9389	0.5506	0.4988
6	<0.0001	0.9389	-	0.9439	0.9204
7	<0.0001	0.5506	0.9439	-	1.0000
8	<0.0001	0.4988	0.9204	1.0000	-

Note: p-values are displayed for paired comparisons

Table 25: Tukey's test for comparing differences in trough concentrations for Treatment C

Study Day	1	5	6	7	8
1	-	<0.0001	<0.0001	<0.0001	<0.0001
5	<0.0001	-	0.9389	0.5506	0.4988
6	<0.0001	0.9389	-	0.9439	0.9204
7	<0.0001	0.5506	0.9439	-	1.0000
8	<0.0001	0.4988	0.9204	1.0000	-

Note: p-values are displayed for paired comparisons

Table 26: Tukey's test for comparing differences in trough concentrations for Treatment D

Study Day	19/27	20/28	21/29	22/30
19/27	-	0.8346	0.8166	0.6063
20/28	0.8346	-	1.0000	0.9788
21/29	0.8166	1.0000	-	0.9840
22/30	0.6063	0.9788	0.9840	-

Note: p-values are displayed for paired comparisons

Applicant's Safety Summary

A total of 90 treatment emergent adverse events (AEs) were reported by 24 of the 32 patients over the course of the study. Seventy-nine of the 90 treatment emergent AEs were mild, 11 moderate and none were severe. Fifty-one of the AEs were probably related to the study treatment. Fourteen of the AEs were possibly related to the study treatment; the remaining 25 were unrelated to the study treatment.

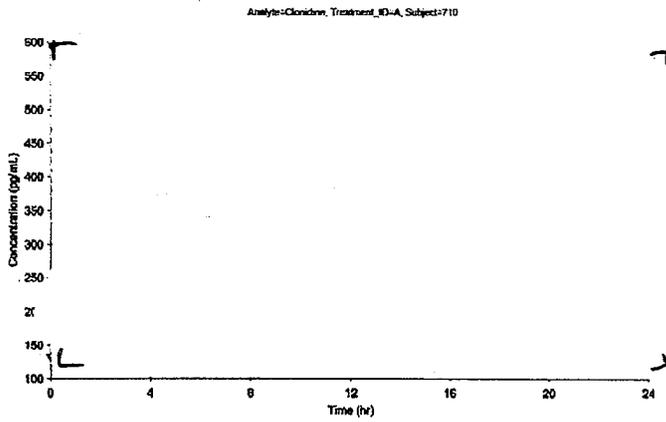
The most commonly reported AE was drowsiness, recurrent drowsiness, or intermittent drowsiness. Other commonly reported AEs were dizziness, hypotension, lightheadedness, dry mouth/xerostomia, fatigue, constipation and headache. In total 30 AEs were reported following Treatment A, 12 AEs were reported following Treatment B, 19 AEs were reported following Treatment C, and 29 AEs were reported following Treatment D. None of the AEs were related to abnormal laboratory evaluations. No other clinically significant abnormalities in vital sign assessments, ECGs or physical exams were observed.

Conclusions

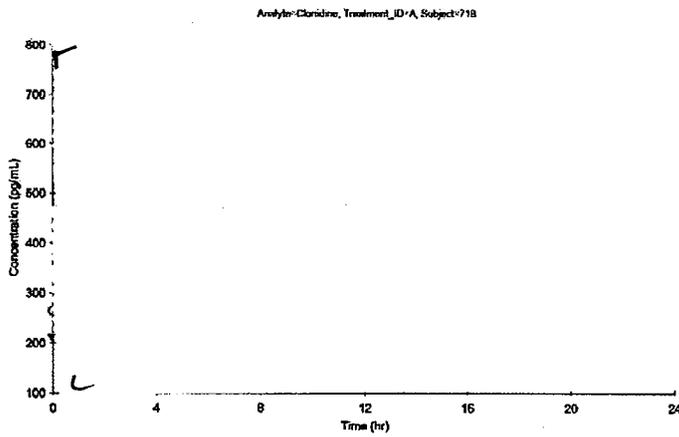
- Steady-state conditions were achieved within six days for all evaluated clonidine formulations and regimens: 0.2 mg QD extended release tablets (Treatment A), 0.6 mg QD extended release tablets (Treatment C), and 0.3 mg q 12 hours immediate release tablets (Treatment D)
- The exposure of clonidine with Treatment C and Treatment D were comparable following at a 0.6 mg clonidine daily dose
- There is reproducibility of individual dosage units for the 0.3 mg extended release tablets based on the relatively low intrasubject variability (< 10 %) following consecutive dosing at steady state

Appendix

Plasma concentration time profiles for two individual subjects receiving extended release formulation on two consecutive days.



b(4)



b(4)

4.2.2 A 3-period, 3-treatment, 3-way crossover bioavailability study of clonidine extended release oral suspension 0.1 mg/mL (2 mL) under fed and fasted conditions (Protocol 1003390)

b(4)

PRINCIPAL INVESTIGATOR	Steven Hinit, M.D., M.P.H., M.P.A
STUDY SITE	CEDRA Clinical Research, San Antonio, Texas
STUDY PERIOD	September to October 2008

Objectives (per Applicant)

- To compare the rate and extent of absorption of a test formulation of Clonidine Extended Release Oral Suspension 2 mL (0.1 mg/mL) by Tris Pharma, Inc. administered under fasted and fed conditions.
- To compare the rate and extent of absorption of a test formulation of Clonidine Extended Release Oral Suspension 2 mL (0.1 mg/mL) to an equivalent oral dose of the commercially available reference product, Catapres IR® (1 x 0.1 mg) tablet manufactured by Boehringer Ingelheim administered at 0 and 12 hours under fasted conditions.

b(4)

b(4)

Study Design

This was an open label, randomized, three-period, three treatment crossover study in which twenty-six (26) adult subjects received separate single-dose administrations of clonidine formulations. The three treatments were as follows:

- Treatment A: single dose of 0.2 mg clonidine extended release oral suspension under fasted conditions (test 1)
- Treatment B: two single doses of 0.1 mg Catapres tablets under fasted conditions (reference)
- Treatment C: single dose of 0.2 mg clonidine extended release oral suspension under fed conditions (test 2)

b(4)

b(4)

Subjects receiving the fasted treatments were administered the study drug following an overnight fast of at least 10 hours prior to the 0-hour dose. Subjects receiving the fed treatment were administered the study drug after an overnight fast of at least 10 hours followed by consumption of a high-fat, high-calorie breakfast* beginning 30 minutes prior to administration of the study drug. When evening doses were indicated for the every 12 hour dosing regimens, doses were administered at least one hour before or after the evening meal. Dosing days were separated by a washout period of at least 7 days.

* The high fat meal was consistent with the recommendations of the Food Effect Guidance (meal contents in Appendix to this study)

Blood (pharmacokinetic) sampling times

Blood samples were collected for pharmacokinetic purposes at the following times: within 60 minutes prior to 0-hour dose administration (predose) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12 (pre-dose for Treatment B), 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 17, 18, 20, 24, 36, 48, and 72 hours after drug administration.

Formulation

- Clonidine Extended Release Oral Suspension 0.1 mg/mL; Lot #: TB-013A (TRIS)
- Reference: Catapres IR® oral tablet 0.1 mg; Lot # 851623 (Boehringer Ingelheim)

Bioanalytical methods

Clonidine concentrations were determined using a validated LC-MS-MS method. The assay performance was acceptable as illustrated in the following table.

Table 27: Performance of clonidine assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the _____ pg/mL range; R > 0.994	Satisfactory
Between day Precision	CV was _____	Satisfactory
Accuracy	QC samples were within _____ of the nominal concentration	Satisfactory
LLOQ	8 pg/ml	Satisfactory
Specificity	Chromatograms were provided and demonstrated specificity	Satisfactory

b(4)

b(4)

Pharmacokinetics

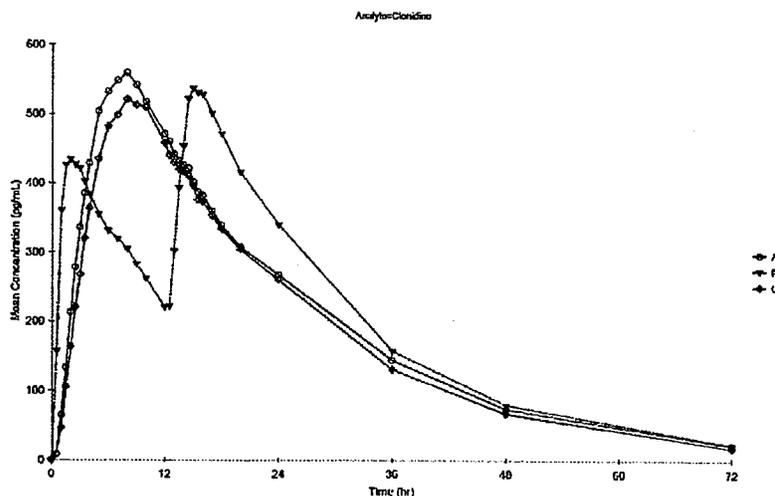
Pharmacokinetic data were analyzed by noncompartmental methods in WinNonlin (Version 4.0, Pharsight Corporation). The following pharmacokinetic measures were estimated: Tmax, Cmax, AUC, AUC_{inf}, AUC_{Extrap}, λ_z, T1/2, Tlast and Clast. Additionally, relative bioavailability and food effect were determined using standard pharmaco-statistical approaches. The 90 % confidence interval for the ratio of the geometric means (Test/Reference) was calculated. The two test treatments were extended release suspension in the fed and fasted states, with the corresponding references of the fasted ER suspension and fasted immediate release clonidine, respectively. Comparable exposure was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

Results

Clonidine Pharmacokinetics

The mean clonidine plasma concentration-time profiles following administration of clonidine ER suspension and IR tablet are shown in the following figure.

Figure 11: Mean clonidine plasma concentration-time profiles after administration of the ER suspension-Fasted (Treatment A), the IR tablet-Fasted (Treatment B), and the ER suspension -Fed (Treatment C) [clonidine daily dose was 0.2 mg for all Treatments]



Clonidine PK measures following administration of Treatments A, B, and C are summarized in the following table.

Table 28: Clonidine PK measures in Food Effect/Relative Bioavailability (BA) Study

Parameter	Treatment A: Test Formulation (Fasted)				Treatment B: Reference Product (Fasted)				Treatment C: Test Formulation (Fed)			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	24	7.42	0.83	11.19	25	15.14	1.00	6.63	25	7.80	1.71	21.90
C _{max} (pg/mL)	24	516	85.3	16.53	25	580	96.7	16.67	25	488	89.4	18.33
AUC _{last} (hr*pg/mL)	24	13040	2378	18.23	25	14690	3105	21.14	25	12830	3035	23.67
AUC _{inf} (hr*pg/mL)	24	13640	2627	19.26	25	15180	3309	21.80	25	13370	3393	25.39
AUC _{Extrap} (%)	24	4.19	3.58	85.44	25	3.10	2.14	69.14	25	3.70	2.38	64.24
λ _z (hr ⁻¹)	24	0.0538	0.0087	16.26	25	0.0580	0.0110	18.95	25	0.0529	0.0112	21.25
T _{1/2} (hr)	24	13.27	2.53	19.07	25	12.44	2.73	21.97	25	13.69	2.99	21.88
T _{last} (hr)	24	69.01	8.11	11.75	25	71.06	4.74	6.68	25	71.05	4.80	6.76
C _{last} (pg/mL)	24	28.5	22.6	79.33	25	24.9	14.4	57.86	25	24.6	15.8	64.25

Pharmacokinetic (statistical) comparisons

The clonidine exposure comparisons are summarized in the following two tables.

