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RESEARCH**

APPLICATION NUMBER:
22-499

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number(s) 22499 (Clonidine ER
suspension)
22500 (Clonidine ER tablet)
Priority or Standard Standard

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Reviewer Name(s) Nancy Xu
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Established Name clonidine hydrochloride
(Proposed) Trade Name (not yet b(4)
approved)
Therapeutic Class Antihypertensive
Applicant Tris Pharma Inc.

Formulation(s) 0.1 mg/mL ER suspension
0.2 mg and 0.3 mg ER tablets
Dosing Regimen Once daily
Indication(s) Hypertension
Intended Population(s) Adults

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1	Recommendation on Regulatory Action	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	7
1.4	Recommendations for Postmarket Requirements and Commitments	7
2	INTRODUCTION AND REGULATORY BACKGROUND	7
2.1	Product Information	7
2.2	Tables of Currently Available Treatments for Proposed Indications	9
2.3	Availability of Proposed Active Ingredient in the United States	9
2.4	Important Safety Issues with Consideration to Related Drugs.....	9
2.5	Summary of Presubmission Regulatory Activity Related to Submission	9
2.6	Other Relevant Background Information	10
3	ETHICS AND GOOD CLINICAL PRACTICES.....	10
3.1	Submission Quality and Integrity:.....	10
3.2	Compliance with Good Clinical Practices	10
3.3	Financial Disclosures.....	11
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	11
4.1	Chemistry Manufacturing and Controls.....	11
4.2	Clinical Microbiology.....	12
4.3	Preclinical Pharmacology/Toxicology	12
4.4	Clinical Pharmacology.....	12
4.4.1	Mechanism of Action.....	12
4.4.2	Pharmacokinetics.....	12
4.4.3	Pharmacodynamics.....	23
5	SOURCES OF CLINICAL DATA.....	31
5.2	Review Strategy	31
7	REVIEW OF SAFETY.....	31
7.4.2	Laboratory Findings	34
7.4.3	Vital Signs.....	35
7.4.4	Electrocardiograms (ECGs)	35
7.6.3	Pediatrics and Assessment of Effects on Growth	35
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	35
8	POSTMARKET EXPERIENCE.....	35
9	APPENDICES	36

Clinical Review
Nancy Xu, MD
NDA 22499 & NDA 22500
clonidine hydrochloride ER oral suspension and tablet

9.1 Literature Review/References	36
9.2 Labeling Recommendations	36

Table of Tables

Table 1	Forms, strengths and dosing instructions of the currently approved and proposed clonidine products	8
Table 2	The Sponsor's Tabular Listing of Clinical Pharmacology Trials.....	13
Table 3	Trial 3317's study design (the sponsor's table)	24
Table 4	Demographics of the Bioavailability Trial 3317, an Open Label, Cross-Over Multiple-Dose Trial with ER and IR Formulations in Patients with Mild to Moderate Hypertension.....	25
Table 5	Serious adverse events with clonidine ER tablets in patients with mild to moderate hypertension (Trial 3317):.....	31
Table 6	Severe bradycardia with clonidine ER tablets in patients with mild to moderate hypertension (Trial 3317)	32
Table 7	Common Adverse Events in Multiple Dose Trial in Mild to Moderate Hypertensive Patients (Trial 3317).....	33

Table of Figures

Figure 1	Simulation of Plasma Clonidine Concentration-Time Profiles In Patients with End Stage Renal Disease on Hemodialysis.....	15
Figure 2	Mean Plasma Concentrations Over Time after Single Doses of Clonidine ER Tablet or Oral Suspension under Fasted and Fed Conditions (Trials 3390 And 3391).....	17
Figure 3	Mean Steady State Plasma Concentration Time Profile for 0.6 Mg Total Daily Dose of ER Clonidine Tablet (2 X 0.3 Mg Tablets QD) and Catapres® IR Tablets (0.3 Mg Q 12 Hours)	19
Figure 4	<i>In Vitro</i> Percent Dissolution Time Profiles of ER and IR Tablets with Alcohol	20
Figure 5	Applying Catapres-TTS Patch with the Last Dose of ER	22
Figure 6	Mean (Standard Error) of Sitting Blood Pressures with 0.2 Mg of ER Clonidine Tablet at Day 1 and Day 7 in Patients with Mild to Moderate Hypertension (N=32).....	26
Figure 7	Mean Systolic and Diastolic Blood Pressures on 0.6 Mg Clonidine ER (Left Panel) and IR Tablets (Right Panel) (N=16 Each Formulation Group)	27
Figure 8	Mean (Standard Error) of Sitting and Standing Heart Rate with 0.2 Mg of ER Clonidine Tablet on Day 1 and Day 7 in Patients with Mild to Moderate Hypertension.....	28
Figure 9	Steady State Heart Rate-Time Profiles 0.2 Mg and 0.6 Mg Dose Levels for ER Clonidine Formulations	29
Figure 10	Mean (SE) of Steady State Heart Rates for 0.6 Mg of Clonidine ER per Day (Left Panel, N=16) and 0.3 Mg Bid of Clonidine IR (Right Panel, N=16).....	30

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical perspective, I recommend approval of clonidine ER (ER) tablet (0.2 and 0.3 mg) and oral suspension (0.1 mg/mL) formulations for the treatment of hypertension in adults. This approval will be contingent on a satisfactory response to the outstanding chemistry issues and an agreement on labeling.

1.2 Risk Benefit Assessment

To support the claim, the sponsor submitted three bioavailability trials with pharmacodynamic (PD) and adverse event data. The pharmacokinetic (PK) results from the trials meet the bioavailability criteria for ER products. Furthermore, despite having a once daily rather than the twice daily dosing regimen for the reference listed immediate release (IR) formulation, the ER formulations meet the area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) criteria for bioequivalence that are used for approving generic products. Minimal plasma concentration (C_{min}) was also maintained within the 80-125% range for the reference listed IR formulation. Moreover, there was no evidence for dose dumping in the presence of food or alcohol. Lastly, the steady state pharmacodynamic (PD) effects on blood pressure and heart rate with the ER formulation are similar to the IR clonidine formulation. Therefore, the PK and PD data support the ER properties and therapeutic equivalence of the ER formulations to the reference IR formulation.

With regard to safety, there is very limited experience with clonidine ER formulations in controlled trials. Nonetheless, based on explorations of the safety data in the three trials, the adverse event profile for the ER formulation is similar to the IR clonidine formulation in the 0.2 and 0.6 mg dose levels. Therefore, despite the small sample sizes for the trials, given the extensive safety experience with IR clonidine over the last 30 years, there are unlikely to be adverse events that have not been previously reported within the studied dose range.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Clonidine, a centrally acting α_2 adrenergic agonist, has been used for over 3 decades for the treatment of hypertension.

The applications for the two 24-hour ER clonidine hydrochloride formulations, oral suspension (NDA 22499) and tablet (NDA22500), were filed under the 505 (b)(2) regulatory pathway. The primary reference listed drug (RLD) is Catapres® immediate release (IR) clonidine hydrochloride tablets, administered twice a day (BID). In addition, the applications make reference to Catapres-TTS®, a clonidine based transdermal product that is applied once weekly. No reference is made to the modified release clonidine product, Jenloga® which was approved during the review of these applications.

The forms, strength and dosing instruction of the currently approved non-generic and proposed clonidine products are summarized in the table below.

Clinical Review
 Nancy Xu, MD
 NDA 22499 & NDA 22500
 clonidine hydrochloride ER oral suspension and tablet

Table 1 Forms, strengths and dosing instructions of the currently approved and proposed clonidine products

Approved Products	Form	Strength	Dosing Instruction			Maximum Dose
			Initial Dose(s)	Dosing Frequency	Titration	
*Catapres® (clonidine hydrochloride)	IR Tablet (scored)	0.1, 0.2, 0.3 mg	0.1 mg bid	Twice a day	Increase by 0.1 mg per day at weekly interval	² 0.6 mg per day
*Catapres-TTS® (clonidine)	ER ¹ Transdermal	0.1, 0.2, 0.3 mg per 24 hours	0.1 mg per day	Every week	Increase by 0.1 mg per day at weekly interval	Up to 0.6 mg per day
Jenloga® (clonidine hydrochloride)	MR Tablet	0.1 mg tab	0.1 mg at bedtime	Twice a day	Increase by 0.1 mg per week	Up to 0.6 mg daily in divided doses (morning and bedtime)
Proposed products						
(clonidine hydrochloride)	ER tablet (scored)	0.2 & 0.3 mg	0.2 mg per day	Once daily	Increase by 0.1mg per day at weekly interval	² 0.6 mg per day
(clonidine hydrochloride)	ER suspension	0.1 mg/mL	0.2 mg per day	Once daily	Increase by 0.1mg per day at weekly interval	² 0.6 mg per day

IR=immediate release, MR=modified release

*Indicates reference listed drugs

¹Achieve therapeutic plasma clonidine levels by 2-3 days after initial application

²Label states '_____'

b(4)

b(4)

b(4)

As shown above, for the adult population in general, the starting daily equivalent doses for all approved clonidine products (Catapres® immediate release tablet, Catapres® transdermal patch, and modified release Clonidine ER) are 0.1 mg to 0.2 mg per day.

Clinical Review
Nancy Xu, MD
NDA 22499 & NDA 22500
clonidine hydrochloride ER oral suspension and tablet

For the scored clonidine IR tablet, the smallest possible starting dose is 0.05 mg bid, which may be used for an elderly population. The approved dose range is from 0.2 mg to 0.6 mg per day. In addition, the clonidine IR label states that "studies have indicated that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been employed." Lastly, the trade name, _____ for the proposed formulations has not been approved. Hence, for the purpose of this review, I will refer to the proposed formulations simply as clonidine ER formulations.

b(4)

b(4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Among the classes of anti-hypertensive medications, currently the mainstay of therapy includes beta-blockers, diuretics, and the blockers of the renin-angiotensin receptor pathway. Clonidine is usually used in patients with inadequately controlled hypertension despite other classes of antihypertensive medications. The three approved forms of clonidine products are shown above in table 1. The clonidine transdermal formulation, Catapres®-TTS, is an ER product which is applied once weekly. ER once a day products are also available in other antihypertensive classes, including beta blockers (e.g. Toprol XL) and calcium channel blockers (e.g. Procardia XL).

