

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-500

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	November 24, 2009
From	Shari L. Targum, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA # 22-499 and #22-500
Supp #	
Proprietary / Established (USAN) names	Proposed Brand name: _____ Clonidine _____ ER Oral Suspension (NDA #022499, IND #101,635) Clonidine _____ ER Tablets (NDA #22,500, IND #102,108)
Dosage forms / strength	0.2 mg (2 mL) to 0.6 mg (6 mL) per day
Proposed Indication(s)	1. Treatment of hypertension
Recommended:	<i>Complete Response pending resolution of CMC issues. Approval if CMC issues are resolved.</i>

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Purpose of Cross-Discipline Team Leader (CDTL) Review

The purpose of this CDTL review is to summarize and integrate the individual reviews for these applications and provide additional commentary and recommendations.

This review is based, in part, on the following reviews:

Chemistry (Amit K. Mitra, Ph.D.); Clinical (Nancy Xu, M.D.); Clinical Pharmacology (Robert Kumi, Ph.D. and Rajanikanth Madabushi, Ph.D.); ONDQA-Biopharmaceutics (Tapash Ghosh, Ph.D.); Pharmacology/Toxicology (Donald Nick Jensen, D.V.M. and Charles Resnick, Ph.D.).

In addition, this review utilized the Agency document "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations (revised March 2003), other publications (Arndts, Frisk-Holmberg), and package inserts of the currently approved clonidine products.

The applications were submitted electronically.

The cross-discipline team leader concurs with the primary medical and clinical pharmacology reviewers in recommending approval of the clonidine formulations, pending resolution of outstanding chemistry issues and agreement on labeling.

The sponsor submitted two applications for an extended-release (ER) clonidine tablet and suspension, respectively. The main evidence of effectiveness is based on pharmacokinetic data, demonstrating similar exposure and maintenance of plasma concentrations within the range obtained with immediate-release (IR) clonidine, in the context of past evidence of a concentration-response relationship, information from the three marketed formulations of clonidine, and a well-characterized safety profile. The applications included only one study in hypertensive patients, without ambulatory blood pressure monitoring or a placebo control;

hence, from this one study, one would not be able to calculate a treatment effect on the basis of blood pressure lowering.

However, the clinical pharmacology results fulfill criteria for extended-release formulation, including relative bioavailability, extended-release characteristics, consistent pharmacokinetics, lack of dose dumping, steady-state equivalence, and dose proportionality.

While pediatric studies should be regarded as a postmarketing requirement, the exact pediatric study design is still under discussion with the sponsor.

CDTL Review Template

1. Introduction to Review

Two formulations of clonidine, an oral suspension and oral tablet, using the same _____ technology, have been submitted for review as separate NDAs. For the purposes of this review, the two applications will be treated as a single review of two formulations (clonidine ER tablet and clonidine ER suspension). b(4)

These two applications are 505 (b) 2 submissions; the primary reference drug is Catapres® and the secondary reference drug is Catapres-TTS. The clinical program for both formulations comprised three bioavailability studies and one pilot study.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Clonidine is a known centrally-acting alpha-agonist approved over 30 years ago as an immediate-release tablet for hypertension (Catapres, NDA 17-407). Catapres is available in 0.1 mg, 0.2 mg and 0.3 mg dosage strengths; the recommended initial dose is 0.1 mg twice daily (lower in elderly) and most commonly employed therapeutic doses have ranged from 0.2-0.6 mg per day in divided doses. In 1984, Catapres TTS, transdermal clonidine (NDA 18-891) was approved as three types of patches (TTS-1, TTS-2, TTS-3), each patch respectively delivering 0.1, 0.2, and 0.3 mg of clonidine per day. The therapeutic doses for TTS are 0.1-0.6 QD, with no added benefit for more than two TTS-3 patches. In September, 2009, during this NDA review, Jenloga®, a modified-release tablet formulation of clonidine was also approved; recommended dosing is 0.1-0.6 mg daily in divided doses (up to 0.3 mg BID). Thus, three formulations of clonidine are currently approved.