Table 29: Statistical analysis of log-transformed systemic exposure parameters of clonidine (Treatment C, fed suspension vs. Treatment A, fasted suspension)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	533.5779	562.2559	94.90	91.72	98.19	1.0000	7.02
ln(AUC _{last})	13007.6383	13673.0813	95.13	90.90	99.56	1.0000	9.38
ln(AUC _{inf})	13400.5050	14119.5535	94.91	90.74	99.26	1.0000	9.25

^a Geometric Mean for the Test Formulation-Fed (Test) and Test Formulation-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

The analysis indicates that food does not alter the bioavailability of clonidine when administered as suspension.

Table 30: Statistical analysis of log-transformed systemic exposure parameters of clonidine (Treatment A, fasted suspension vs. Treatment B, fasted tablet)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	555.4745	569.7750	97.49	93.52	101.63	1.0000	8.07
ln(AUC _{last})	13556.5463	14336.0992	94.56	91.05	98.21	1.0000	7.35
ln(AUC _{inf})	14000.1785	14797.7035	94.61	91.15	98.20	1.0000	7.24

^a Geometric Mean for the Test Formulation-Fed (Test) and Test Formulation-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Reviewer's Comment: The statistical data indicate that the exposure (AUC and C_{max}) of the oral suspension is comparable to that of the immediate release tablet at the same daily dose. The AUC comparisons are more relevant than the C_{max}, because the two formulations have a different

number of peaks (1 for suspension vs. 2 for tablet). It is noted that the applicant's C_{max} comparison is based on the second peak of IR to single peak of ER suspension; the basis for the selection of the second peak is unclear. Nevertheless, the C_{max} comparison supports the conclusion that ER and IR achieve comparable clonidine exposure.

Applicant's Safety Summary

Forty-three treatment emergent AEs were reported by 20 of the 26 subjects over the course of the study. Twenty-nine of the 43 AEs were mild, 14 moderate and none were severe. Thirty-three of the AEs were definitely or probably related to the study drug. Eight of the AEs were possibly related to the study treatment; the remaining 2 were unrelated or unlikely related to study treatment. Several events of clinically significant hypotension and orthostatic hypotension were noted on the adverse event listing. These were expected in association with clonidine hydrochloride administration. No other clinically significant abnormalities in vital signs or physical exams were observed.

Conclusions

- Food does not lead to dose dumping with the clonidine suspension; food had no significant effect on the rate or extent of absorption of the test formulation of Clonidine _____
Extended Release Tablets
- The clonidine exposure following administration of 0.2 mg clonidine for Clonidine _____
Extended Release Tablets is comparable to that of the reference listed drug product (RLD) Catapres IR® by Boehringer Ingelheim under fasted conditions.

b(4)

Appendix

Menu

Study Menu 1003390-SA

Study Day	Breakfast	Lunch	Dinner	Snack
-1				<ul style="list-style-type: none"> • Assorted chips • Assorted cookies • 12 oz. (360 ml) Root Beer
1	<p><u>Treatment C ONLY</u></p> <ul style="list-style-type: none"> • 2 eggs fried in butter (yolks will be broken) • 2 strips bacon • 4 oz. hash brown potatoes • 2 slices toast • 2 pats butter • 240 mL Whole milk (8 oz.) 	<ul style="list-style-type: none"> • Chicken Breast • White Rice • Black Beans • Broccoli • Dinner roll • 1 pat butter • 1 bag of potato chips • 12 oz. (360 mL) water 	<ul style="list-style-type: none"> • Pot roast • Mashed potatoes • Whole Corn • Dinner roll • 2 pats of butter • Carrot Cake • 12 oz. (360 mL) Sprite 	<ul style="list-style-type: none"> • 1 small cup vanilla ice cream • 4 oz. Peaches • 360 ml water (required)
2	<ul style="list-style-type: none"> • 2 waffles • 2 oz. syrup • 8 oz. 2% milk • 120 mL water 	<ul style="list-style-type: none"> • Ham and American cheese sub (white bread, lettuce, tomato and mayonnaise) • Plain potato chips • Fresh fruit cup • 12 oz. (360 mL) Sprite 	<ul style="list-style-type: none"> • Beef lasagna • Salad with Italian dressing • Garlic bread • 12 oz. (360 mL) Lemonade 	

Subjects receiving Treatment C will begin ingesting the following high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 1000 calories) breakfast approximately 30 minutes prior to administration of the drug.

- 2 eggs fried in butter
- 2 strips of bacon
- 2 slices of toast with butter
- 4 ounces of hash brown potatoes
- 8 ounces of whole milk

This meal contains approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories. An equivalent meal may be substituted with documentation of the menu and caloric contents.

4.2.3 A 3-period, 3-treatment, 3-way crossover bioavailability study of clonidine ~~_____~~ extended release tablet (1 x 0.2 mg) under fed and fasted conditions (Protocol 1003391) b(4)

PRINCIPAL INVESTIGATOR	Steven Hinitt, M.D., M.P.H., M.P.A
STUDY SITE	CEDRA Clinical Research, LLC, San Antonio, Texas 78217
STUDY PERIOD	October 2008

Objectives

- To compare the rate and extent of absorption of a test formulation of Clonidine ~~_____~~ Extended Release (1 x 0.2 mg) tablet by Tris Pharma, Inc. administered under fasted and fed conditions. b(4)
- To compare the rate and extent of absorption of a test formulation of Clonidine ~~_____~~ Extended Release (1 x 0.2 mg) tablet to an equivalent oral dose of the commercially available reference product, Catapres IR® (1 x 0.1 mg) tablet manufactured by Boehringer Ingelheim administered at 0 and 12 hours under fasted conditions. b(4)

Study Design

This was an open-label, randomized, three-period, three-treatment crossover study. Twenty-six (26) healthy subjects were enrolled. Healthy adult subjects received separate single-dose administrations of Clonidine ~~_____~~ Extended Release (1 x 0.2 mg) tablet under fasted and fed conditions. Subjects also received Catapres IR® (1 x 0.1 mg) administered at 0 and 12 hours under fasted conditions. Subjects receiving the fasted treatments were administered the study drug following an overnight fast of at least 10 hours prior to the 0-hour dose. Subjects receiving the fed treatment were administered the study drug after an overnight fast of at least 10 hours followed by consumption of a high-fat, high-calorie breakfast* beginning 30 minutes prior to administration of the study drug. Dosing days were separated by a washout period of at least 7 days. b(4)

* The high fat meal was consistent with the recommendations of the Food Effect Guidance (meal contents in Appendix to this study)

Blood (pharmacokinetic) sampling times

Blood samples were collected for pharmacokinetic purposes at the following times: within 60 minutes prior to 0-hour dose administration (predose) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12 (pre-dose for Treatment B), 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 17, 18, 20, 24, 36, 48, and 72 hours after drug administration.

Formulation

- Clonidine ~~_____~~ Extended Release Tablets 0.2 mg; Lot #: TB-021A (TRIS) b(4)
- Catapres IR® clonidine hydrochloride 0.1 mg tablet; Lot # : 851623 (Boehringer Ingelheim)

Bioanalytical methods

Clonidine concentrations were determined using a validated LC-MS-MS method. The assay performance was acceptable as illustrated in the following table.

Table 31: Performance of clonidine assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the _____ pg/mL range; $R > 0.988$	Satisfactory
Between day Precision	CV was _____	Satisfactory
Accuracy	QC samples were within _____ of the nominal concentration	Satisfactory
LLOQ	8 pg/ml	Satisfactory
Specificity	Chromatograms were provided and demonstrated specificity	Satisfactory

b(4)

b(4)

Pharmacokinetics

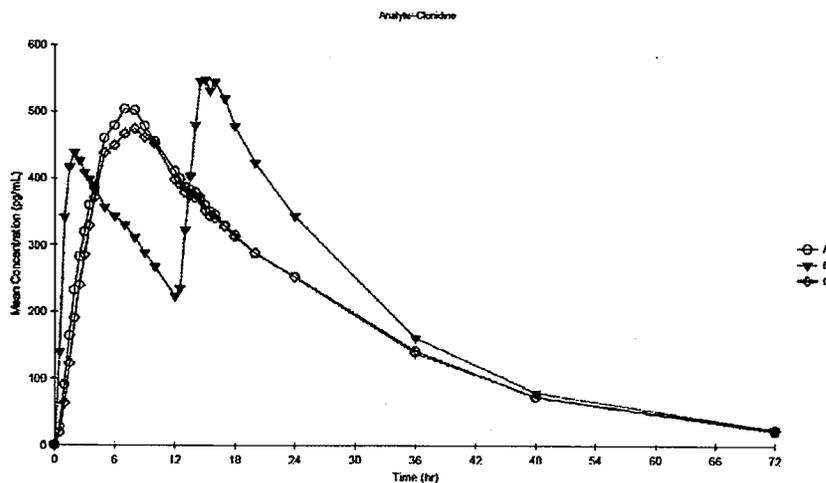
Pharmacokinetic data were analyzed by noncompartmental methods in WinNonlin (Version 4.0, Pharsight Corporation). The following pharmacokinetic measures were estimated: T_{max} , C_{max} , AUC, AUC_{inf} , AUC_{Extrap} , λ_z , $T_{1/2}$, T_{last} and C_{last} . Additionally, relative bioavailability and food effect were determined using standard pharmaco-statistical approaches. The 90 % confidence interval for the ratio of the geometric means (Test/Reference) was calculated. The two test treatments were extended release tablets in the fed and fasted states, with the corresponding references of the fasted ER suspension and immediate release clonidine, respectively. Comparable exposure was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

Results

Clonidine Pharmacokinetics

The mean clonidine plasma concentration-time profiles following administration of the various clonidine formulations are depicted in the following figure.

Figure 12: Mean clonidine plasma concentration-time profiles after administration of 0.2 mg extended release clonidine fasted (Treatment A), 0.1 mg immediate release clonidine given twice (12 hours a



part) under fasted conditions (Treatment B), and 0.2 mg extended release clonidine fed (Treatment C)

Clonidine PK measures following administration of Treatments A, B, and C are summarized in the following table.