2.3 Availability of Proposed Active Ingredient in the United States

Clonidine hydrochloride, the active ingredient for the ER formulations, is available in the United States. This active ingredient is the same as that used in the reference clonidine IR formulation.

2.4 Important Safety Issues with Consideration to Related Drugs

Not applicable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In a pre-IND meeting held on April 4, 2008, the following issues were discussed and agreements reached.

1) If the sponsor shows that formulations "produce plasma concentrations in the therapeutic range (concentrations achieved by 0.2 to 0.6 mg clonidine)" of the reference product, there would be no need for "additional clinical assessment (e.g. PK/PD) study". In addition, the sponsor was requested to demonstrate the following:

- properties of a sustained release
- no dose dumping by food effect study, and
- consistent PK performance between individual units.

2) On the number and type of multiple-dose studies for the ER formulations to support approval, the sponsor asserted that the tablet formulation " _____ and drug release rate in both formulations is controlled ' _____' Therefore, the sponsor argued both formulations should exhibit similar release profiles *in vitro* and *in vivo*. Based on the sponsor's assertions, the Division agreed that "if the sponsor can show similar dissolution profiles throughout the shelf-life of the products, a single multi-dose PK study using the *tablet* formulation is likely to be sufficient."

b(4)

3) The requirement for pediatric studies for both ER formulations was emphasized to the sponsor. The Division noted that the pediatric study requirements will not delay approval of an adult product.

2.6 Other Relevant Background Information

No other relevant background information is available.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity:

The quality of the submission was generally acceptable. The following items were missing, but later submitted upon requests.

a) Case report forms for trial 3317 were received on June 25, 2009, after a request made in the 74-day letter, which was sent on April 16, 2009.

b) Datasets of demographics, vitals and adverse events in readable format were received on July 10, 2009 upon a couple of requests, first of which was sent in the 74-day letter on April 16, 2009.

c) Laboratory values for trial 3317 were received on September 28, 2009.

3.2 Compliance with Good Clinical Practices

Acceptable. According to the sponsor, the studies were conducted in accordance with the current revision of the Declaration of Helsinki of October 2000 modified by the 2002 World Medical Association's clarification of 2002.

Clinical Review
Nancy Xu, MD
NDA 22499 & NDA 22500
clonidine hydrochloride ER oral suspension and tablet

3.3 Financial Disclosures

The sponsor certifies that there is no evidence of conflict of interest by any of the investigators for both NDAs.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Clonidine hydrochloride is [redacted] ER properties were [redacted] b(4)

[redacted] this process forms [redacted] Both the clonidine ER tablet and suspension formulations use this [redacted] coating technology. Currently, there is no drug with this particular type of [redacted] coating on the US market. b(4)

In the oral suspension formulation, [redacted] coating. b(4)

The drug concentration of the ER oral suspension is 0.1 mg/mL. The drug product is manufactured in the ER tablet form in two strengths, 0.2 and 0.3 mg. The tablet is scored to facilitate breaking of the tablet into two halves. According to chemistry manufacturing and controls reviewer, Dr. Amit Mitra, the dissolution data comparing profiles from two halves of the scored ER tablet to that of the intact tablet provide assurance of uniform distribution of dosage upon breaking. Therefore, the lowest possible dosage with the ER scored tablet is 0.1 mg. b(4)

From chemistry manufacturing and controls (CMC) perspective, there are several outstanding issues that could delay approval. First, [redacted] was found to be deficient by the Office of Generic Drugs' review of the Drug Master File. The sponsor's responses to these deficiencies are pending review at this time. Secondly, the [redacted] coating [redacted] outside the traditionally recommended specification range. This impurity could be problematic for this chronic use drug, and is pending further evaluation. Third, a study still needs to be conducted to ensure that the extractable materials from the oral suspension container comply with USP criteria. b(4)

4.2 Clinical Microbiology

Not relevant

4.3 Preclinical Pharmacology/Toxicology

Not relevant

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Clonidine is a centrally acting α_2 -adrenergic agonist. It reduces sympathetic outflow from the central nervous system, peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

4.4.2 Pharmacokinetics

The key rationale for approving clonidine ER formulations on the basis of bioequivalence (defined as producing AUC and C_{max} within 80% to 125% of the reference listed product, clonidine IR) is that bioequivalence equates therapeutic equivalence in a study population. In the review of PK and PD, I will summarize the data and discuss whether the ER formulations and the reference listed clonidine IR product are biologically and therapeutically equivalent and the implications for the proposed products' labeling.

The applications include PK studies and literature references to support the existence of an exposure (concentration)-response relationship for clonidine. One pilot and three pivotal bioavailability (BA) studies were submitted in these applications. The primary objectives in these trials are bioavailability comparisons, and there are no clinical efficacy primary endpoints. The trials are summarized in Table 2 below.

Table 2 The Sponsor's Tabular Listing of Clinical Pharmacology Trials

Study No.	Study Objective	Study Design	Treatments [Product ID]	Subjects (No. M/F) Type Age: Mean (Range)
M1FT07010	A Pilot Relative Bioavailability Study of Clonidine 0.1 mg/mL ER Oral Suspension v. Catapres® 0.1 mg Tablets under Fasting Conditions	Randomized, Single-Dose, 2-Way Crossover, 2-Treatment, Open-Label, Under Fasted Conditions	Clonidine ER Oral Suspension 1 x 0.2 mg Dose under fasting conditions RD0072-065 [Treatment A] Catapres® IR Tablets 2 x 0.1 mg Dose under fasting conditions 755411 [Treatment B]	12 (10M/2F) Healthy subjects 38 years old (22-52)
1003390	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	Randomized, Single-Dose, 3-Way Crossover, 3-Treatment, Open-Label, Under Fed and Fasted Conditions	Clonidine ER Oral Suspension 1 x 0.2 mg Dose under fasting conditions TB-013A [Treatment A] Catapres® IR Tablets 2 x 0.1 mg Dose under fasting conditions 851623 [Treatment B] Clonidine ER Oral Suspension 1 x 0.2 mg Dose under fed conditions TB-013A [Treatment C]	26 (12M/14F) Healthy subjects 29 years old (20-53)
1003391	A 3-Period, 3-Treatment, 3-Way Crossover Bioavailability Study of Clonidine Extended Release Tablet (0.2 mg) Under Fed and Fasted Conditions	Randomized, Single-Dose, 3-Way Crossover, 3-Treatment, Open-Label, Under Fed and Fasted Conditions	Clonidine ER Tablets 1 x 0.2 mg Dose under fasting conditions TB-021A [Treatment A] Catapres® IR Tablets 2 x 0.1 mg Dose under fasting conditions 851623 [Treatment B] Clonidine ER Tablets 1 x 0.2 mg Dose under fed conditions TB-021A [Treatment C]	26 (8M/18F) Healthy subjects 39 years old (21-64)
1003317	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 Extended Release Tablets Versus Catapres® at a 0.6 mg Daily Dose in Mild to Moderate Hypertensive Patients	Multi-Dose, Steady State, 4-Treatment, Open-Label, Partially-Randomized ¹	Clonidine ER Tablets 1 x 0.2 mg Dose under fasting conditions TB-021A [Treatment A] Clonidine ER Tablets 2 x 0.2 mg Dose under fasting conditions TB-021A [Treatment B] Clonidine ER Tablets 2 x 0.3 mg Dose under fasting conditions TB-020A [Treatment C] Catapres® IR Tablets 2 x 0.3 mg Dose under fed conditions 755233 [Treatment D]	32 (27M/5F) Mild to Moderate Hypertensive Patients 43 years old (21-72)

(Source: the sponsor's CSR in section 5.2, Tabular Listing of Clinical Studies)

¹ Patients received treatment A followed by treatment B during phase 1 (upward titration phase) and treatment B followed by treatment A during phase 3 (downward titration phase). During phase 2, patients received treatments C and D in randomized crossover fashion.

As shown above, in the open-label crossover trials 3390 and 3391, clonidine ER tablet and suspension formulations (at strength of 0.2 mg per day) were respectively compared to the reference Catapres® IR in healthy subjects. Both studies had a 7-day washout period between each treatment. In the open-label crossover, force titration, partially randomized trial (3317), clonidine ER dose levels 0.2, 0.4 and 0.6 mg per day were tested in patients with mild and moderate essential hypertension who are on two or fewer antihypertensive medications during the screening phase. These tested daily ER doses were the doses of the approved clonidine products and the most common

Clinical Review
Nancy Xu, MD
NDA 22499 & NDA 22500
clonidine hydrochloride ER oral suspension and tablet

therapeutic doses used for the treatment of hypertension. The study was designed to compare steady state exposures between the ER and IR tablets. There were up- and down-titration phases. There was no washout period between phases or treatments.

Dr. Robert Kumi reviewed the pharmacokinetic parameters of clonidine ER formulations as compared to the reference IR formulation. Please see his review for details. Briefly, he found that the applications met the bioavailability criteria for ER products for ER products as specified in the CFR and Bioavailability Guidance. Specifically, the ER oral suspension and tablet products:

- met the ER claims (decreases dosing frequency)
- demonstrated no dose dumping in the presence of food (high fat meal) (Figure 2 and Figure 4 below)
- obtained systemic exposures (AUC) and C_{max} equivalent (within the 80% to 125%) to the reference listed IR product, Catapres® after single dose administration under fasted conditions (see Figure 2 and Figure 4 below).