The clonidine ER formulation achieves extended release characteristics via the _____, b(4)
_____ in both products, the clonidine drug
substance: _____

_____ The clonidine tablet is _____ b(4)
_____, the drug release is controlled by _____ b(4)

Table 1. Regulatory History

Date	Meeting	Discussion points
April 4, 2008	Pre-IND meeting (101,635)	• NDA may be filed as 505(b)2; • Approved Catapres tablet supports proposed dosing regimen; • If the sponsor could show similar dissolution profiles, a single multi-dose PK study using the tablet formulation is likely to be sufficient; • No other clinical studies (except pediatric assessments) required; • Approval will primarily be driven by the ability of proposed formulations to produce plasma concentrations achieved by 0.2-0.6 mg clonidine; • Extended release products should satisfy CFR requirements for controlled release formulations (e.g., food effect, intra-subject variability, steady-state performance, minimization of peak-trough fluctuation) • The sponsor should assess <i>in vitro</i> dissolution of controlled release formulation over a wide range of alcohol concentrations.

3. CMC/Microbiology/Device

The CMC review is pending at this time.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved issues.

4.1. General nonclinical pharmacology/toxicology considerations.

No new pharmacology/toxicology studies were submitted as part of this application. Since this was a 505(b)(2) application, the sponsor has relied on the Agency's findings of safety and efficacy for Catapres® in lieu of performing additional animal studies.

4.2. Carcinogenicity:

Clonidine is not carcinogenic to mice or rats at doses up to 6 or 9 times the maximum recommended daily human dose (mg/m² basis).

4.3. Reproductive toxicology:

Clonidine does not affect fertility of rats at doses as high as 150 µg/kg (or about 3 times the maximum recommended daily human dose on a mg/m² basis).

4.4. Other notable issues (*resolved*)

Sodium polystyrene sulfonate USP _____ is included as an inactive ingredient at _____ for the 0.2 mg and 0.3 mg Clonidine _____ ER tablets, respectively, and at _____ for the Clonidine _____ ER Oral suspension. At clonidine doses of 0.2-0.6 mg per day, _____ doses are approximately _____ per day (or about _____ mg/kg in a 60 kg human). At the highest dose of 2.4 mg clonidine, the maximum dose of _____ is about _____, or about _____ in a 60 kg human, i.e. a higher daily dose than is delivered by any approved product that uses this compound as an inactive ingredient. At doses of 15-60 g/day, polystyrene sulfonate sodium is used as an active drug ingredient (Kayexalate®, Kionex®, etc.) for the treatment of hyperkalemia by adsorption of potassium from the GI tract.

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However, a total daily dose of clonidine ER 0.6 mg would deliver a maximum of _____ of _____ less than the total daily dose of this ingredient _____ that is delivered when patients are treated with typical doses of 30 mg Roxocodone SR tablets, the FDA-approved drug that includes the highest dose of _____ as an inactive ingredient. According to Dr. Jensen's review, there is no evidence that the use of _____ in Roxocodone SR has caused side effects. Therefore, if we are not recommending clonidine ER doses above 0.6 mg per day, this issue appears to be resolved.

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5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology supports approval of both clonidine extended release products. The basis for this approval recommendation is exposure matching and achieving concentrations in the range of approved products; and lack of clinical impact of *in vitro* alcohol dissolution findings (dose dumping).

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The application has met the following criteria for an extended-release product: decrease in dosing frequency; lack of dose dumping in the presence of food; steady state performance (evaluated by AUC) of ER tablets were equivalent to that of Catapres tablets; plasma clonidine levels within 0.2-2.0 ng/mL as achieved with other clonidine products; consistent PK performance between individual dosage units; systemic exposure (suspension and tablet) to clonidine (AUC) equivalence to the reference approved immediate release product, Catapres, after single dose administration under fasted conditions.