Table 32: Clonidine PK measures in Food Effect/Relative BA Study

Parameter	Treatment A: Test Formulation (Fasted)				Treatment B: Reference Product (Fasted)				Treatment C: Test Formulation (Fed)			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	25	7.72	1.24	16.10	24	14.63	2.95	20.17	26	8.27	1.56	18.89
C _{max} (pg/mL)	25	575	108	18.72	24	571	109	19.17	26	539	105	19.48
AUC _{last} (hr*pg/mL)	25	14090	3186	22.61	24	14480	3736	25.79	26	13160	3258	24.75
AUC _{inf} (hr*pg/mL)	25	14560	3352	23.02	24	14970	3935	26.29	26	13560	3389	25.00
AUC _{Extrap} (%)	25	3.15	1.40	44.54	24	3.15	1.70	53.80	26	2.88	1.42	49.40
λ _z (hr ⁻¹)	25	0.0546	0.0098	17.88	24	0.0592	0.0105	17.67	26	0.0572	0.0089	15.54
T _{1/2} (hr)	25	13.06	2.20	16.83	24	12.09	2.28	18.82	26	12.38	1.81	14.61
T _{last} (hr)	25	70.08	6.65	9.48	24	69.00	8.11	11.75	26	69.25	7.83	11.30
C _{last} (pg/mL)	25	24.0	10.7	44.39	24	26.3	13.3	50.49	26	21.2	10.3	48.57

Pharmacokinetic (statistical) comparisons

The clonidine exposure comparisons are summarized in the following two tables.

Table 33: Statistical analysis of log-transformed systemic exposure parameters of clonidine (Treatment C, fasted ER tablet vs. Treatment A, fasted IR tablet)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	533.5779	562.2559	94.90	91.72	98.19	1.0000	7.02
ln(AUC _{last})	13007.6383	13673.0813	95.13	90.90	99.56	1.0000	9.38
ln(AUC _{inf})	13400.5050	14119.5535	94.91	90.74	99.26	1.0000	9.25

^a Geometric Mean for the Test Formulation-Fed (Test) and Test Formulation-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Table 34: Statistical analysis of log-transformed systemic exposure parameters of clonidine (Treatment C, fed ER tablet vs. Treatment A, fasted ER tablet)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	474.8903	508.7359	93.35	89.68	97.17	1.0000	8.09
ln(AUC _{last})	12298.3958	12840.2871	95.78	91.85	99.88	1.0000	8.46
ln(AUC _{inf})	12770.1697	13411.1350	95.22	91.34	99.26	1.0000	8.39

^a Geometric Mean for the Test Formulation-Fed (Test) and Test Formulation-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

The analysis indicates that food does not alter the bioavailability of clonidine when administered as ER tablets.

Reviewer's Comment: *The statistical data indicate that the exposure (AUC and Cmax) of the ER tablets is comparable to that of the immediate release tablet at the same daily dose. The AUC comparisons are more relevant than the Cmax, because the two formulations have a different number of peaks (1 for tablet vs. 2 for tablet). It is noted that the applicant's Cmax comparison is based on the second peak of IR to single peak of ER suspension; the basis for the selection of the second peak is unclear. Nevertheless, the Cmax comparison supports the conclusion that ER and IR tablets achieve comparable clonidine exposure.*

Applicant's Safety Summary

A total of 58 treatment emergent AEs were reported by 19 of the 26 subjects over the course of the study. Forty-three of the 58 AEs were mild, 15 moderate and none of the AEs were severe. Forty-five of the AEs were probably related to the study drug. Seven of the AEs were possibly related to the study treatment; and the remaining six were not related to study treatment. The most commonly reported AEs were hypotension (n=19) and drowsiness (n=9). None of the AEs were related to abnormal laboratory evaluations. Several events of clinically significant hypotension and orthostatic hypotension were noted on the adverse event listing. These were expected in association with clonidine hydrochloride administration. No other clinically significant observations or changes in safety parameters were identified in the subject population during the study conduct.

Conclusions

- Food does not cause dose dumping with clonidine ER tablets; food had no significant effect on the rate or extent of absorption of the test formulation of Clonidine _____ Extended Release Oral tablets b(4)
- The test formulation of Clonidine _____ Extended Release achieves comparable exposure to the reference listed drug product (RLD) Catapres IR® by Boehringer Ingelheim under fasted conditions. b(4)

Study Appendix

Study Menu 1003391-SA

Study Day	Breakfast	Lunch	Dinner	Snack
-1				<ul style="list-style-type: none"> • Assorted chips • Assorted cookies • 12 oz. (360 ml) Root Beer
1	<p><u>Treatment C ONLY</u></p> <ul style="list-style-type: none"> • 2 eggs fried in butter (yolks will be broken) • 2 strips bacon • 4 oz. hash brown potatoes • 2 slices toast • 2 pats butter • 240 mL Whole milk (8 oz.) 	<ul style="list-style-type: none"> • Chicken Breast • White Rice • Black Beans • Broccoli • Dinner roll • 1 pat butter • 1 bag of potato chips • 12 oz. (360 mL) water 	<ul style="list-style-type: none"> • Pot roast • Mashed potatoes • Whole Corn • Dinner roll • 2 pats of butter • Carrot Cake • 12 oz. (360 mL) Sprite 	<ul style="list-style-type: none"> • 1 small cup vanilla ice cream • 4 oz. Peaches • 360 ml water (required)
2	<ul style="list-style-type: none"> • 2 waffles • 2 oz. syrup • 8 oz. 2% milk • 120 mL water 	<ul style="list-style-type: none"> • Ham and American cheese sub (white bread, lettuce, tomato and mayonnaise) • Plain potato chips • Fresh fruit cup • 12 oz. (360 mL) Sprite 	<ul style="list-style-type: none"> • Beef lasagna • Salad with Italian dressing • Garlic bread • 12 oz. (360 mL) Lemonade 	

Subjects receiving Treatment C will begin ingesting the following high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 1000 calories) breakfast approximately 30 minutes prior to administration of the drug.

- 2 eggs fried in butter
- 2 strips of bacon
- 2 slices of toast with butter
- 4 ounces of hash brown potatoes
- 8 ounces of whole milk

This meal contains approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories. An equivalent meal may be substituted with documentation of the menu and caloric contents.

4.2.4 A pilot relative bioavailability study of clonidine 0.1 mg/ml extended release oral suspension versus Catapres® 0.1 mg tablets under fasting conditions

Reviewer Note on evaluation of Study

This study was conducted as a pilot study, thus was not reviewed in detail. Overall the findings from this study are consistent with those of the "pivotal" fasted study (1003390): the extended release oral suspension achieved comparable clonidine exposure to the immediate release formulation. The synopsis of the pilot study follows.

SYNOPSIS

Study Title	A PILOT RELATIVE BIOAVAILABILITY STUDY OF CLONIDINE 0.1 MG/ML EXTENDED RELEASE ORAL SUSPENSION VERSUS CATAPRES® 0.1 MG TABLETS UNDER FASTING CONDITIONS
Clinical Investigator	<u>Principal Investigator:</u> Gilbert R. Weiner, D.O., A.O.B.F.P., C.P.I. Medical Director (Miami) Allied Research International – Cetero Research
Study Management	
Study Period	Period 1 (Dosing Day): 02-Dec-07 Period 2 (Dosing Day): 09-Dec-07
Date of first enrolment	01-Dec-07
Date of last completed	12-Dec-07
Objectives	The objective of this pilot study was to assess the relative bioavailability of an extended release oral suspension containing 0.1 mg/mL clonidine (Tris Pharma Inc.) given as a single dose versus equivalent doses of Catapres® 0.1 mg tablets (Boehringer Ingelheim) in healthy adult subjects when administered under fasting conditions.
Methodology	This was an open label, randomized, two-period, two-treatment crossover pilot study under fasting conditions. A seven day washout period was observed between the doses.
Number of Subjects (planned and analyzed)	A total of 12 subjects were enrolled in the study as planned and 11 subjects completed the study. Subject 02 voluntarily withdrew in Period 2. Samples obtained from Subjects 01, 03-12 were included in the pharmacokinetic and statistical analysis.

b(4)

Treatment/Dose/ Route/Duration	<p><u>Test Product (A):</u> 2 ml of an extended release oral suspension containing 0.1 mg/mL clonidine (Tris Pharma Inc.) was administered at 0 hours with approximately 240 mL (8 fluid ounces) of room temperature water after an overnight fast.</p> <p><u>Reference Product (B):</u> 0.1 mg Catapres® tablet (Boehringer Ingelheim) was administered at 0 and 12 hours (for a total of 0.2 mg) with approximately 240 mL (8 fluid ounces) of room temperature water after an overnight fast of at least 10 hours.</p>												
<p>Results:</p> <p><i>Safety</i> All subjects tolerated the investigational product. No serious adverse events were experienced.</p> <p><i>Pharmacokinetic and Statistics</i> The pharmacokinetic results are listed below for Clonidine.</p> <p style="text-align: center;">Ratios of LSM (90% Confidence Intervals)</p> <table border="1" data-bbox="469 930 980 1192"> <thead> <tr> <th>Parameter</th> <th>(A) vs (B)</th> </tr> </thead> <tbody> <tr> <td>AUC₀₋₁₂</td> <td>134.3 (125.41 - 143.88)</td> </tr> <tr> <td>AUC₀₋₂₄</td> <td>105.3 (97.46 - 113.77)</td> </tr> <tr> <td>AUC_{0-t}</td> <td>96.0 (89.23 - 103.23)</td> </tr> <tr> <td>AUC_{0-inf}</td> <td>96.5 (89.93 - 103.50)</td> </tr> <tr> <td>C_{max}</td> <td>97.1 (83.57 - 112.77)</td> </tr> </tbody> </table>		Parameter	(A) vs (B)	AUC ₀₋₁₂	134.3 (125.41 - 143.88)	AUC ₀₋₂₄	105.3 (97.46 - 113.77)	AUC _{0-t}	96.0 (89.23 - 103.23)	AUC _{0-inf}	96.5 (89.93 - 103.50)	C _{max}	97.1 (83.57 - 112.77)
Parameter	(A) vs (B)												
AUC ₀₋₁₂	134.3 (125.41 - 143.88)												
AUC ₀₋₂₄	105.3 (97.46 - 113.77)												
AUC _{0-t}	96.0 (89.23 - 103.23)												
AUC _{0-inf}	96.5 (89.93 - 103.50)												
C _{max}	97.1 (83.57 - 112.77)												

CONCLUSIONS

The ratios of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed parameters AUC_{0-t}, AUC_{0-inf} and C_{max} for clonidine were within the 80-125% FDA acceptance range.

In this pilot study, bioequivalence between Clonidine 0.1 mg/mL extended release oral suspension (Tris Pharma Inc.) and 0.1 mg Catapres® tablet (Boehringer Ingelheim) was demonstrated, when 0.1 mg/mL clonidine extended release oral suspension (Tris Pharma Inc.) was administered as 0.2 mg (2 mL) at 0 hours and 0.1 mg Catapres® tablet (Boehringer Ingelheim) was administered as 1 × 0.1 mg at 0 and 12 hours for a total of 0.2 mg under fasting conditions.