Furthermore, at steady state, the concentrations for the ER tablet were largely within the therapeutic range of 0.2 to 2.0 ng/mL. In addition, steady state AUC, C_{max} and C_{min} are supportive of dose-linearity within the 0.2 mg and 0.6 mg dose levels (Dr. Kumi's review, table 6). Moreover, the ER tablet formulation (0.3 mg) provided consistent pharmacokinetic (PK) performance between individual dosage units (Dr. Kumi's review, table 7). Lastly, Dr. Kumi expects the steady state performances of the suspension and the tablet to be similar since both formulations utilize identical _____ technology and exhibit similar single dose PK characteristics. Therefore, based on the above findings and reasons, Dr. Kumi recommended approval for these products. b(4)

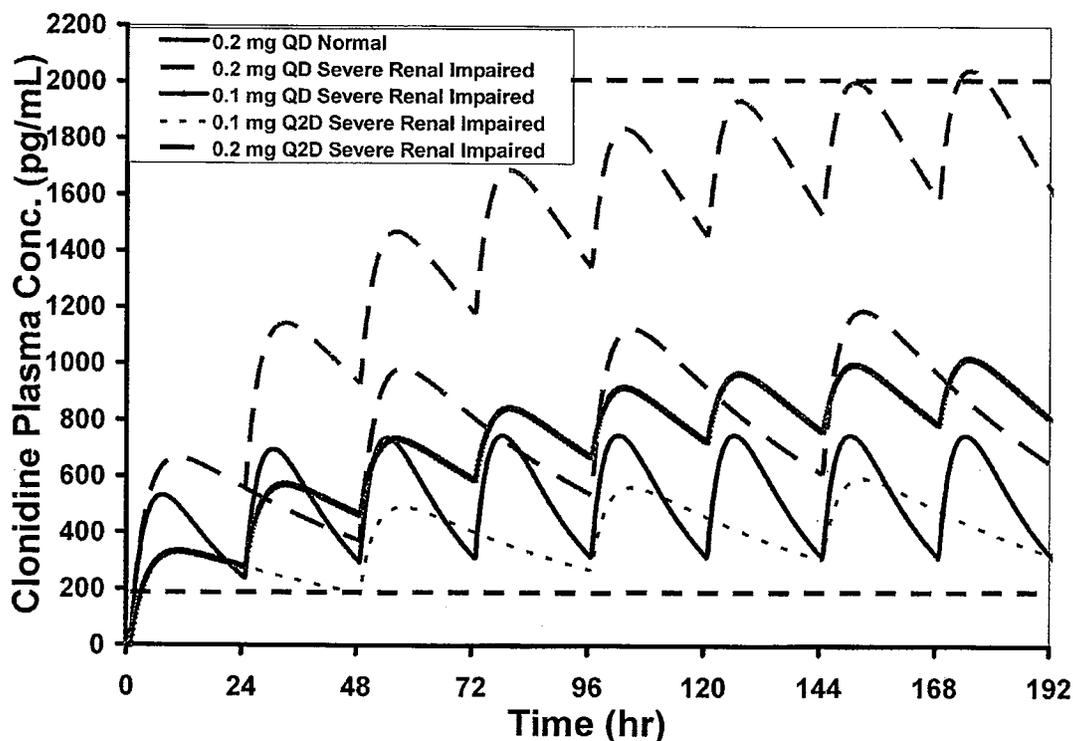
Compared with the IR formulation, the ER formulations met the AUC and C_{max} criteria for bioequivalence that are used for approving generic products. However, with different dosing intervals, the ER and IR formulations technically can not be called "bioequivalent". Below, I will highlight in more detail the key PK data on the RLD and the two proposed ER formulations. Lastly, based on comparisons of the PK and PD properties of ER and IR products, I will discuss my recommendations for the labeling of the ER products.

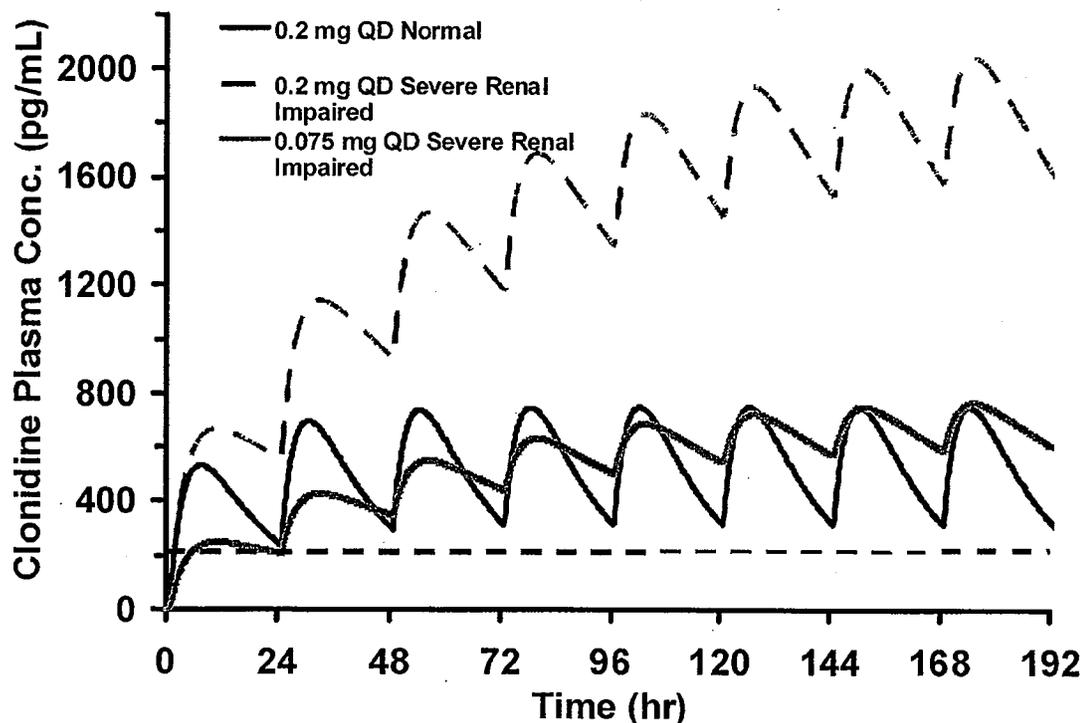
According to the clonidine hydrochloride IR label, following oral administration, about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours and about 50% of the absorbed doses are metabolized in the liver.

After a single dose of the clonidine ER tablet and oral suspension in fasted and fed conditions, the mean plasma half-lives (~ 13 hours) in healthy subjects are similar to that to the mean plasma half-life of IR clonidine (12.7 hours) (see table 32, Dr. Kumi's review for details). The steady state half-life of clonidine ER tablet is approximately 20.0 +/- 12 hours (table 18, Dr. Kumi's review).

According to the label, the half-life of clonidine IR "may increase up to 41 hours in patients with severe impairment of renal function," corresponding to a decrease in renal clearance. According to Hutler et al, 1979, in six patients with end stage kidney disease receiving hemodialysis with cordis-dow hollow fiber Model 5 and Gambro-Lundia 13.5 parallel plate dialyzers, the half-life of clonidine is increased up to 41 hours. Furthermore, only 5% of the total body stores of clonidine were removed during a 5 hour dialysis treatment. This increase represents a 3.5-fold increase as compared to that of healthy subjects. Since clonidine ER formulations were not directly studied in patients with renal impairment (see Table 4 below), to determine the appropriate starting dose of the ER formulations for the anuric end stage renal disease patients receiving hemodialysis, Dr. Madabushi simulated the concentration-time profiles of several dosing regimens in severe renal impairment (see Figure 1 below).

Figure 1 Simulation of Plasma Clonidine Concentration-Time Profiles In Patients with End Stage Renal Disease on Hemodialysis