Relevant findings from Dr. Kumi's review include:

- Acceptance of a log-linear relationship between clonidine concentrations (AUC) and blood pressure lowering from 0.2-2 ng/mL;
- Clonidine concentrations above 2 ng/mL result in an attenuated response, where there is less than proportional BP reduction with increasing concentration;

- Concentrations above 4 ng/mL do not yield any additional benefit.
- The IR formulation in the range of 0.1 and 0.6 mg achieves concentrations of 0.2ng/mL and 2 ng/mL, respectively.
- The cited literature and IR data were used in the development of Catapres-TTS, which was engineered such that one 3.5 cm² patch would approximate the AUC obtained with 0.1 mg/day of oral IR clonidine.
- Clonidine will be titrated to effect (achieving a blood pressure reduction).

Evidence of a log-linear concentration-response relationship (clonidine plasma concentrations 0.2-2 ng/mL) is seen in the literature (example below):

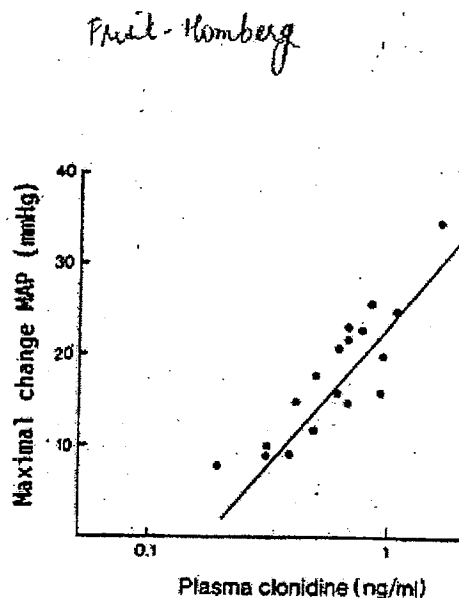


Figure 2 Relationship between individual maximal blood pressure response (expressed as maximal change in mean arterial blood pressure (MAP)) and the plasma concentration of clonidine (log scale). $r=0.86$, $p<0.01$, slope 12.99, intercept 4.99.

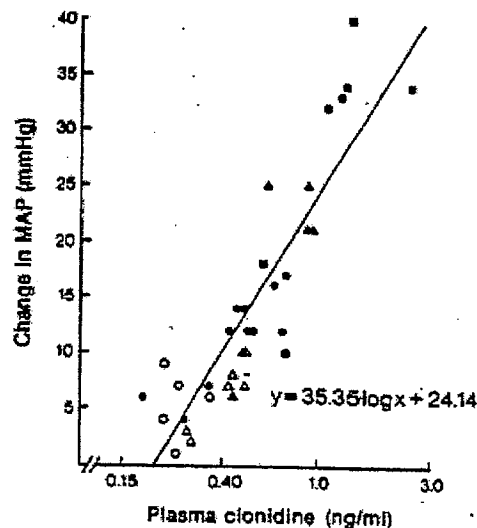


Figure 3 Relationship between reduction of blood pressure (MAP) mean of group and mean plasma concentrations of clonidine (log scale) after different doses: 75 µg (○), 100 µg (△), 150 µg (□), 200 µg (◇), and 275 µg (■), and at all points of time during pseudoequilibrium of distribution, $r=0.89$, $P<0.02$.

Figure 1. Evidence of a log-linear relationship between clonidine plasma concentrations (0.2-2 ng/mL) and mean arterial pressure (MAP) (Source: Summary Basis of Approval, NDA 18-891)

The sponsor submitted four studies:

1. A single-dose crossover fasting bioavailability (BA) study comparing clonidine 0.1 mg/mL ER oral suspension and Catapres 0.1 mg tablets in 12 healthy volunteers.
2. Two single-dose three-way crossover studies (identical design) comparing Catapres (2 x 0.1 mg, fasting) to clonidine ER oral suspension (0.2 mg, fasting vs. fed); and clonidine ER oral tablets (2 x 0.1 mg fasting) clonidine ER oral tablets (2 x 0.1 mg, fed), and Catapres IR (2 x 0.1 mg, fasting), respectively.
3. A multiple dose steady-state study comparing clonidine ER (0.2 mg, fasting; 2 x 0.2 mg, fasting, 3 x 0.2 mg, fasting) and clonidine IR 93 x 0.2 mg, fed) in 32 patients with mild-moderate hypertension.