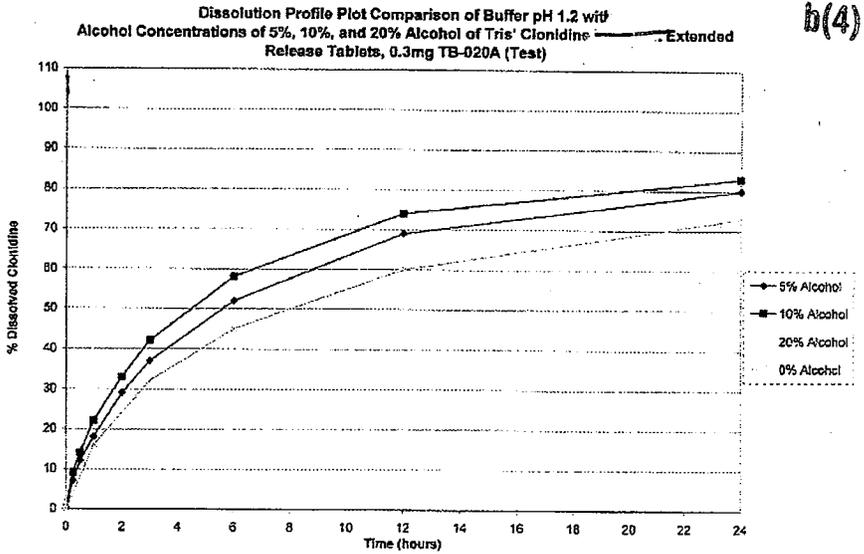
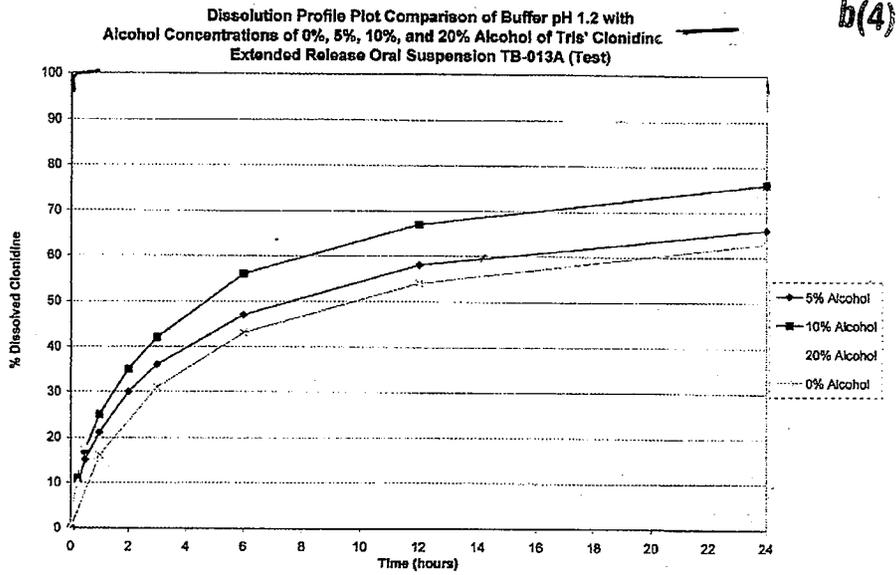
This study was performed and conducted in compliance with Good Clinical Practices and in accordance with applicable USA regulatory guidelines.

- Medium: pH1.2 (0.1 N HCl) with alcohol content of 0, 5, 10 and 20 % in a total volume of 900 mL
- Sampling times: ranged from 0 to 24 hrs, but less intensive sampling with 0 % alcohol vs. other alcohol contents

Dissolution Profile Comparisons

The following two figures compare the dissolution of the ER formulations in media with different alcoholic content.

Figure 13: Dissolution profiles to evaluate dose dumping via alcohol



The applicant concluded that dissolution increases with increasing alcoholic content, but the increase in dissolution is not great enough to suggest that dose dumping occurs. This observation is accurate but appears to be based primarily on qualitative means (visual inspection); f2 data were not provided, as recommended in Dissolution Guidance. Consequently, this reviewer decided to conduct f2 calculations to provide a semi-quantitative context to the alcohol dissolution findings. Per the dissolution guidance, $f_2 \geq 50$ indicates dissolution profile similarity (Same), whereas values < 50 indicate profiles are different.

Three types of f2 values were generated and were based on the reference dissolution profile and the number of hours dissolution was considered for.

1. Comparison of various alcohol concentrations vs. no alcohol (0 %)
 - Pro- this assessment is the best control as it assesses the absolute impact of alcohol
 - Con- the data for the relevant time frame ($\leq 3 - 5$ hr) are limited; the utility and potential clinical relevance of time points beyond 3 hr is unclear
2. Comparison of 10 % and 20 % vs. 5 % alcohol over a 3 hr period
 - Pro- this assessment is potentially the most clinically relevant and provides a reasonable number of time-matched points
 - Con- this assessment does not provide an absolute reference for the impact of alcohol
3. Comparison of 10 % and 20 % vs. 5 % alcohol over a 24 hr period
 - Pro- this assessment provides the largest number of time-matched points
 - Con- this assessment does not provide an absolute reference, and the utility and potential clinical relevance of time points beyond 3 hr is unclear

Reviewer Note on Suitability of 5 % as a reference medium

The f2 observations support the use of 5 % alcohol as a reference medium because dissolution of clonidine is comparable in 5 % and 0 % alcoholic media (see Table below).

The following table summarizes the f2 information.

Table 35 : Reviewer Generated f2 estimations*

Formulation Comparison	Time duration	F2 value	Conclusion
0.1 mg/mL ER Suspension			
5 % vs. 0 %	0 – 24 hr	66.4	Same
10 % vs. 0 %	0 – 24 hr	45.8	Different
20 % vs. 0 %	0 – 24 hr	24.4	Different
10 % vs. 5 %	0 – 24 hr	59.6	Same
20 % vs. 5 %	0 – 24 hr	30.8	Different
10 % vs. 5 %	0 – 3 hr	72.0	Same
20 % vs. 5 %	0 – 3 hr	40.6	Different
0.3 mg ER tablet			
5 % vs. 0 %	0 – 24 hr	80.4	Same
10 % vs. 0 %	0 – 24 hr	57.9	Different
20 % vs. 0 %	0 – 24 hr	30.3	Different
10 % vs. 5 %	0 – 3 hr	72.0	Same
20 % vs. 5 %	0 – 3 hr	34.8	Different

* The f2 calculations and raw dissolution data are included in the Appendix to this study

Observations

- 1) The dissolution characteristics of tablets and suspension were similar qualitatively
- 2) Both 24 hr- and 3 hr-based comparisons indicate that 20 % alcohol produced dissolution profiles that were different from no alcohol or 5 % alcohol
- 3) Apart from the 24 hr-based comparison of 10 % alcohol vs. 0 %, all 5 % and 10 % alcohol media had similar dissolution profiles relative to the reference (0 % or 5 % alcohol, as applicable).

Conclusions (In vitro Information)

- The amount of clonidine dissolved increases numerically with increasing alcohol percentage for both extended release formulations (suspension and tablets)
- Based on similarity factor testing, the dissolution at 20 % alcohol is different from that without alcohol (0 %); however, the amount released is not significant enough to suggest that unacceptable dose dumping occurs.

Abbreviated Report: Potential Impact of Alcohol Consumption on release characteristics of ER clonidine

The following table depicts the steps followed in the modeling process.

Step	Rationale	Observation
Tablet information used (PK and dissolution)	Single (SD) and multiple dose (MD) data available at 0.2 mg dose level; dissolution data available. Results for tablet should be applicable to suspension	Data were robust (sufficient for compartmental modeling)
Modeled single dose data using WinNonlin	A one compartment first order absorption model was evaluated with and without lag time	Model including lag time was better than that without: AIC criteria and visually, better fit of terminal phase and closer to Cmax
Simulated MD data using WinNonlin fit from SD data	Determine if modeling would be useful to predict steady state values which serve as external validation	Steady state profiles were reasonably well predicted
Compared Simulated MD data to observed MD data: visually comparison using Excel	Evaluate the comparability of simulated vs. observed profiles (Day 7 and Day 8) at 0.2 mg dose level	Plots suggested that fit was satisfactory, but some differences existed 1) Simulated Cmax ~ 2 - 11 % higher than observed Cmax 2) Simulated Cmin ~ 17 % lower than observed Cmin 3) Simulated slope of terminal phase comparatively steeper than that of observed. Estimated half-life of ~10 hrs reasonably comparable to the NCA terminal half-life of 12 – 13 hr
Altered absorption rate and Tlag to generate different disposition profiles	These manipulations represent the potential effect of alcohol. Based on in vitro data, alcohol will increase the rate of drug release, and minimize or eliminate lag time	Generated time-courses for comparison.
Inspected and compared profiles	Evaluate the changes in profiles due to changing absorption rate constant (ka) and Tlag	Profiles with absorption rates that were approximately three times greater (ka = 1 hr ⁻¹) than that observed without alcohol (ka = 0.3 hr ⁻¹) and no lag time had higher Cmax (18 %) and lower Cmin (~ 19 %). These differences represent the potential effect of alcohol

Highlights of Modeling Results [Parameter Estimate (%CV)]

Parameter	One compartment model with lag time	One compartment without lag time
AIC criteria	277.1	333.9
CL/F (mL/hr)	14971.45 (2.79)	16055.67 (7.17)
V/F (mL)	253445.57 (3.28)	199324.67 (20.86)
K01 (hr ⁻¹)	0.30 (6.38)	0.17 (25.38)
K10 (hr ⁻¹)	0.06 (5.83)	0.08 (27.44)
Tlag (hr)	0.85 (6.25)	NA

Highlights of Key Assumptions and Potential Limitations of these Assumptions

Assumptions	Comments and Potential Limitations
CL/F and V/F are not affected in the presence of alcohol	This is a reasonable assumption, however one must note that clonidine has complex kinetics, including presystemic metabolism and entero-hepatic recycling.
The alteration in k_a lasts throughout the dosing interval	This represents a worst case scenario. Alteration in reality may only occur during initial two hours of the absorption phase when alcohol and clonidine are in the stomach.
Simulated data adequately represent or are consistent with observed data	The simulations reasonably predict the mean steady state concentration time profiles. However, mean simulated and observed profiles are not identical. Also one can expect inter-patient variability in pharmacokinetics that the mean data do not take into account.
In vitro alcohol findings have a direct correlation with in vivo alcohol findings	No in vitro in vivo correlation has been demonstrated for clonidine in this respect

Summary and Conclusion

The following summary and conclusions are made with the previously noted assumptions.

The modeling exercise suggests that patients receiving extended release clonidine products, who have their absorption characteristics modified (increase k_a , without lag time) by alcohol (associated with binge drinking) consumption, are likely to have relatively higher C_{max} and lower C_{min} than their counterparts who do not consume alcohol. Relative to the immediate release formulation (without alcohol), ER formulations taken with alcohol may yield higher peaks and lower troughs. The clinical impact, if any of these potential changes in concentration is unclear. However, the described situation is not likely to occur because the alcohol-clonidine interaction will be limited to a two to three hour window vs. the 24-hour window.

Labeling Recommendation

The labeling should reflect the in vitro alcohol findings and include a statement that clonidine concentration changes (increased C_{max} and decreased C_{min}) are possible upon consumption of alcohol.