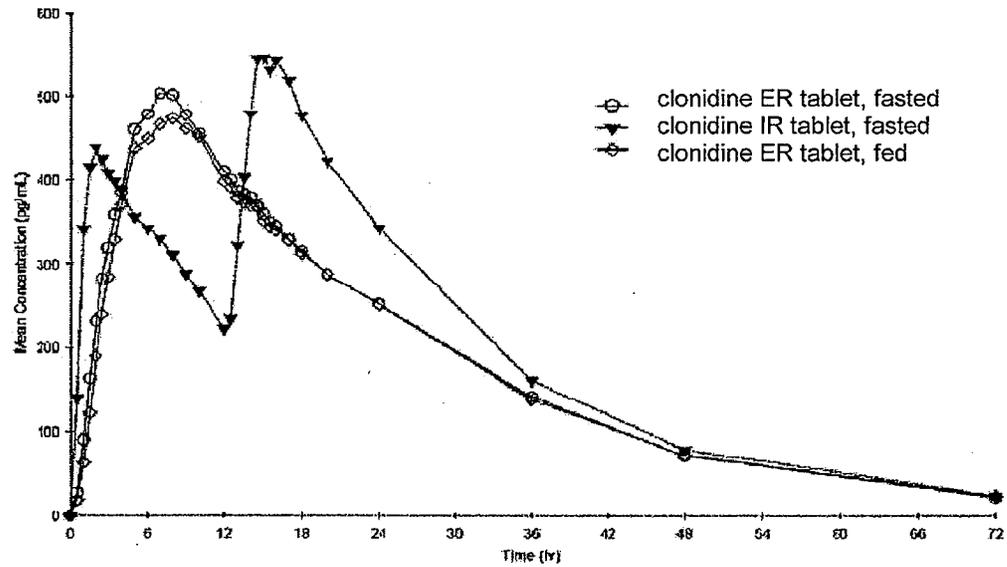
Source: Dr. Dr. Madabushi's simulations

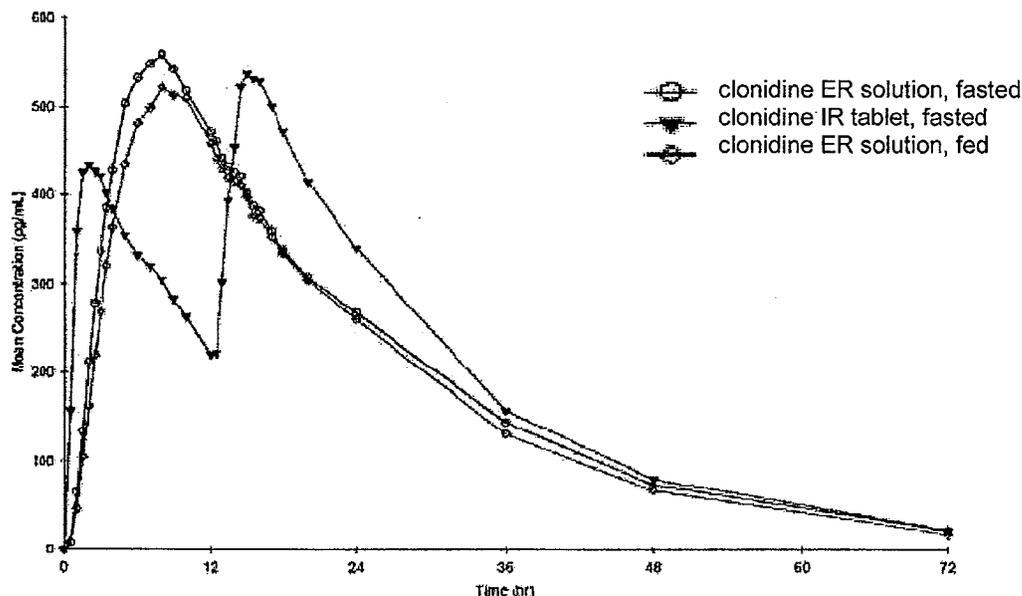
As shown above, the reference plasma clonidine concentration time profile (blue line) represents the 0.2 mg once-a-day dosing regimen in subjects with normal kidney function. Compared to the reference, under a 0.2 mg once-a-day dosing regimen in anuric patients with end stage kidney disease on hemodialysis (purple line), there is a 2.7-fold increase in C_{max} (2045 pg/mL) at steady state. Starting with a dose of 0.1 mg per day (orange line, upper panel), there was a 35% increase in C_{max} (1022 pg/mL) and a 2.5-fold increase in C_{min} (815 pg/mL) compared to the reference. The peak-to-trough ratio at steady-state is smaller with 0.1 mg (1.3) compared to 0.2 mg per day (2.3), which could lead to less blood pressure fluctuation during the day. Therefore, the 0.1 mg once daily starting dose in hemodialysis patients could reasonably approximate the reference C_{max} exposure and has a dosing schedule that is conducive for compliance. With this dosing regimen, however, there is the potential for tighter than expected blood pressure control, sedation, heart rate effects compared to administering 0.2 mg in patients with normal renal function, as reflected by the higher C_{min} and AUC values. Dosing with 0.075 mg of clonidine per day (green line, lower panel) most closely approximates the PK parameters of the reference at steady state. Please also see the labeling section for dosing my recommendations.

It is worth noting that in patients with moderate to severe kidney impairment, *not* on dialysis, medical literature (Niarchos et al, 1978) indicates less than expected blood pressure response to clonidine as compared to patients without renal impairment. This observation is also seen with other classes of anti-hypertensive and might be related in part to fluid retention with renal impairment. Therefore, in this population, clonidine dosage can be initiated at the same dose as for patients without renal impairment and titrated per individual's benefit and risk assessment. Please also see the labeling section for dosing my recommendations.

Next, I will summarize the single dose and steady state plasma concentration time profiles for clonidine ER and IR formulation(s) through the graphic representations below.

Figure 2 Mean Plasma Concentrations Over Time after Single Doses of Clonidine ER Tablet or Oral Suspension under Fasted and Fed Conditions (Trials 3390 And 3391)





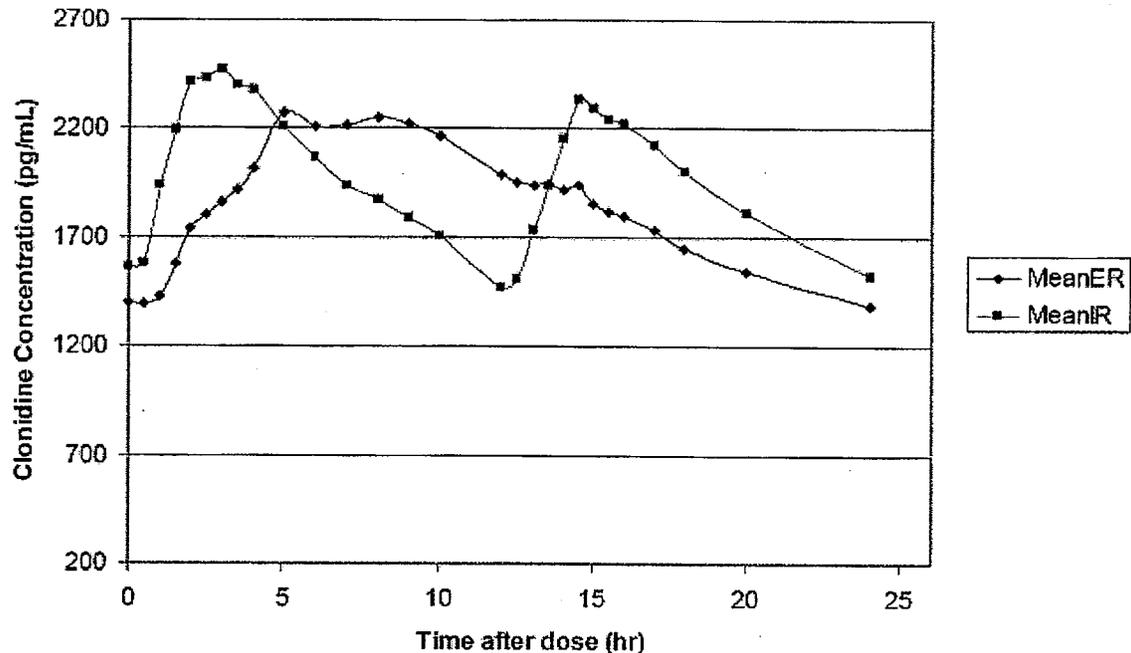
(Source: Dr. Robert Kumi's review, figures 1 and 2)

The figure above illustrates mean plasma concentrations over time after single doses of clonidine ER tablet (upper panel) or oral suspension (lower panel) under fasted and fed conditions compared to the daily equivalent dose of clonidine IR under fasted condition.

Reviewer's comment: As shown above, the AUCs of the ER and IR formulations, at the same daily equivalent dose, are similar as expected. Despite the difference in dosing frequency between ER and IR formulations, the C_{max} and C_{min} for the ER formulations are reasonably similar to the IR formulation (within the 80 to 125% range of IR).

The two ER formulations also have similar plasma concentration time profiles, as expected given the similar dissolution time profile (see Dr. Tapash Ghosh's review, table 3). Furthermore, food had minimum impact on the concentration time profiles for both ER formulations. The close proximity of C_{max} in ER formulations in the presence and absence of food with that of RLD provides reassurance that C_{max} driven adverse event profile is similar to that of RLD. Similar C_{min} provides reassurance that therapeutic concentrations will be maintained.

Figure 3 Mean Steady State Plasma Concentration Time Profile for 0.6 Mg Total Daily Dose of ER Clonidine Tablet (2 X 0.3 Mg Tablets QD) and Catapres® IR Tablets (0.3 Mg Q 12 Hours)

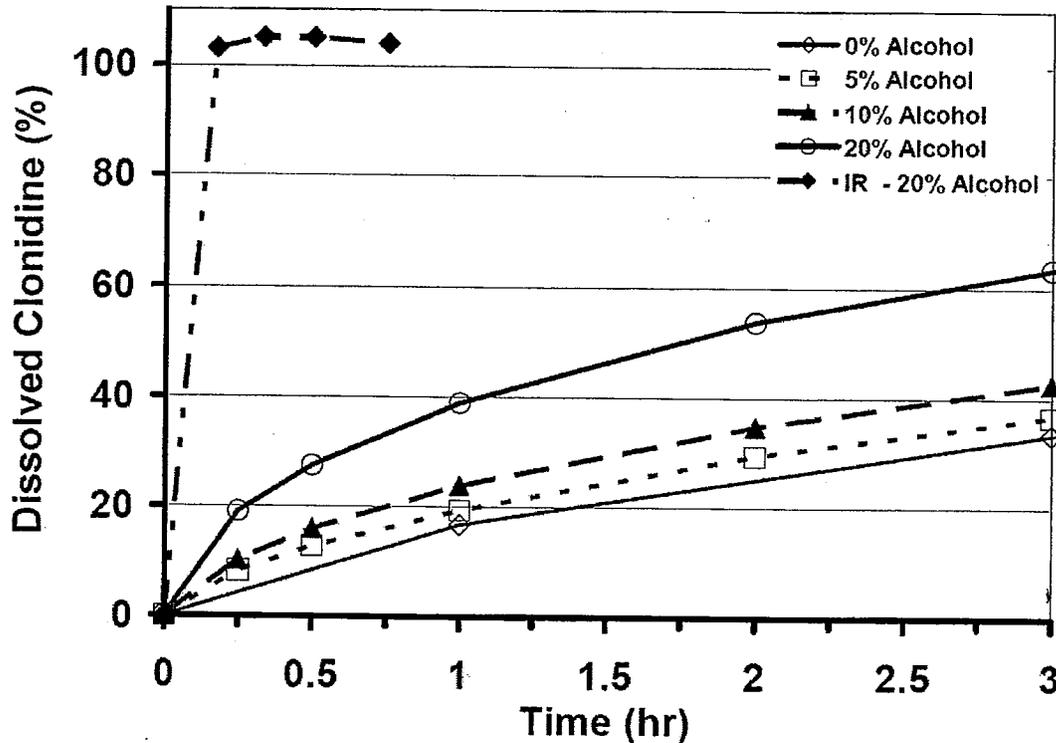


(Source: Dr. Robert Kumi's review, section 2.2.4.2)

Reviewer's comment: At steady state, the ER formulation has lower and more gradual onset of Cmax and lower Cmin than the equivalent daily dose of clonidine IR formulation. The geometric means and the respective 90% CI of Cmax, Cmin and AUC for the ER formulation are also within the acceptable range of 80-125% of the IR formulation over a 24-hour period and therefore support the ER claim (see Dr. Kumi's review, tables 21 and 22 for summary data).