Bioavailability:

The relative bioavailability of single-dose 0.2 mg clonidine ER suspension and tablet was comparable to that of IR clonidine (source: Dr. Kumi's review):

Table 2. Comparison of single-dose 0.2 mg 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
C _{max}	90.2	86.1-94.6	97.5	93.5-101.6
AUC _t	90.9	87.3-94.6	94.6	91.1-98.2

T/R = Test/Reference

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.

C_{max}* comparison is based on C_{max} of ER vs. second peak of IR

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Steady-state exposure:

Steady state was attained within six days following QD administration of clonidine ER. The IR formulation also achieved steady state within six days on a twice daily schedule.

At steady-state, clonidine ER 0.6 mg QD and Catapres IR (0.3 mg Q12h) appear to have comparable concentrations. Clonidine C_{max} (ER C_{max} vs. second peak of IR), C_{avg} and C_{min} are also comparable for the two formulations (statistics not shown, please see Dr. Kumi's review for further details).

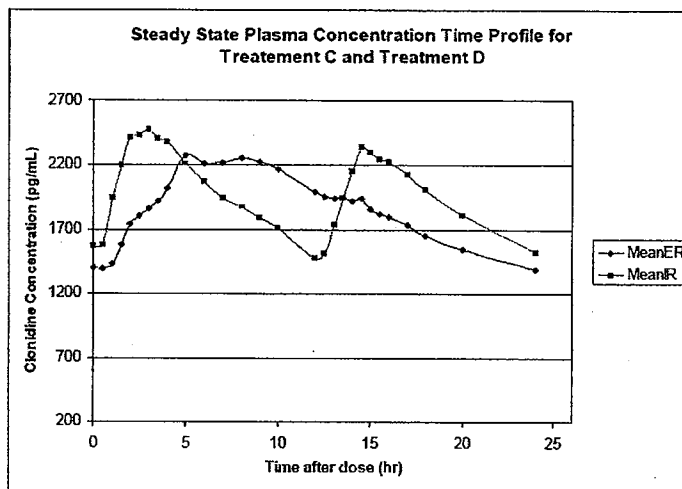


Figure 2. Plasma concentration time profiles for Treatment C (clonidine ER 2 x 0.3 mg tablets) and Treatment D (clonidine IR 0.3 mg Q 12 h). Source: primary clinical pharmacology review.

Dose Proportionality:

The applicant did not perform a dose-proportionality study. Clonidine exposure at steady state appears to be dose proportional over the 0.2-0.6 mg daily dose range, as suggested by the clinical pharmacology reviewer (Dr. Kumi) and the literature.

Table 3. Assessment of clonidine ER dose proportionality (source: clinical pharmacology review)

Value	Actual		Dose Normalized		
Measure	0.2 QD	0.6 QD	0.2 QD	0.6 QD	Ratio
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

Pharmacokinetic Performance between Individual Dosage Units:

The ANOVA CV% for the comparisons of C_{min}, C_{max} and AUC (0-24) across study days within treatment (Clonidine ER tablet 2 x 0.3 mg QD and Catapres 0.3 mg BID) was less than 10% for the ER formulation, supporting consistent pharmacokinetic performance. Also supportive of PK consistency is the comparability of plasma concentration-time profiles for two consecutive days in the same individual (not shown; please see Dr. Kumi's review for further details).

Table 4. Estimation of intra-subject variability for Treatment C and D (based on comparison of two consecutive dosing days; steady state Day 1 vs. Day 2. (Source: Dr. Kumi)

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

Steady State Exposure Comparisons:

Figures 3 and 4 below demonstrate that administration of clonidine 0.2 and 0.6 mg/day achieve concentrations that fall within concentrations of approved clonidine products. In addition, the curves appear similar despite measurements on different days, supporting consistent pharmacokinetic performance.