Plots

Legend: All data are based on a 0.2 mg daily dose

References (observed data with dashed lines)

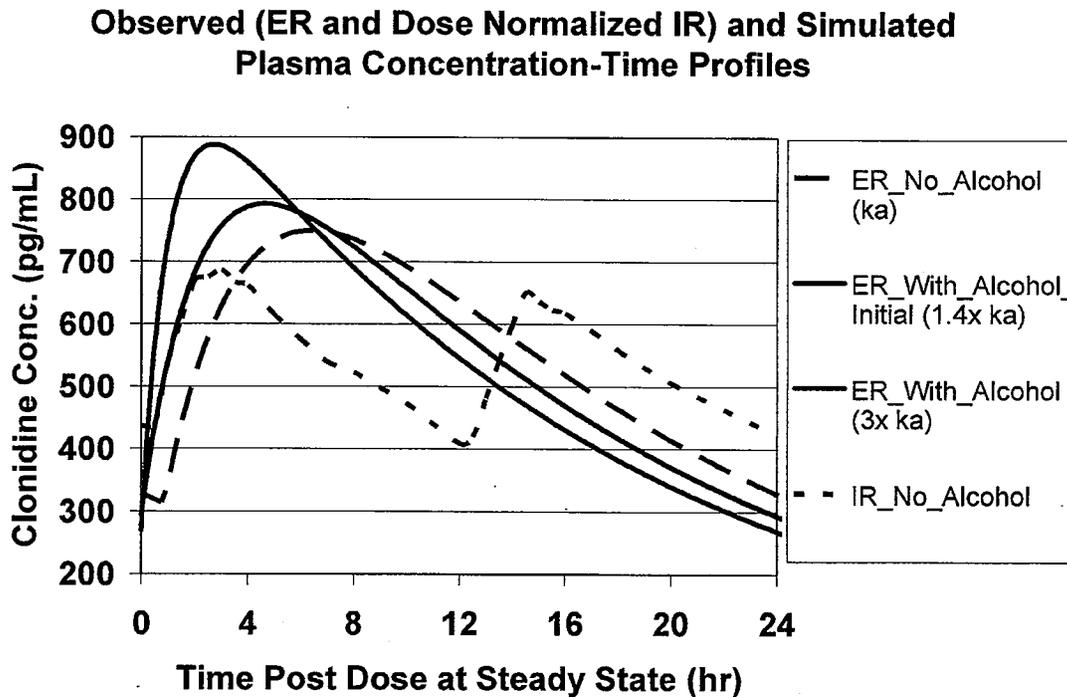
ER_With_Alcohol – $k_a = 1$ and there is no lag time for ER formulation; serves as 3x increase in absorption rate constant representing the likely worst-case scenario effect of alcohol.

ER_With_Alcohol_Initial – $k_a \sim 0.425$ (value based on in vitro studies that suggest 40% increase in release).

ER_No_Alcohol – $k_a = 0.3 \text{ hr}^{-1}$ and $T_{lag} = 0.85 \text{ hr}$ (represents initial condition with no alcohol)

IR_No_Alcohol – profile obtained from observed data at 0.3 mg q 12 hr and using dose proportional assessment from ER tablet (0.6 mg QD vs. 0.2 mg QD)

Plots of observed and simulated data to evaluate the potential effect of alcohol on clonidine pharmacokinetics



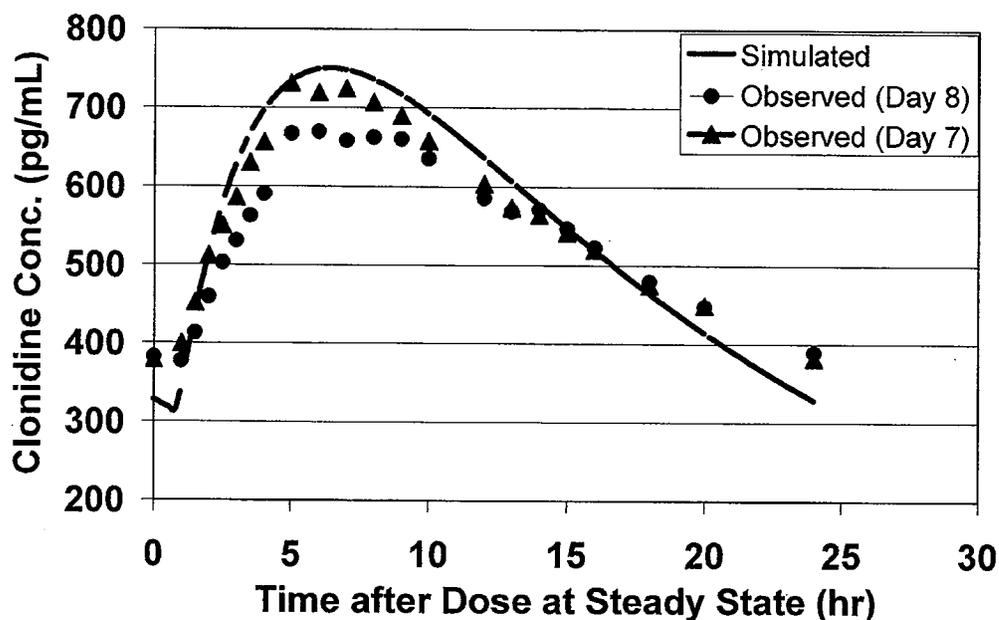
Observations: If alcohol presence results in 3-fold higher absorption for the ER formulations (reflected in k_a)

- C_{max} increases from a value of ~ 750 to 900 pg/mL
- C_{min} reduces from 330 to 270 pg/mL .
- The C_{max} with alcohol is about 200 pg/mL greater than with the IR formulation; whereas the C_{min} is about 150 pg/mL lower.

WinNonlin simulation for steady state- suitability of model

Simulated (data generated using WinNonlin: single dose to multiple dose projection)

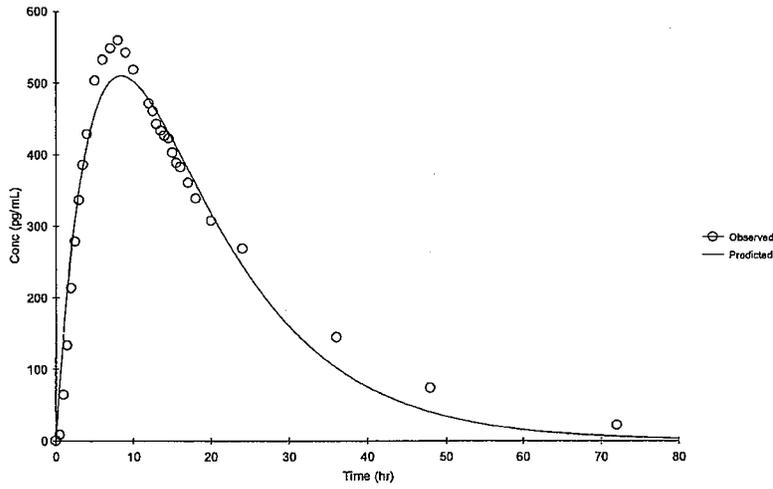
Observed and Simulated (Predicted) Plasma Concentration-Time Profiles for Clonidine ER tablets (0.2 mg QD)



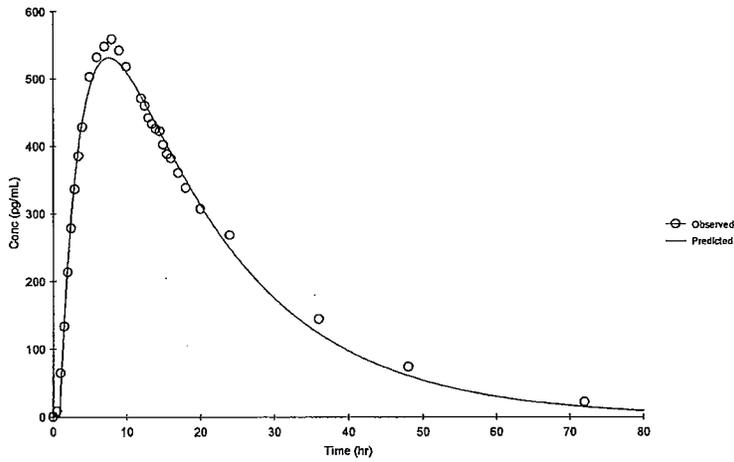
Observations: Simulated fit is closer to Day 7 observed data than Day 8. Similar magnitude of concentrations is achieved with simulated and observed. Although, simulated fit is not identical to observed data, simulations will be useful to estimate the impact of varying absorption (effect of alcohol).

Plots obtained for initial WinNonlin Fitting for Single Dose Data

- Model without lag time



- Model with lag time



WinNonlin Output for Model Fitting of Single Dose Data

Input File: Workbook - [Clonidine_Fast_Tablet_Susp_Simul.pwo]

Date: 09/04/2009
Time: 10:08:33

WINNONLIN NONLINEAR ESTIMATION PROGRAM
Version 5.2.1 Build 2008033011
Core Version 19Dec2006

Listing of input commands

```
MODEL -3
N VARIABLES 5
NPOINTS 1000
XNUMBER 1
YNUMBER 2
NCONSTANTS 3
CONSTANTS 1,200,0
METHOD 2 'Gauss-Newton (Levenberg and Hartley)'
ITERATIONS 50
MISSING 'Missing'
DATA 'WINNLIN.DAT'
BEGIN
```

Computation of initial estimates completed.

The following default parameter boundaries were generated.

Parameter	Lower Bound	Upper Bound
V_F	0.000	2.639
K01	0.000	2.235
CL_F	0.000	0.1437

Date: 09/04/2009
Time: 10:08:33

WINNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION	WEIGHTED_SS	V_F	K01	CL_F
0	50036.8	0.2639	0.2235	0.1437E-01
		RANK = 3 CONDITION NO. = 7.806		
1	40571.3	0.2135	0.1780	0.1599E-01
		RANK = 3 CONDITION NO. = 11.93		
2	39245.8	0.2049	0.1736	0.1590E-01
		RANK = 3 CONDITION NO. = 12.82		
3	39210.7	0.2000	0.1683	0.1606E-01

```

RANK = 3 CONDITION NO. = 13.93
4 39206.1 0.1998 0.1684 0.1605E-01
RANK = 3 CONDITION NO. = 13.93
CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN 0.000100
5 39205.2 0.1993 0.1678 0.1606E-01

```

```

Date: 09/04/2009
Time: 10:08:33

```

WINNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER	UNITS	ESTIMATE	STANDARD_ERROR	CV%
UNIVAR_CI_LOW	UNIVAR_CI_UPP	PLANAR_CI_LOW	PLANAR_CI_UPP	
V_F	mL	199324.665779	41573.399020	20.86
114166.065777	284483.265782	75184.512442	323464.819117	
K01	1/hr	0.167836	0.042592	25.38
0.080592	0.255081	0.040656	0.295017	
CL_F	mL/hr	16055.665684	1151.309918	7.17
13697.332155	18413.999212	12617.799328	19493.532040	

```

Date: 09/04/2009
Time: 10:08:33