Lastly, the current Office of Generic Drugs Guidance requires a demonstration that alcohol does not result in "premature release of the drug (aka dose dumping)". An *in vitro* dissolution study, performed to evaluate the impact of alcohol on the release characteristics of the clonidine ER tablet, showed that in the presence of a medium containing 20% alcohol at pH 1.2 (equivalent to consuming 1 standard drink of 80 proof distilled spirits), dissolution was increased by approximately 40% as compared to a medium without any alcohol at pH 1.2 over a 3 hour period (Figure 4). In comparison, in the presence of a 20% alcohol medium, the IR tablet completely dissolved in less than 15 minutes, which is much more rapidly than the ER tablet

Figure 4 In Vitro Percent Dissolution Time Profiles of ER and IR Tablets with Alcohol



(Source: Dr. Rajanikanth Madabushi's review, figure 1)

Reviewer comment:

Assuming that in the human gastrointestinal tract, the 20% alcohol is in continuous contact with clonidine for 3 hours, and all of the dissolved clonidine is absorbed, the 40% increase in dissolution observed in vitro could result in a 40% increase in drug absorption rate (K_a).

Not directly tested in the vitro assay is the effect on dissolution with 40% alcohol (7 standard drinks of 80 proof distilled spirits), which is meant to simulate the worst-case alcohol-effect scenarios.

To explore the potential worst-case scenarios on clonidine plasma concentration-time course and blood pressure, Dr. Rajanikanth Madabushi performed modeling and simulation. For his simulation, he assumed a 100% increase in K_a to represent the effect with 40% alcohol. Based on this model, exposing clonidine ER tablet to 40% alcohol in the gastrointestinal tract for 3 hours could increase steady state C_{max} by approximately 13% and decrease C_{min} by 18% as compared to ER without any concomitant alcohol exposure. Based on these results and the known log linear relationship between blood pressure and serum clonidine concentration, Dr. Madabushi

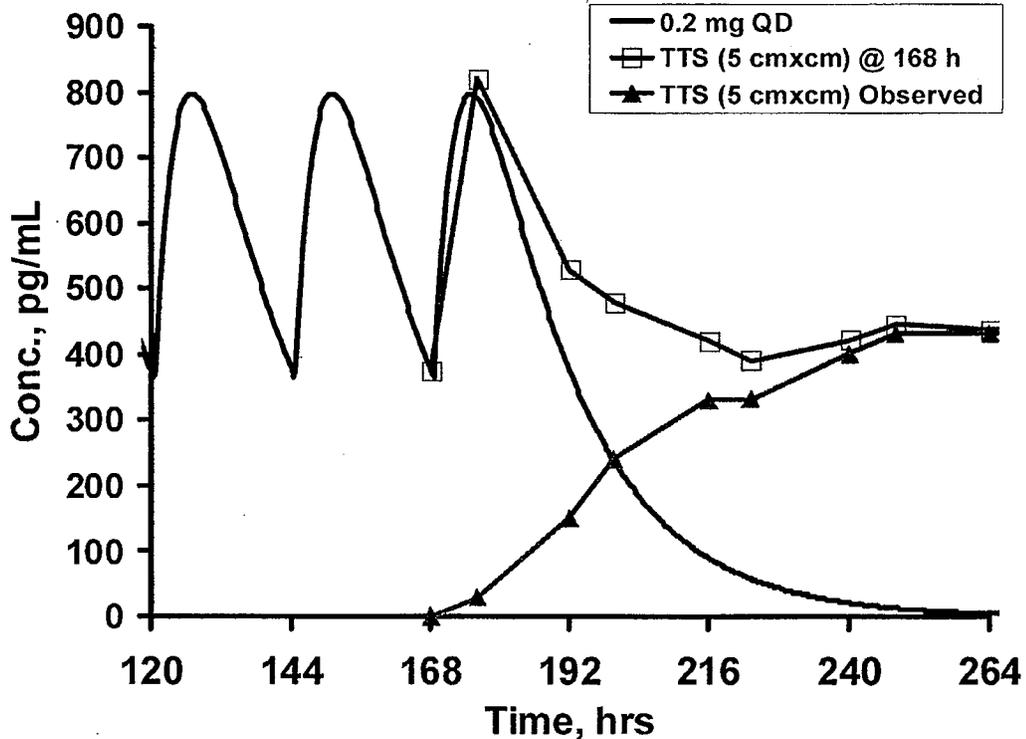
Clinical Review
Nancy Xu, MD
NDA 22499 & NDA 22500
clonidine hydrochloride ER oral suspension and tablet

predicted that even with this worst-case scenario, the increase in clonidine input rate has minimum effect on steady state blood pressures. Please see Dr. Madabushi's review for more detail.

In conclusion, despite different dosing intervals, single dose and steady state PK parameters for the ER formulation(s) are reasonably similar to the RLD IR formulation. Furthermore, the ER tablets (0.2 mg and 0.3 mg) exhibited controlled release properties when compared to IR tablets at the equivalent daily dose levels. In addition, based on *in vitro* dissolution and Dr. Madabushi's simulations, there is no expectation of dose dumping by alcohol. Taken together, despite different dosing intervals, the ER formulations can be considered biologically equivalent to the RLD IR formulation based on PK parameters.

Lastly, there are two issues that are not only specific to the clonidine ER formulations. First the transdermal TTS patch has a significant slower onset rate (approximately 3 days to achieve C_{max}) and dosing regimen (apply once weekly) as compared to the ER formulation. To determine an appropriate switching regimen between clonidine ER to transdermal formulation, Dr. Madabushi extracted the concentration-time course from the Catapres TTS approval summary (figure 4b on Page 11). He then applied the principle of superposition, adding the ER and TTS concentration time courses (see figure below).

Figure 5 Applying Catapres-TTS Patch with the Last Dose of ER



Source: Dr. Dr. Madabushi's simulation
TTS (5 cm², observed): plasma concentration time profile for starting TTS patch in a clonidine naïve patient.

As shown above by the pink line, applying the TTS patch with the last dose of daily equivalent ER formulation will result in exposure similar to that seen with the patch, and maintain plasma clonidine concentrations within the steady state ER range during the transition phase. Please see my recommendations for switching from clonidine ER to TTS patch in the labeling section.

Second, refining clonidine's dose adjustment in patients with renal impairment is an issue not specific to the ER formulations, but potentially pertinent to all clonidine hydrochloride formulations. With the prolonged plasma half-life of clonidine in anuric patients with end stage kidney disease on hemodialysis, without adjusting the clonidine dosage, the clonidine accumulation could result in significant increase in clonidine exposures at steady state. The impact of this finding on labeling will to be discussed in sections for literature review (9.1) and labeling review (9.2).

4.4.3 Pharmacodynamics

In this section, I will discuss relevant PD findings with a focus on trial 3317 conducted in patients with hypertension. Specifically, I will discuss the initial and steady state blood pressure and heart rate effects of clonidine ER formulation, examine the dose relationship, and compare the steady state PD effects between ER and IR formulations.

Trial 3317 is the single multiple-dose trial with an ER formulation in patients with hypertension. It was designed as a bioavailability trial with the following eligibility criteria and study design.

Objective:

A Study to Evaluate the Steady-State Plasma Concentrations of 0.2 mg Tris Clonidine ER Tablets and Steady-State Plasma Concentration of Tris Clonidine ER versus Catapres at 0.6 mg Daily Dose in Mild to Moderate Hypertensive Patients.

Main inclusion criteria:

- 1) mild to moderate hypertension, defined by having on two different days, mean of two measurements with sitting systolic blood pressure ≥ 140 mmHg and ≤ 180 mmHg, and sitting diastolic blood pressure ≥ 90 mmHg and ≤ 115 mmHg
- 2) On two or less antihypertensive medications
- 3) Between 18 and 75 years of age.

In addition, none of the patients were previously on approved clonidine products. The patients were to discontinue their existing antihypertensive medications for 2 weeks prior to starting on this trial.

Main exclusion criteria:

- 1) Coronary insufficiency, myocardial infarction, cerebrovascular disease, chronic renal failure, bradyarrhythmia, disorders of cerebral or peripheral perfusion, heart failure or coronary heart disease, diabetes.
- 2) Concomitant use of beta-blockers
- 3) History of drug abuse, including alcohol abuse.

The study design for trial 3317 is illustrated in the table below.

Clinical Review
 Nancy Xu, MD
 NDA 22499 & NDA 22500
 clonidine hydrochloride ER oral suspension and tablet

Table 3 Trial 3317's study design (the sponsor's table).

	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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(Source: sponsor's CSR, 3317 protocol)

Since the objectives of the trial were focused on steady state PK parameters, PK and vitals were not assessed immediately after up-titration to the 0.6 mg dose level with ER tablet or immediately after switching between IR to ER tablets at the 0.6 mg daily

equivalent dose level. The time points for vitals were not the same in the three dose levels (0.2 mg, 0.4 and 0.6 mg). At the 0.4 mg dose level, only the post-dosing 4-hour vitals collection was scheduled for all patients. The number of blood pressure measurements per patient differed at respective time points. If a patient had orthostatic hypotension, vitals measurements were often repeated for that particular time point. The length of blood pressure monitoring also differed per patient. In the first one to two days of the initiation, titration or formulation switching phases, patients were to remain semi-recumbent for at least 4 hours after morning medication dosing and 2 hours after the evening IR dosing in the study center. Orthostatic blood pressures were monitored. If orthostatic changes were observed, the patients were to remain semi-recumbent, monitored with repeat measurements until the out-of-range orthostatic changes were no longer observed. At that point, patients were discharged home without further ambulatory blood pressure monitoring.