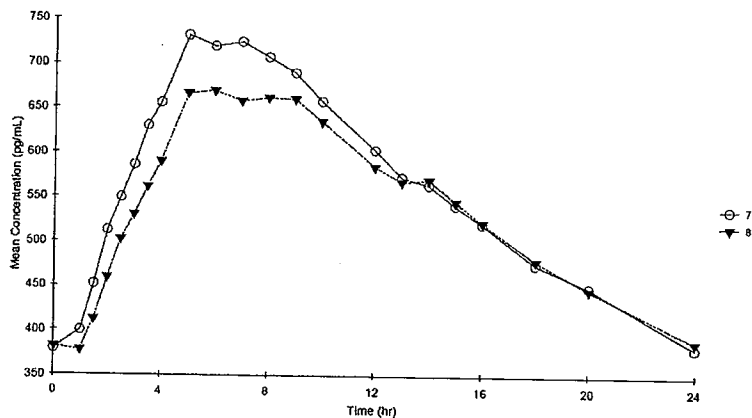


Figure 3. Mean clonidine plasma concentration vs. time after administration of clonidine ER 0.2 mg QD (healthy volunteers) on Study Day 7 and Study Day 8 (steady-state).

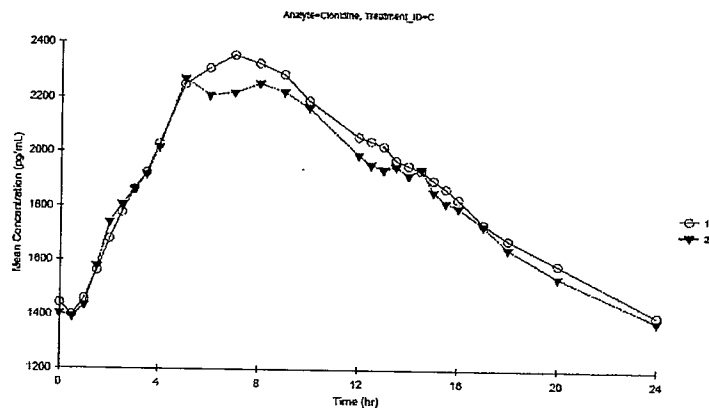


Figure 4. Mean clonidine plasma concentration vs. time after administration of clonidine ER 0.6 mg (2 x 0.3 mg) QD (healthy volunteers) on Steady State Day 1 (Study Days 21 and 29) and Steady State Day 2 (Days 22 and 30).

Food Effect:

The bioavailability of clonidine ER oral suspension or tablet was not affected by administration of a high-fat meal as seen in the figures below (Source: clinical pharmacology review)

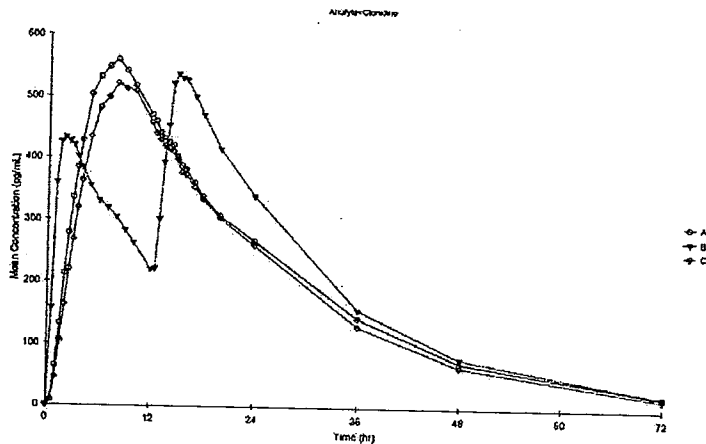


Figure 5: Food Effect Plasma concentration time profiles for suspension (upper panel) and tablet (lower panel) following administration of clonidine ER formulations (0.2 mg single dose) [Treatment A is under fasted conditions, Treatment B is the reference IR formulation, and Treatment C is under fed conditions]

Dissolution Profiles: According to Drs. Marroum and Ghosh (ONDQA-Biopharmaceutics), immediate-release formulations typically exhibit a biphasic dissolution pattern, with a rapid rise followed by a plateau phase; one might expect ~ 85% dissolution by the first 2 hours.

The dissolution profiles displayed below (clonidine 0.2 mg ER results are consistent, not shown) show a triphasic pattern, with about 30-50% dissolution at 3 hours and about 50-70% dissolution at 6 hours. These dissolution data support the extended-release characteristics of clonidine.