```

WINNONLIN NONLINEAR ESTIMATION PROGRAM

*** VARIANCE - COVARIANCE MATRIX OF THE ESTIMATES ***

PARAMETER	V_F	K01	CL_F
V_F	0.172835E-02		
K01	0.174229E-02	0.181404E-02	
CL_F	-0.428569E-04	-0.422754E-04	0.132551E-05

*** CORRELATION MATRIX OF THE ESTIMATES ***

PARAMETER	V_F	K01	CL_F
V_F	1.00000		
K01	0.983972	1.00000	
CL_F	-0.895392	-0.862128	1.00000

*** EIGENVALUES OF (Var - Cov) MATRIX ***

NUMBER	EIGENVALUE
1	0.5659E+10
2	0.4927E+08

3 0.3983E+06

Condition_number= 119.2

Date: 09/04/2009
Time: 10:08:33

WINNONLIN NONLINEAR ESTIMATION PROGRAM

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION 1

X	OBSERVED Y	PREDICTED Y	RESIDUAL	WEIGHT	SE-PRED	STANDARDIZED RESIDUAL
0.000	0.000	0.000	0.000	1.000		
0.5000	8.210	79.14	-70.93	1.000	4.474	-1.909
1.000	64.20	148.8	-84.58	1.000	7.745	-2.310
1.500	133.0	209.8	-76.82	1.000	10.04	-2.131
2.000	213.0	263.1	-50.07	1.000	11.56	-1.407
2.500	278.0	309.3	-31.25	1.000	12.47	-0.8859
3.000	336.0	349.1	-13.07	1.000	12.92	-0.3721
3.500	385.0	383.1	1.882	1.000	13.04	0.5364E-01
4.000	428.0	412.0	16.02	1.000	12.92	0.4562
5.000	503.0	456.1	46.87	1.000	12.31	1.327
6.000	532.0	485.1	46.89	1.000	11.62	1.318
7.000	548.0	501.9	46.08	1.000	11.10	1.290
8.000	559.0	509.0	49.97	1.000	10.82	1.395
9.000	542.0	508.5	33.51	1.000	10.71	0.9347
10.00	518.0	502.0	16.02	1.000	10.66	0.4465
12.00	471.0	476.4	-5.401	1.000	10.47	-0.1504
12.50	460.0	468.2	-8.157	1.000	10.40	-0.2269
13.00	442.0	459.4	-17.39	1.000	10.33	-0.4835
13.50	433.0	450.2	-17.18	1.000	10.27	-0.4775
14.00	426.0	440.6	-14.62	1.000	10.22	-0.4062
14.50	422.0	430.8	-8.778	1.000	10.20	-0.2438
15.00	402.0	420.7	-18.71	1.000	10.21	-0.5199
15.50	388.0	410.5	-22.49	1.000	10.26	-0.6250
16.00	382.0	400.2	-18.16	1.000	10.36	-0.5049
17.00	360.0	379.3	-19.33	1.000	10.73	-0.5393
18.00	338.0	358.6	-20.55	1.000	11.31	-0.5762
20.00	307.0	318.0	-11.03	1.000	13.00	-0.3143
24.00	268.0	244.8	23.21	1.000	17.16	0.6982
36.00	144.0	101.6	42.41	1.000	22.24	1.409
48.00	73.40	39.78	33.62	1.000	16.93	1.008
72.00	21.70	5.833	15.87	1.000	5.343	0.4284

CORRECTED SUM OF SQUARED OBSERVATIONS = 890863.
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 890863.
SUM OF SQUARED RESIDUALS = 39205.2
SUM OF WEIGHTED SQUARED RESIDUALS = 39205.2
S = 37.4190 WITH 28 DEGREES OF FREEDOM
CORRELATION (OBSERVED,PREDICTED) = 0.9797

WEIGHTED CORRELATION (OBSERVED,PREDICTED) = 0.9797

AIC criteria = 333.87349
SBC criteria = 338.17546

AUC (0 to last time) computed by trapezoidal rule = 14094.1

Date: 09/04/2009
Time: 10:08:33

WINNONLIN NONLINEAR ESTIMATION PROGRAM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS

PARAMETER	UNITS	ESTIMATE	STANDARD_ERROR	CV%
AUC	hr*pg/mL	12456.661962	892.342404	7.16
K01_HL	hr	4.129896	1.046988	25.35
K10_HL	hr	8.605145	2.362736	27.46
K10	1/hr	0.080550	0.022106	27.44
Tmax	hr	8.410361	0.316074	3.76
Cmax	pg/mL	509.627655	10.749567	2.11

NORMAL ENDING

Recommendation

The dissolution data and modeling information indicate that high concentrations of alcohol (large amounts associated with binge drinking) may increase the rate of clonidine release from ER products, resulting in increased Cmax and decreased Cmin. However, the clinical impact of these concentration changes is unclear as they are of relatively small magnitude. Nevertheless, the label should indicate that alcohol consumption should be avoided during clonidine administration with ER formulations to avoid modification of the clonidine release properties. A clinical study is not deemed necessary at this time. It is noted that clonidine labeling currently states that alcohol may potentiate clonidine's CNS depressant effects.

9 Page(s) Withheld

 ✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

4.3 NDA Filing and Review Form/Refusal to File Criteria

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	22-499/22-500	Brand Name	
OCP Division (I, II, III, IV, V)	I	Generic Name	Clonidine ER Suspension/Tablets
Medical Division	Cardiovascular and Renal	Drug Class	
OCP Reviewer	Robert O. Kumi	Indication(s)	Anti-hypertensive
OCP Team Leader	Angelica Dorantes	Dosage Form	Suspension/Tablet
Pharmacometrics Reviewer	N/A	Dosing Regimen	0.2 to 0.6 once daily
Date of Submission	03/02/2009	Route of Administration	Oral
Estimated Due Date of OCP Review	10/03/2009	Sponsor	Tris
Medical Division Due Date	10/10/2009	Priority Classification	Standard
PDUFA Due Date	12/03/2009		

b(4)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				

Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2		Pilot study with suspension; Steady state evaluation for tablet- both compared to immediate release (IR) tablet
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	2		Tablet/suspension given in fed and fasted; included IR tablet
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	X			
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		Alcohol dissolution information not included in total number of studies

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Waiver requested for suspension
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			Some sections do not have appropriate links
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)				
Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			
Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			
General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
 ___ Yes ___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. Potentially, request clarification regarding dissolution information to be submitted- will it include additional alcohol dissolution information

Robert O. Kumi, Ph.D. 03/16/2009

 Reviewing Clinical Pharmacologist Date

Angelica Dorantes, Ph.D.

 Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22499	ORIG-1	TRIS PHARMA INC	CLONIDINE ER ORAL SUSPENSION b(4)
NDA-22500	ORIG-1	TRIS PHARMA INC	CLONIDINE ER ORAL TABLETS b(4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT O KUMI
09/09/2009

RAJANIKANTH MADABUSHI
09/09/2009

This sign-off represents concurrence with the primary reviewer's conclusions except for interpretation of the potential alcohol effect and the associated labeling recommendations. I will be writing a memo reflecting my interpretation of the potential alcohol effect and the corresponding implication on the labeling recommendations

ONDQA (Biopharmaceutics) Review

NDA: 22-499 and 22-500
Submission Date: 02/03/09
Product: Clonidine hydrochloride extended release oral suspension (0.1 mg/ml) and extended release oral tablets (0.2 & 0.3 mg)
Type of Submission: Original NDA
Sponsor: Tris Pharmaceutical Co., Ltd.
Reviewer: Tapash K. Ghosh, Ph.D.

Background: These 505(b)(2) NDAs, are for two new dosage forms of clonidine HCl, NDA 22-499 (ER oral suspension) and NDA 22-500 (ER tablet). Both formulations use the same extended release technology, but are formulated differently. Clonidine is a well-known centrally acting alpha-agonist which was originally approved under the tradenames Catapres and Catapres TTS as immediate release tablets (NDA 17-407) and a transdermal patch (NDA 18-891) respectively. Currently, no extended release oral dosage form is approved for clonidine.

One pilot and three pivotal bioavailability (BA) studies were sponsored by Tris Pharma Inc. in support of the NDA submissions. The application does not include a safety and efficacy study of clonidine ER formulations, but relies on demonstration of maintenance of plasma concentrations (pharmacokinetic/BA studies) within the range obtained with approved clonidine products. The three pivotal studies comprised two single dose trials and one repeat (multiple) dose trial. The single dose study was an open-label, randomized and three-way crossover study performed under fasting and fed conditions, where the following two comparisons were made:

- ER dosage form under fasted conditions vs. ER dosage form under fed conditions (food effect evaluation)
- ER dosage form under fasted conditions vs. IR dosage form under fasted conditions (relative bioavailability evaluation).

In the repeat dose trial, an open label, partially randomized, two-way cross over study design was employed at the 0.2 and 0.6 mg daily dose level. The primary comparison in this study was ER tablet vs. IR tablet at steady state (exposure comparison).

As no multiple-dose study was undertaken with the suspension, a biowaiver was requested for evaluating the pharmacokinetics of the suspension at steady state. However, as this issue is not considered as a traditional "Biowaiver" request ONDQA deals with, this issue will not be addressed in this review.

This review will focus on the proposed *in-vitro* dissolution specification. As Dr. Robert Kumi of Office of Clinical Pharmacology has already addressed the effect of alcohol on

the dissolution of clonidine ER formulations (Assessment of alcohol induced dose dumping), this review does not address that aspects of the submission in detail. Also, as the tablets are scored, comments have been made on this issue.

Recommendation:

- *The Agency's IVIVC guidance on setting dissolution specifications without an IVIVC recommends that the range at any dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Based on the evaluation of dissolution data, the reviewer proposes the following specifications for the ER dosage forms:*

Dosage Form	Strength	1 hr	3 hr	6 hr	24 hr
Suspension	0.1 mg/ml	NMT			NLT
Tablet	0.2 mg	NMT			NLT
Tablet	0.3 mg	NMT			NLT

b(4)

- *The Agency does not recommend MR dosage forms to be scored in the first place. In general, for scored tablets, we do like to see that dissolution profiles from two halves of the scored tablet is similar (shape and f2) to that of the intact tablet. We recommend that the sponsor submit dissolution data comparing profiles from two halves of the scored tablet to that of the intact tablet as an amendment within a regulatory applicable time frame.*

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

Drug Products:

Clonidine hydrochloride extended release oral suspension:

Clonidine hydrochloride (0.1 mg/mL) is formulated as an extended release oral suspension using _____ excipients. Clonidine hydrochloride is

_____. Extended release properties of the suspension were achieved _____

b(4)

_____. The final formulation also contains a citric acid _____

b(4)

_____, xanthan gum and _____ polysorbate 80 _____, glycerin and purified water, methyl and propylparaben _____, and a flavoring agent.