Results:

Table 4 Demographics of the Bioavailability Trial 3317, an Open Label, Cross-Over Multiple-Dose Trial with ER and IR Formulations in Patients with Mild to Moderate Hypertension

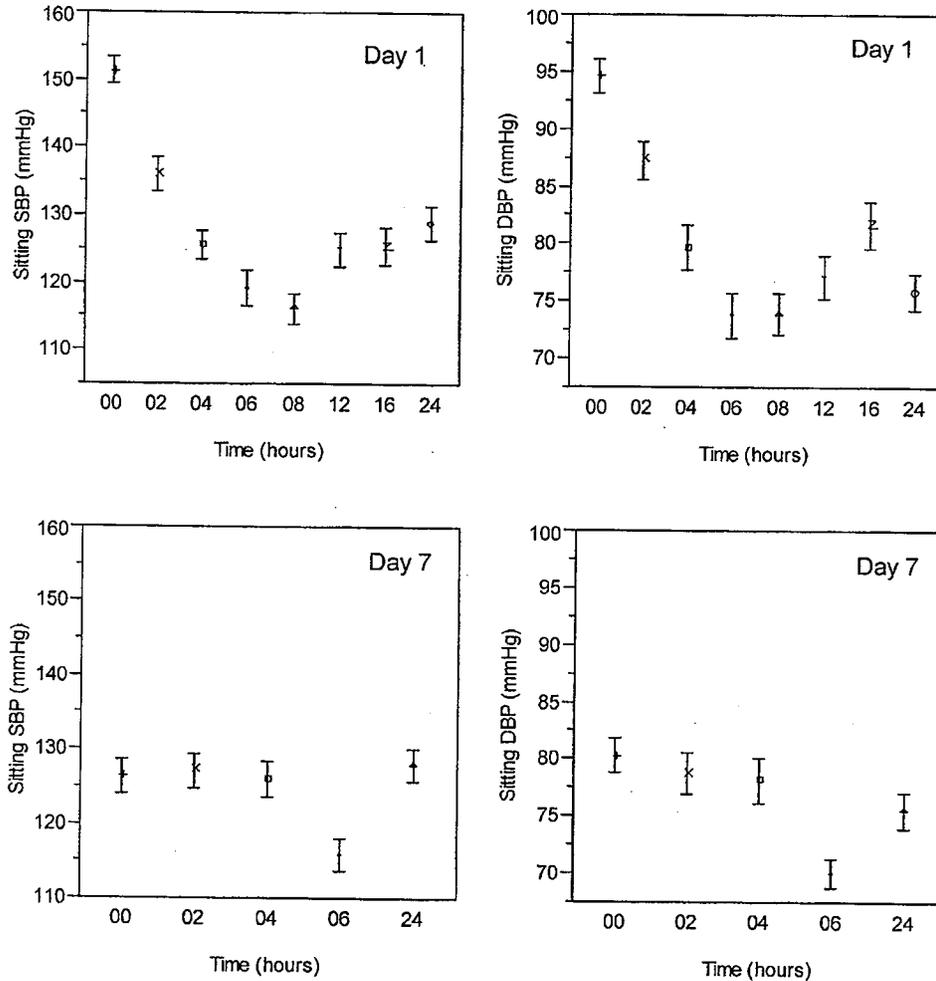
	Mean +/-SD n(%) N= 32
Age (years)	44 +/- 14
Weight (kg)	86 +/- 15
Sex	
Female	5 (16%)
Male	26 (84%)
Race	
Black	14 (45%)
White	16 (52%)
Other	1 (3%)
Serum Creatinine (mg/dL)	1.0 +/- 0.2
Estimated CrCl by CG ¹	116 +/- 36

¹ CG = Cockcroft-gault

As shown above, the sample size for the trial was small. Except for the one patient with moderate renal impairment [estimated creatinine clearance (eCrCl) of 36 mL/min], all other patients had eCrCl greater than 60 mL/min. All, except for one patient (age 72 year old), were less than 65 years of age. This is also an imbalance in the female to male ratio in this trial.

Figure 6 illustrates the blood pressure effects of 0.2 mg of clonidine ER tablet in clonidine-naïve hypertensive patients in the 24 hours after the first dose and at steady state.

Figure 6 Mean (Standard Error) of Sitting Blood Pressures with 0.2 Mg of ER Clonidine Tablet at Day 1 and Day 7 in Patients with Mild to Moderate Hypertension (N=32)

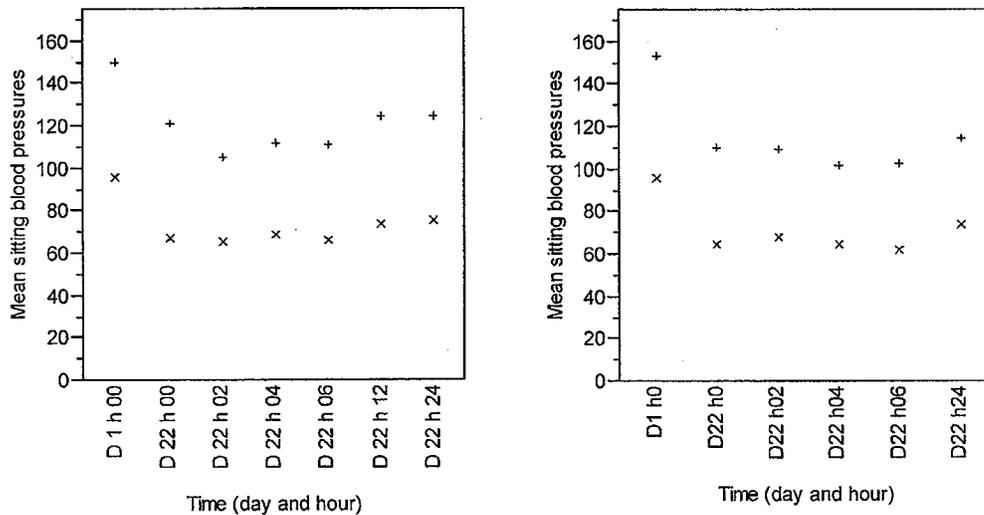


As shown in above, a single dose of ER tablet on Day 1 significantly reduces the sitting mean systolic and diastolic blood pressures (DBP). The maximum reduction in systolic blood pressure (SBP) is -37 mmHg, and DBP -21 mmHg. The time to maximum mean blood pressure reduction appears to correspond with T_{max} (approximately 8 hours), and therefore, consistent with a drug effect. Compared to Day 1, the blood pressures are slightly further reduced at steady state (Day 7) by 6 hours post-dosing, as judged by the absolute blood pressure measurements. The absolute blood pressure effects are similar after a single dose and at steady state.

Without a placebo control arm, the magnitude of blood pressure reduction attributable to the drug effect can not be determined.

In these applications, clonidine IR was not studied in the hypertensive population at the 0.2 mg dose level; consequently, comparing blood pressure reductions with clonidine ER versus IR formulations could not be performed. However, this comparison could be performed at the 0.6 mg dose level (see Figure 7).

Figure 7 Mean Systolic and Diastolic Blood Pressures on 0.6 Mg Clonidine ER (Left Panel) and IR Tablets (Right Panel) (N=16 Each Formulation Group)



+ mean SBP at baseline (day 1 hour 0) and steady state of the 0.6 mg dose level (day 22)
x mean DBP at baseline (day 1 hour 0) and steady state of the 0.6 mg dose level (day 22)

To prevent the confounding by the residual effect of the initial treatment, only the initial treatment group (n=16) was selected for the comparison of IR versus ER formulations at the 0.6 mg dose level.

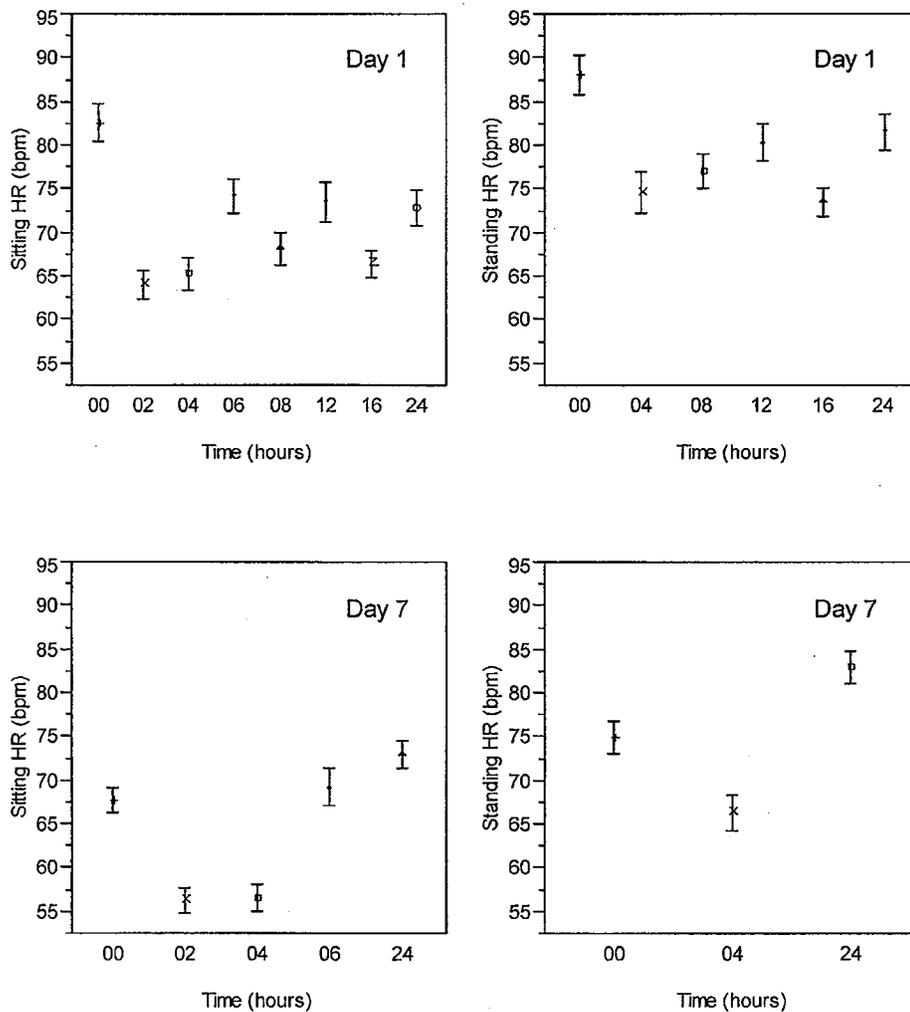
As show above, the magnitude of blood pressure reductions at steady state for at a given dose level (0.6 mg) are similar despite the difference in the dosing frequency between ER and IR formulations. Figure 7 is consistent with the expected therapeutic equivalence of ER and IR formulations at steady state.