A.

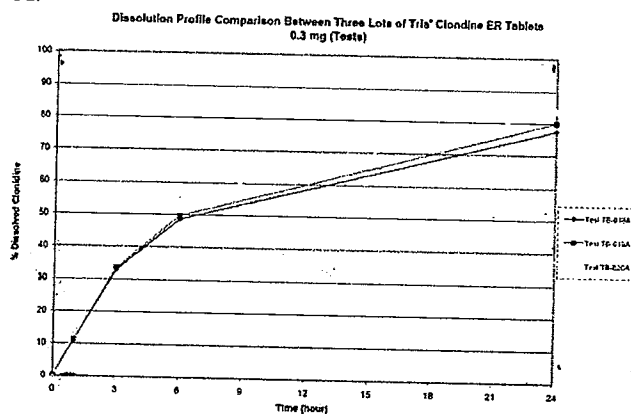
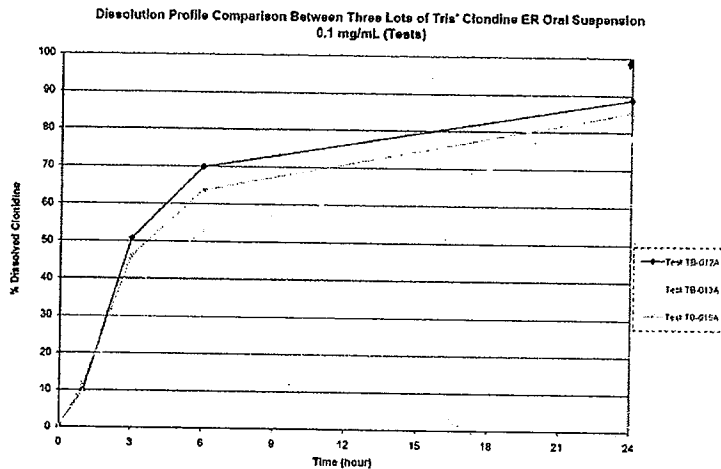


Figure 6. Dissolution profiles for clonidine ER 0.3 mg tablets (A) and 0.1 mg/ml suspension (B) (Source: ONDQA-Biopharmaceutics review: Dr. Ghosh)

B.



Effect of alcohol on dissolution:

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.

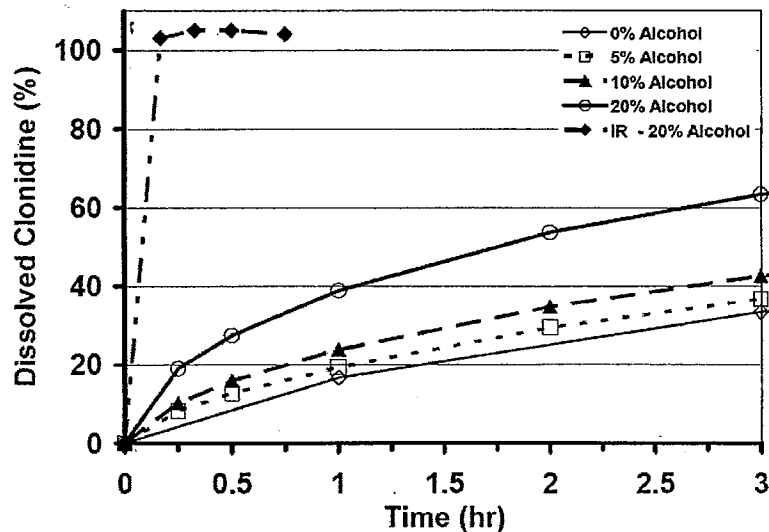
According to the primary clinical pharmacology review (Dr. Kumi), *in vitro* data showed a 40% increase in dissolution of the ER formulation in a medium with 20% alcohol at pH 1.2, compared to medium without any alcohol at pH 1.2 over a 3 hour period. This 40% delta is maintained over a 24 hours period although, as the reviewer acknowledges, time points beyond 5 hours are unlikely to be relevant.

The clinical pharmacology reviewer agreed that dose dumping dose not occur at 5% and 10% alcohol concentrations.