Formulation Data: Suspension

Ingredients	Quantity (mg/ml)	Quantity (%)
Sodium Polystyrene Sulfonate _____	_____	_____
Clonidine Hydrochloride USP	0.1	0.01
Povidone USP _____	_____	_____
Polyvinyl Acetate _____	_____	_____
Triacetin USP		
Purified Water USP		
Citric Acid USP (Anhydrous)		
Polysorbate 80 NF _____		
High Fructose Corn Syrup _____		
Sucrose NF _____		
Glycerin USP		
Methylparaben NF		
Propylparaben NF		
Xanthan Gum NF _____		
Strawberry Banana Flavor _____	_____	_____

b(4)

b(4)

b(4)

¹ Sodium Polystyrene Sulfonate USP _____
² Amount represents _____
³ Amount represents _____

b(4)

Clonidine hydrochloride extended release oral tablet:

Clonidine hydrochloride extended release tablets are formulated using _____ excipients. Clonidine hydrochloride is _____

_____. Extended release properties were achieved _____

b(4)

b(4)

Formulation Data: Tablets

Ingredients	Quantity	%	Quantity	%
	(mg/tablet) 0.2 mg ER tab		(mg/tablet) 0.3 mg ER tab	
Sodium Polystyrene Sulfonate				
Clonidine Hydrochloride USP	0.2		0.3	
Povidone USP				
Potassium Acetate				
Triacetin USP				
Microcrystalline Cellulose NF				
Lactose Monohydrate NF				
Croscopovidone NF				
Dental-Type Silica NF				
Magnesium Stearate NF				
(includes)				
Titanium Dioxide				
Polyethylene Glycol				
Hypromellose				
(includes):				
Talc				
Polydextrose				
FD & C Yellow #6 Aluminum Lake				
Titanium Dioxide				
D&C Yellow #10 Aluminum Lake				
Fractionated Coconut Oil				
Maltodextrin				
Total				
¹ Sodium Polystyrene Sulfonate				
² Amount				
³				

b(4)

b(4)

b(4)

Dissolution

Dissolution Method Development

Clonidine hydrochloride is water soluble. The dissolution method was developed to discriminate between different formulations, manufacturing process changes, and as a tool to predict the quality of the product.

Dissolution method development was initially started with Clonidine ER Suspension. Clonidine ER Tablet formulation was developed later using the tablet was designed

b(4)

b(4)

Since the same Clonidine

b(4)

_____ was used in suspension and tablets, a common dissolution method was developed.

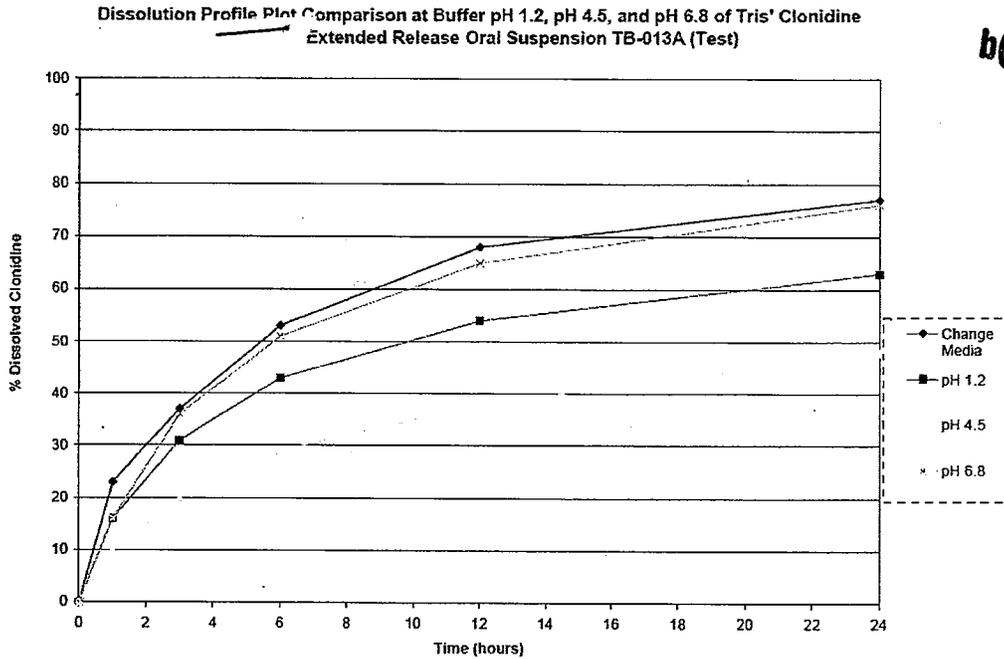
b(4)

Dissolution Media Selection

The dissolution profiles of the Clonidine _____, ER formulations in pH 1.2, 4.5, 6.8, and change media environments are shown in the 3 figures below. The percent of dissolved clonidine is lower for the formulations at pH 4.5 than in the pH 1.2, 6.8, and change media environments.

b(4)

Figure 1



Analytical Method Validation

Validation of the HPLC Test Method (M-029-DIS) for Dissolution of Clonidine Hydrochloride in Clonidine _____ Extended Release Oral Suspension, 0.1 mg per mL was performed according to signed protocol; MVP-029-DIS. The method validation studies were conducted to verify the following critical analytical parameters.

b(4)

1. Specificity
2. Linearity
3. Accuracy
4. System precision
5. Method Precision
6. Intermediate Precision
7. Robustness
8. Solution Stability
9. Filter Study

The method validation study for Dissolution of Clonidine Hydrochloride in Clonidine _____ Extended Release Oral Suspension, 0.1 mg per mL was performed using HPLC and with UV detection at _____. The column used was Alltech (Grace) Alltima C8, 150 mm x 4.6 mm, 5- μ m. The mobile phase was isocratic, Buffer: Methanol (63:37, v/v).

b(4)

Based on the method validation results, it is concluded that the test method for Clonidine _____ Extended Release Oral Suspension, 0.1 mg per mL (M-029-DIS) is specific, linear over the concentration range studied, accurate, precise and robust for routine QC release purpose.

b(4)

Summary of In Vitro Description, Assay, and Dissolution Studies

In vitro dissolution studies were conducted with the Clonidine _____ ER Tablet (0.2 mg and 0.3 mg), Clonidine _____ ER Oral Suspension, and Catapres tablet. The dissolution profiles were obtained in a change media (acidic changed to neutral) environment using the USP Apparatus II (paddle) at 50 rpm and 37°C as shown below:

b(4)

Dissolution Conditions

Apparatus	: USP Apparatus II (Paddle)
Speed	: 50 rpm
Medium	: 495 mL 0.1N HCl for 1-hour, after 1 hour sampling, add 400 mL 0.27M Phosphate Buffer Solution
Temperature	: 37°C \pm 0.5°C
Filter	: 10 μ m
Sampling Volume	: 5 mL
Time Interval	: 1, 3, 6, 24 hours

Twelve samples were tested for the Clonidine ~~ER~~ ER formulations at 1, 3, 6, and 24 hours; 6 samples were tested for the Catapres tablets at 30 minutes. For suspension, a weighed quantity (5 mL) of Oral Suspension sample and for tablets, one tablet was transferred into the bottom of the vessel containing the initial Dissolution Medium and start to run the apparatus. At the end of each time interval, collect 5 mL of the sample from the vessel through a 10 µm in-line filter. Filter through 0.45 µm filter discarding about 3 mL of sample and collect into HPLC vial. The percent dissolved met the sponsor's proposed specification parameters for both Clonidine ~~ER~~ ER formulations and the Catapres tablets when the products were tested in the change media environment (see below).

b(4)

b(4)

Table 3 Mean (SD) Dissolution Profiles for Clonidine ~~ER~~ ER Tablet Formulation, Clonidine ~~ER~~ ER Oral Suspension Formulation, and Catapres Tablet (Environment was 0.1 N Hydrochloric Acid Solution for 1 hour, after 1 hour 0.27 M Phosphate Buffer was Added to Become pH 6.8)

b(4)

	1 hr	3 hr	6 hr	24 hr
ER Tablets				
0.2 mg				
Batch # TB-014A	11.0 (0.41)	40.6 (1.12)	60.2 (1.19)	88.6 (1.71)
Batch # TB-016A	8.4 (0.37)	27.8 (1.22)	43.3 (1.45)	73.4 (2.79)
Batch # TB-021A ^a	10.7 (0.30)	38.5 (1.07)	57.3 (1.60)	86.0 (2.15)
0.3 mg				
Batch # TB-018A	11.2 (0.39)	33.0 (0.82)	48.7 (1.52)	77.6 (1.78)
Batch # TB-019A	11.2 (0.61)	33.5 (1.06)	49.8 (2.02)	80.1 (3.94)
Batch # TB-020A ^b	13.0 (0.45)	38.1 (1.31)	55.6 (2.43)	83.8 (2.88)
ER Oral Suspension				
Batch # TB-012A	9.8 (1.99)	50.7 (1.36)	69.9 (1.35)	88.7 (1.55)
Batch # TB-013A ^c	9.5 (0.66)	36.7 (0.96)	52.9 (0.99)	78.6 (1.02)
Batch # TB-015A	11.5 (0.54)	45.9 (1.40)	63.7 (1.58)	85.3 (2.18)
	30 min			
Catapres Tablets				
0.1 mg				
Lot # 851623 ^d	105.6 (1.75)			
0.3 mg				
Lot # 755233 ^e	100.3 (2.24)			

b(4)

b(4)

b(4)

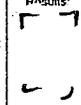
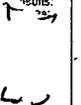
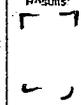
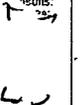
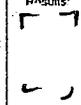
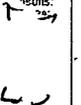
^a Batch used in Studies 1003391 and 1003317

^b Batch used in Study 1003317

^c Batch used in Study 1003390

^d Lot used in Studies 1003390 and 1003391

^e Lot used in Study 1003317

Analytical Tests	Clonidine Product ER Oral Suspension, v.v. mg/mL			Clonidine Product ER Tablet, v.v. mg/mL			Clonidine Product ER Tablet, v.v. mg/mL			Reference Product Catapres [®] Tablets 0.1 mg	Reference Product Catapres [®] Tablets 0.3 mg
	TB-012A	TB-013A	TB-015A	TB-014A	TB-016A	TB-021A	TB-018A	TB-019A	TB-020A	851623	755233
Description	Light beige viscous suspension	Light beige viscous suspension	Light beige viscous suspension	White, capsule shaped coated tablet, debossed with "NP2" on one side and scored on the other side	White, capsule shaped coated tablet, debossed with "NP2" on one side and scored on the other side	White, capsule shaped coated tablet, debossed with "NP2" on one side and scored on the other side	Yellow, capsule shaped coated tablet, debossed with "NP3" on one side and scored on the other side	Yellow, capsule shaped coated tablet, debossed with "NP3" on one side and scored on the other side	Yellow, capsule shaped coated tablet, debossed with "NP3" on one side and scored on the other side	Pale pink oval tablets, scored on one side and debossed "BI" on the other side	Pale orange oval tablets, scored on one side and debossed "BI" on the other side
Assay	102.5, 101.5%	97.4, 88.3%	97.2, 97.2%	101.2, 104.4%	102.9, 100.9%	98.7, 98.1%	100.8, 101.6%	99.8, 99.4%	99.5, 98.9%	100.1, 100.2%	100.6, 100.5%
Dissolution (Test n=12) (Ref n=8)	1-hr: 9.8% (8.4-15.0%) 20.2%	1-hr: 9.5% (8.5-10.9%) 7.0%	1-hr: 11.5% (10.7-12.4%) 4.7%	1-hr: 10.6% (10.3-11.6%) 3.7%	1-hr: 8.4% (7.8-9.1%) 4.5%	1-hr: 10.7% (10.0-11.2%) 2.8%	1-hr: 11.2% (10.4-11.8%) 3.5%	1-hr: 11.2% (9.8-12.3%) 5.4%	1-hr: 13.0% (12.2-13.9%) 3.4%	30 min: 105.6% (103.4-107.6%) 1.7%	30 min: 100.3% (97.3-102.7%) 2.2%
Mean (Range) %RSD	3-hr: 50.7% (40.8-54.0%) 2.7%	3-hr: 36.6% (35.6-38.3%) 2.2%	3-hr: 45.9% (43.3-48.8%) 3.1%	3-hr: 40.6% (39.1-42.8%) 2.8%	3-hr: 27.8% (28.2-29.7%) 4.4%	3-hr: 38.5% (36.5-40.6%) 2.8%	3-hr: 33.0% (31.8-34.4%) 2.5%	3-hr: 33.5% (30.4-34.8%) 5.2%	3-hr: 38.1% (35.6-40.0%) 3.4%	Individual Results: 	Individual Results: 
	6-hr: 66.0% (68.3-73.2) 1.9%	6-hr: 52.9% (51.5-54.9) 1.9%	6-hr: 63.7% (60.7-67.0) 2.5%	6-hr: 60.1% (58.2-62.2) 2.0%	6-hr: 69.9% (40.7-45.2) 3.4%	6-hr: 57.3% (54.5-59.8) 2.8%	6-hr: 48.7% (46.9-52.1) 3.1%	6-hr: 49.8% (45.0-52.7) 4.1%	6-hr: 55.6% (50.9-60.1) 4.4%	Individual Results: 	Individual Results: 
	24-hr: 88.7% (86.7-92.0%) 1.7%	24-hr: 78.5% (76.5-80.4%) 1.3%	24-hr: 85.3% (82.1-88.8%) 2.6%	24-hr: 88.6% (84.5-91.3%) 1.9%	24-hr: 73.4% (68.6-77.9%) 3.8%	24-hr: 88.0% (82.6-90.4%) 2.5%	24-hr: 77.6% (75.5-81.7%) 2.3%	24-hr: 80.1% (72.4-84.6%) 4.9%	24-hr: 84.0% (77.4-81.2%) 4.1%	Individual Results: 	Individual Results: 