Furthermore, comparing to the blood pressures with the ER formulation at the 0.2 mg dose level, there are further incremental reductions in SBP and DBP at the 0.6 mg dose level for a given time point after dosing. The relationship between increasing dose and further reduction in blood pressure is not steep, and appears consistent with the known

log linear relationship of blood pressure and drug exposure (for the log-linear equation, please see Dr. Madabushi's review).

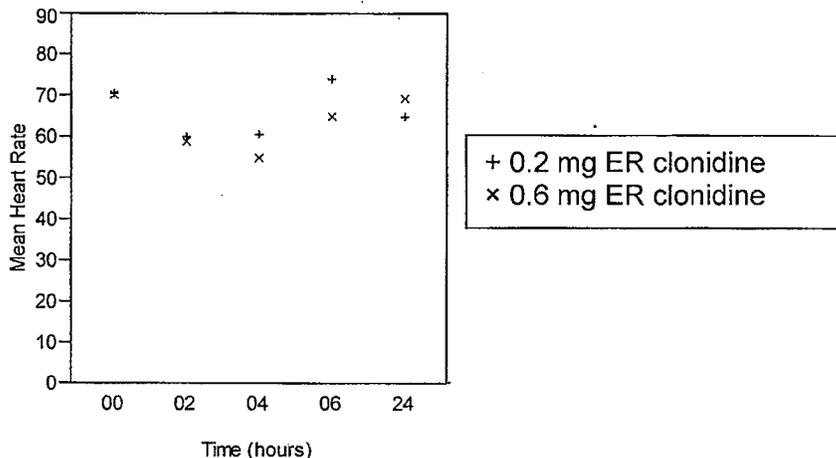
Clonidine has been known to cause bradycardia, and therefore, I explored the effects on heart rate with the ER formulation.

Figure 8 Mean (Standard Error) of Sitting and Standing Heart Rate with 0.2 Mg of ER Clonidine Tablet on Day 1 and Day 7 in Patients with Mild to Moderate Hypertension



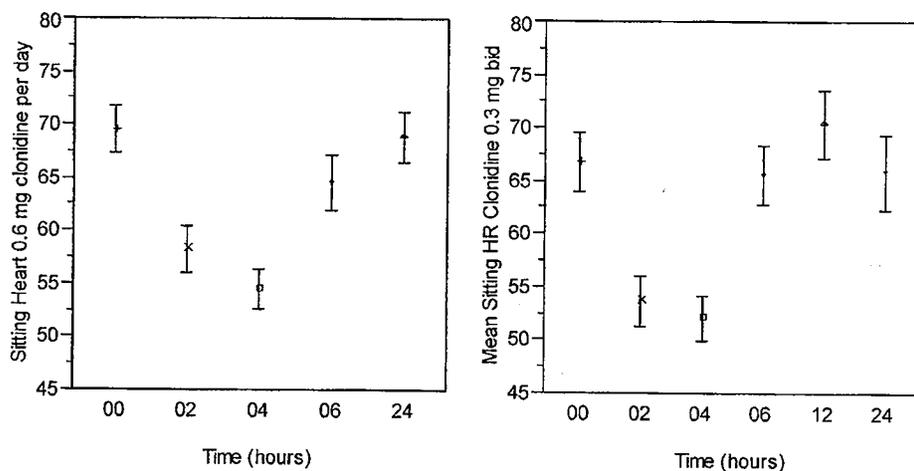
As shown above, after the first dose of ER tablet (Day 1, n=32), there is a rapid (within 2 hours after dosing) and significant (-19 bpm) reduction in mean sitting heart rate. The time to maximum mean sitting heart rate reduction occurs earlier than T_{max}, which averages at approximately 8 hours. By 8 hours, some of the reduction in sitting heart rate has recovered. In contrast, the mean standing heart rates are higher, indicating appropriate compensatory heart rate response with postural change. Similar to Day 1, the Day 7 (steady state, n=32) mean sitting heart rate also rapidly declines with dosing, but reaches a slightly lower level. On Day 7, standing heart rates are obtained on 4 and 6 hours after dosing. At these time points, mean standing heart rates are higher than the corresponding mean sitting heart rates.

Figure 9 Steady State Heart Rate-Time Profiles 0.2 Mg and 0.6 Mg Dose Levels for ER Clonidine Formulations



As shown above, the change in mean heart rates time profiles with 0.2 (n=32) and 0.6 mg of ER clonidine (n=32) are similar. This shows that in the dose range of 0.2 to 0.6 mg, there is no steep dose relationship of heart rate reduction with clonidine in this study population.

Figure 10 Mean (SE) of Steady State Heart Rates for 0.6 Mg of Clonidine ER per Day (Left Panel, N=16) and 0.3 Mg Bid of Clonidine IR (Right Panel, N=16)



As shown above, the mean effects of clonidine on steady state heart rates are similar with 0.6 mg ER per day and 0.3 mg IR bid.

As discussed earlier, at the 0.6 mg dose level, the 32 patients were randomized 1:1 to receiving either the twice-daily clonidine IR 0.3 mg or the once-daily ER 0.6 mg at the first treatment phase followed by crossing over to the alternative treatment without washout. As such, to prevent the confounding by the residual effect of the initial treatment, only the initial treatment group (n=16) was selected for the comparison of IR versus ER formulations. The smaller sample size (n=16) explains the wider standard error as compared to the earlier figures (n=32). More importantly, the standard errors are no wider in clonidine ER group (left panel) as compared to clonidine IR (right panel), suggesting that the studied ER lot exhibit similar timed drug release characteristics.

In summary, despite limited PD data in these applications, the blood pressure lowering and heart rate effects of the ER formulations appear consistent with the IR clonidine formulation at steady state. This similarity supports therapeutic equivalence between clonidine IR and ER formulations. Lastly, within the 0.2 to 0.6 mg dose range, the relationship between dose on blood pressure and heart rate are gradual. Therefore, I do not expect the small differences in C_{max} prior to steady state (Figure 2) to cause clinically significant difference in C_{max}-related hypotension or bradycardia in this trial population.

5 Sources of Clinical Data

The main source of data was from NDA 22499 and 22500 PK / PD clinical pharmacology study report, datasets and case report forms. The relevant results were discussed in Clinical Pharmacology section.

5.2 Review Strategy

I focused my review in addressing the clinical implications of the above mentioned PK/PD findings found in the three clinical pharmacology studies for which I have PK and PD, adverse event datasets. In addition, I reviewed the abbreviated study report for the small (n=12) pilot study, M1FT07010. I reviewed and concur with Dr. Rob Kumi's conclusions that the two ER formulations meet the criteria for bioavailability for ER products based on comparisons of PK parameters to the RLD. I reviewed the summary and modeling and simulation results of ER compared to IR formulations under conditions of food and alcohol. I also evaluated the blood pressure, heart rate (see PD section), adverse event and laboratory data (see section 7 review of safety) to assess whether the ER formulations were therapeutic equivalence to the IR formulations. Section 6, the integrated review of efficacy is not applicable here, and therefore is deleted.

7 Review of Safety

Trials 3317, 3390, and 3391 were used to evaluate safety of the ER formulations. The three trials included 84 subjects/patients, of whom 32 were patients with mild to moderate hypertension. In the three trials, there were no deaths. The nonfatal serious adverse events and common adverse events will be discussed separately in hypertensive patients versus healthy subjects. In this section I will first discuss AEs in hypertensive patients, trial 3317, as they are most relevant to the labeling.

Trial 3317:

Table 5 Serious adverse events with clonidine ER tablets in patients with mild to moderate hypertension (Trial 3317):

Serious Adverse Events in Multiple Dose Study 3317	ER 0.2 (N=32)		ER 0.4 (N=32)		ER 0.6 (N=31)		IR 0.3 bid (N=32)	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Bradycardia with symptoms	0	(0)	0	(0)	0	(0)	1	3
Contusion	0	(0)	0	(0)	0	(0)	1	3

As shown above, in the hypertensive patients, the incidences of serious adverse events, contusion and symptomatic bradycardia were similar. In addition, the incidence and severity of orthostatic hypotension, and tachycardia at steady state were similar with ER compared to IR tablets at the equivalent dose level of 0.6 mg per day. Furthermore, serious but rare adverse events were similar with the ER and IR formulations. Specifically, there was no syncope or pre-syncope seen in the multiple dose study in the mild to moderate hypertensive population. Lastly, it is worth pointing out that for bradycardia, the sponsor defined bradycardia as an adverse event only if it was symptomatic; as a result one patient with (HR greater than 50) met that definition.

In terms of severe adverse events, I explored the incidence of severe bradycardia which I defined as a nadir heart rate less than 40 beat per minutes (bpm) regardless of symptoms. To me, a waking heart rate in the 30s that represents a significant (average -40 bpm) and dose-related reduction from baseline consistent with a clonidine effect, even if asymptomatic, may be a harbinger to symptomatic bradycardia, particularly if clonidine were combined with other heart rate lowering agents. Therefore, severe bradycardia constitutes a severe adverse event. The incidence of severe bradycardia is presented below.

Table 6 Severe bradycardia with clonidine ER tablets in patients with mild to moderate hypertension (Trial 3317)

Severe Adverse Events in Multiple Dose Study 3317	ER 0.2 (N=32)		ER 0.4 (N=32)		ER 0.6 (N=16)		IR 0.3 bid (N=16)	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Severe bradycardia (HR <40) regardless of symptoms	0	(0)	0	(0)	3	(19)	3	(19)

For the 0.6 mg level, to prevent confounding by the residual effect from the initial randomized treatment, only the initial treatment groups (n=16 in ER or IR formulation cohort, respectively) were selected for the comparison of IR versus ER formulations.