b(4)

b(4)

Individual Results of *In Vitro* Dissolution Studies for Suspension:

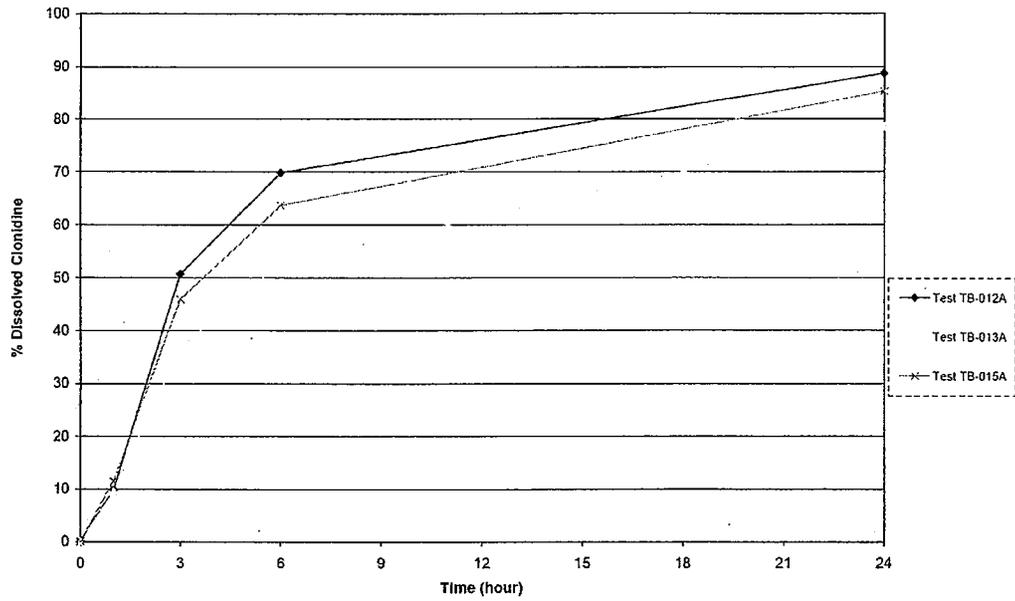
Sample No.	Lot: TB-012A				Lot: TB-013A				Lot: TB-015A			
	1 hr	3 hr	6 hr	24 hr	1 hr	3 hr	6 hr	24 hr	1 hr	3 hr	6 hr	24 hr
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	9.8	50.7	70.0	88.7	9.5	36.6	52.9	78.5	11.5	45.9	63.7	85.3
Range												
%RSD	20.2	2.7	1.9	1.7	7.0	2.2	1.9	1.3	4.7	3.1	2.5	2.6

b(4)

b(4)

b(4)

Dissolution Profile Comparison Between Three Lots of Tris' Clonidine ER Oral Suspension
0.1 mg/mL (Tests)



Individual Results of *In Vitro* Dissolution Studies for Tablets 0.2 mg:

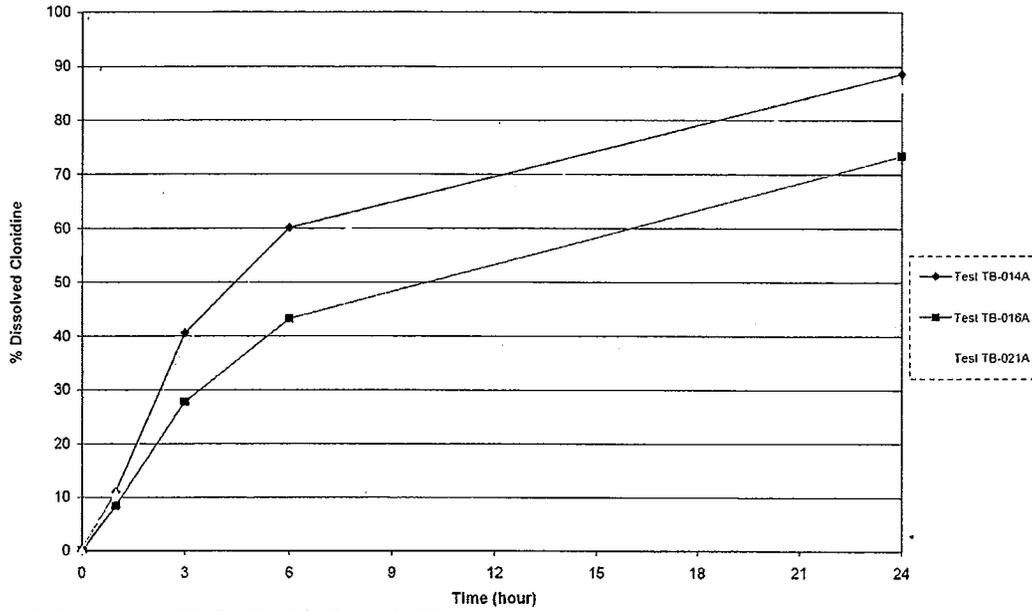
Sample No.	Lot: TB-014A				Lot: TB-016A				Lot: TB-021A			
	1 hr	3 hr	6 hr	24 hr	1 hr	3 hr	6 hr	24 hr	1 hr	3 hr	6 hr	24 hr
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	10.9	40.6	60.1	88.6	8.4	27.8	43.3	73.4	10.7	38.5	57.3	86.0
Range	_____				_____				_____			
%RSD	3.7	2.8	2.0	1.9	4.5	4.4	3.4	3.8	2.8	2.8	2.8	2.5

b(4)

b(4)

b(4)

Dissolution Profile Comparison Between Three Lots of Tris' Clondine ER Tablets
0.2 mg (Tests)



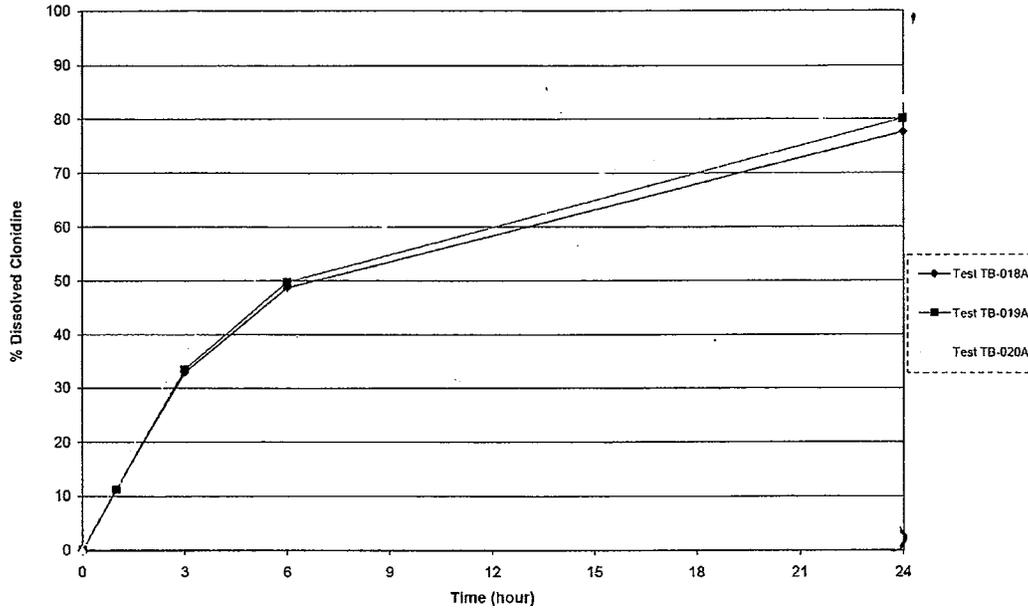
Individual Results of *In Vitro* Dissolution Studies for Tablets 0.3 mg:

Sample No.	Lot: TB-018A				Lot: TB-019A				Lot: TB-020A			
	1 hr	3 hr	6 hr	24 hr	1 hr	3 hr	6 hr	24 hr	1 hr	3 hr	6 hr	24 hr
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	11.2	33.0	48.7	77.6	11.2	33.5	49.8	80.1	13.0	38.1	55.6	84.6
Range	-----				-----				-----			
%RSD	3.5	2.5	3.1	2.3	5.4	3.2	4.1	4.9	3.4	3.4	4.4	4.1

b(4)

b(4)

Dissolution Profile Comparison Between Three Lots of Tris' Clondine ER Tablets
0.3 mg (Tests)



Proposed Specification:

Based on the dissolution data from the above mentioned batches of oral suspension and tablets, the sponsor proposed the following specifications for both oral suspension and oral tablets:

Dissolution Conditions	Apparatus:	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400 mL of 2.7 M Phosphate Buffer
	Volume:	495 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications	1 hour	NMT _____
	3 hour	_____
	6 hour	_____
	24 hour	NLT _____

b(4)

However, the Agency's IVIVC guidance on setting dissolution specifications without an IVIVC recommends that the range at any dissolution time point specification is ± 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Based on the evaluation of dissolution data, the reviewer proposes the following specifications:

Dosage Form	Strength	1 hr	3 hr	6 hr	24 hr
Suspension	0.1 mg/ml	NMT _____	_____	_____	NLT _____
Tablet	0.2 mg	NMT _____	_____	_____	NLT _____
Tablet	0.3 mg	NMT _____	_____	_____	NLT _____