As shown above, the incidence of severe bradycardia was the same with ER and IR formulations at the 0.6 mg level.

Common Adverse Event:

There were no adverse event related discontinuations in the clonidine ER arms in the three trials.

Table 7 displays the most common treatment-emergent adverse events (AEs) reported by more than one patient (>5%) at any dose level in the mild to moderate hypertensive patients, multiple dose trial 3317.

Table 7 Common Adverse Events in Multiple Dose Trial in Mild to Moderate Hypertensive Patients (Trial 3317)

Adverse Events in Multiple Dose Study, 3317	ER 0.2 tablet (N=32)		ER 0.4 tablet (N=32)		ER 0.6 tablet (N=31)		IR 0.3 bid tablet (N=32)	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Total number of AE	31		12		18		29	
Subjects with at least one AE	16	(50)	7	(22)	7	(22)	11	(34)
Constipation	3	(9)	1	(3)	0	(0)	1	(3)
Diarrhea	0	(0)	2	(6)	0	(0)	0	(0)
Dizziness	3	(9)	1	(3)	4	(13)	3	(9)
Dry mouth	1	(3)	3	(9)	1	(3)	1	(3)
Fatigue	2	(6)	1	(3)	1	(3)	1	(3)
Headache	3	(9)	0	(0)	0	(0)	0	(0)
Hypotension	0	(0)	0	(0)	0	(0)	2	(6)
Orthostatic hypotension	0	(0)	0	(0)	1	(3)	2	(6)
Paresthesia	2	(6)	1	(3)	0	(0)	1	(3)
Somnolence	5	(16)	1	(3)	3	(9)	2	(6)

Most common adverse events (incidence $\geq 5\%$) in at least one of the dose groups (0.2, 0.4, and 0.6 mg) are somnolence, paresthesia, dry mouth, fatigue, dizziness, headache, and diarrhea. The profile of adverse events appears similar with ER tablet as compared to IR formulation in this small open-label, cross-over trial without washout period or placebo control group. The common adverse events reported with clonidine ER formulation were seen with the IR formulation, with the exception of diarrhea. Diarrhea which occurred in two subjects (6%) in the ER 0.4 mg dose level but none in the ER 0.2 or 0.6 mg dose levels. Diarrhea was not an adverse reaction mentioned in the clonidine IR label. There is no clear dose relationship with any of these common adverse events in this small trial. When comparing across the same daily dose of 0.6 mg, both the total number of adverse events and the number of subjects with at least one adverse event appear less in the ER than IR tablet in this small open label trial.

Withdrawal Due To AE:

There was no withdrawal due to AE in trial 3317.

Trials in Healthy Human Subjects:

In the single dose trial (3390) with ER suspensions in healthy non-hypertensive subjects, one subject (2%) developed pre-syncope with orthostatic hypotension upon standing at Tmax, 8 hour after taking 0.2 mg of ER suspension while fasting. Subsequently, at Tmax after a 0.2 mg dose of ER suspension taken under fed condition, she developed syncope upon standing. On the day of syncope, her pre-dose blood pressure was 97/50 mmHg, which was lower than the inclusion blood pressure criteria and was her lowest baseline blood pressure before treatments. In addition, her pre-dose heart rate was fast at 94 bpm. Her syncope episode apparently resolved after one minute. Blood pressure, heart rate, EKG immediately after the syncope episode was not provided. Subsequent blood pressure at 12 hours was unremarkable, as was routine EKG at the end of the study, 3 days later. Despite limited information surrounding the syncope episode, the pattern of her syncope and pre-syncope episodes were consistent with an orthostatic etiology, potentially from a drug effect. However, her corresponding plasma clonidine concentration was lowest for the syncope episode (534 pg/mL) compared to her pre-syncope episode (566 pg/mL). Furthermore, she tolerated daily equivalent dose of clonidine IR formulation, 0.1 mg bid, despite having the highest plasma clonidine concentration (588 ng/mL) for this subject. Therefore, her apparent orthostatic symptoms did not correlate with her plasma clonidine level. Lastly, this subject's serum clonidine concentrations were within the range of concentrations of the other subjects examined in the same trial. Therefore, in this development program, it appears that this PD response is limited to this patient.

In summary, there is very limited experience with clonidine ER with controlled trials. Based on explorations of this limited data, the adverse event profile for the ER formulation is similar to the IR clonidine formulation in the tested dose range of 0.2 to 0.6 mg. Therefore, despite the small sample sizes for the trials, given the extensive safety experience with IR clonidine over the last 30 years, there are unlikely adverse events that are not previously reported in the studied dose range.

Lastly, from my review of safety, I identified an issue that may impact the labeling of clonidine products in general. I found the incidence (19%) of severe bradycardia (nadir HR less than 40 regardless of symptoms), which is the same with IR and ER clonidine formulations in trial 3317, to be higher than what our IR label currently suggests (bradycardia 5 in 1000). My finding is consistent with known bradycardia signal: symptomatic bradycardia can result from concomitant use of clonidine and other agents that lower heart rate. Please see recommendation in the labeling section 9.2.

7.4.2 Laboratory Findings

Laboratory data, including comprehensive metabolic panel, CBC with differential and urine analysis, were reviewed. No clinically significant laboratory abnormalities were observed in clonidine ~~ER~~ ER formulations as compared to clonidine IR formulation.

b(4)

Clinical Review
Nancy Xu, MD
NDA 22499 & NDA 22500
clonidine hydrochloride ER oral suspension and tablet

7.4.3 Vital Signs

The results were discussed in the section 4.4 Clinical Pharmacology.

7.4.4 Electrocardiograms (ECGs)

No significant ECG findings were observed.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor will defer pediatric study under PREA for the treatment of hypertension in pediatric patients ages 1 to 17 in both formulations after their approval in adult population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No relevant data in this application. Please refer to the IR clonidine label. Clonidine does not have drug abuse potential.

8 Postmarket Experience

There are extensive postmarket experiences with clonidine products, which are reflected in our labels. However, as far as I know, this particular formulation has not been approved in any country. Therefore, I do not have relevant postmarket experience to review as it pertains to this formulation.

9 Appendices

9.1 Literature Review/References

Please see Dr. Kumi (page 9) and Dr. Madabushi's reviews for the relationship between PK and PD.

On November 10, 2009, I performed searches on pubmed, EMBASE, google scholar on the following two topics:

- 1) A search with the terms "clonidine" and "dose limiting toxicity" yielded no articles. This is consistent with a drug with a relatively wide therapeutic index.
- 2) A search with the terms "clonidine" and "renal dose adjustment", "clonidine" and "renal dysfunction" and "dosage" yielded one reference article by Piepho R. W. Antihypertensive Therapy in the Aged Patient, Clinical Pharmacokinetic Considerations, Drugs and aging, 1991, 1:3 (194-211). According to this article, clonidine dose should be initiated slowly in elderly, particularly these with renal dysfunction. The dosing recommendation in the Piepho article was based on an primary research article by Hulter et al., 1979, Clinical Efficacy and PK of Clonidine in Hemodialysis and Renal Insufficiency, J. Lab Clin Med. The Hulter article found the half-life of clonidine was prolonged to 41 hours in anuric hemodialysis patients (n=3). The study had limited information on patients with moderate to severe kidney disease not on dialysis (n=3 in the range of creatinine clearance 30-60 mL/min per 1.73m²). In this study (n=12), the clonidine dose was titrated per blood pressure response and adverse event (e.g. drowsiness). The mean daily dose of clonidine for the study was 0.15 mg.

From the Hulter article's reference section, I also located a primary research article by Niarchos et al, 1978, Role of Renin and Aldosterone Suppression in the Antihypertensive Mechanism of Clonidine, The American Journal of Medicine, 65 (4), 614-618. According to Niarchos, blood pressure response was attenuated in patients with renal impairment (mean serum creatinine of 2.3+/- 0.4 mg/dL). This article did not comment on dose related adverse event of clonidine.

9.2 Labeling Recommendations

I have the following recommendations for labeling. Rationales for recommendations are provided, if they were not mentioned already in the earlier sections.

Section 2 Dosage and administration:

Clinical Review
Nancy Xu, MD
NDA 22499 & NDA 22500
clonidine hydrochloride ER oral suspension and tablet

1) Delete " _____

Insert under section 2.1 _____
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2) The titration increment of 0.1 mg per day is consistent with the label of the currently approved clonidine IR and transdermal products for chronic hypertension, although not directly studied in this application. At the same titration increment of 0.1 mg per day, the time to blood pressure effect of ER formulation should be faster than approved ER transdermal formulation based on their relative release rates. As a consequence, I believe using the 0.1 mg titration increment for the ER formulation is not objectionable.

3) Add:

b(4)

4) Section 2.3 Renal impairment
The additions are in italic.

7

b(4)

Clinical Review
Nancy Xu, MD
NDA 22499 & NDA 22500
clonidine hydrochloride ER oral suspension and tablet

5) Clinical pharmacology section (12)

5) 12.1 Mechanism of Action

Delete:

5

7

b(4)

Insert:

The patient's maximum blood pressure decrease occurred within 6 to 8 hours.

6) Adverse-event section:

There is very limited experience with clonidine ER formulations with controlled trial. Based on this limited experience, the adverse event profile is similar to the immediate-release clonidine formulation.

7) Precautions:

Drug Interactions

Add the following:

Monitor heart rate in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction, e.g., digitalis, calcium channel blockers, and beta-blockers. Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concomitantly with diltiazem or verapamil.

Rationale: Based on the incidence of severe bradycardia (HR less than 40) in trial 3317, conducted patients without abnormal EKGs or concomitant use of beta-blocker, I agree with the Division's recent revision of the clonidine IR product label to heighten the awareness of bradycardia.

8) Recommendations for labeling specific to clonidine IR products:

In Adverse Events section:

5

7

b(4)

I recommend clarifying if the above stated incidence of bradycardia refers to symptomatic bradycardia. If so, revise the label for added clarity.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22499

ORIG-1

TRIS PHARMA INC

CLONIDINE ER
ORAL SUSPENSION

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

/s/

NANCY N XU
11/18/2009