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 8.

- Under similar conditions, ~100% dissolution is achieved in 10 min for Catapres, the IR formulation.

Figure 8: 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) (Source: clinical pharmacology team leader memo)



- Further, 100% clonidine was not released even after 24 hrs in contact with alcohol. 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 will be evident only on the fraction of the _____ that are in substantial contact with alcohol.

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A robust compartment model was developed to describe the plasma clonidine time course following single-dose administration of an ER tablet. Based on "worst case" simulations (scenarios where alcohol and the ER formulation interact for greater than six hours), C_{max} can be expected to increase by 10-15% compared to IR clonidine in the absence of alcohol, translating into a 1-2 mm Hg increase of maximal reduction in mean arterial pressure, compared to IR clonidine and based on the log-linear relationship from the literature. The C_{min} is expected to decrease by 20-23% compared to IR clonidine, which would translate into a 3-4 mm Hg maximal change in mean arterial pressure. Dr. Madabushi has also cited the C_{min} between-subject variability of 40-50% and intra-subject variability of 31% for the IR formulation. Given these points, concomitant alcohol administration may lead to a small blood pressure effect that is unlikely to be of clinical significance.

Dr. Kumi, in his review, felt that the observed signal with alcohol was significant enough to warrant a precautionary statement in the label, reflecting the fact that excessive alcohol consumption may increase the rate of clonidine release, modifying the intended slower delivery rate of the product.

According to the ONDQA-Biopharmaceutics reviewer (Dr. Ghosh), comparative dissolution profiles of the split vs. whole tablets were similar for the 0.2 mg and 0.3 mg tablets.

5.2. Drug-drug interactions

Drug-drug interactions were not evaluated in these applications.

5.3. Pathway of Elimination

The role of intrinsic and extrinsic factors on clonidine exposure-response was not evaluated in these applications.

5.4. Demographic interactions/special populations

Demographic interactions and special populations were not explored in these applications.

Drs. Xu and Madabushi explored, via the literature and simulations, the issue of clonidine plasma concentrations in subjects with renal impairment (see Figure 1, primary medical review). Based on these simulations, Dr. Xu made dosing recommendations for patients with moderate to severe renal impairment and end-stage kidney disease on maintenance dialysis. I concur with these labeling recommendations.

5.5. Thorough QT study or other QT assessment

A thorough QT study or other assessment of QT interval was not submitted. While we do not have a TQT study for clonidine, the proposed dosing (up to 0.6 mg daily) is not higher than the concentrations achieved with immediate-release clonidine, with a longstanding record of use. Lacking a safety signal for torsade de pointes or sudden death, I do not have a strong reason to require a QT study in this application.

5.6. Other notable issues (*resolved or outstanding*)

None

6. Clinical Microbiology N/A

7. Clinical/Statistical

These NDAs did not include efficacy/safety studies. The primary endpoints of the pivotal studies were pharmacokinetic parameters.

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The dose range studied, 0.2-0.6 mg daily, is similar to the recommended dosing and concentrations in approved clonidine products. Higher doses were not studied.

7.1.2. Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

The clinical studies are summarized in the clinical pharmacology section (also see Table 2, primary medical review). In Study 3317 (32 hypertensive patients), blood pressure was not a prespecified efficacy endpoint and there was no related analysis plan. The protocol did not specify measurements in the same arm or number of replicate measurements. Dr. Xu noted that if a patient had orthostatic hypotension, vitals were often repeated for that particular time point (the protocol specified an algorithm for repeat orthostatic measurements if orthostasis was elicited in an individual patient).

Figure 6 of the primary medical review displays decreases in sitting systolic and diastolic blood pressures with a peak effect at about 6-8 hours (corresponding with Tmax). However, while potentially reassuring, interpretability of this result is limited by the lack of a placebo group. Figure 7 of this review comparing systolic and diastolic blood pressures of 0.6 mg clonidine ER and IR tablets also offers supporting evidence to the pharmacokinetic results of bioequivalence.

Dr. Xu's exploration of heart rate changes (Figures 8 and 9, primary medical review) is limited by the lack of a control group; however, there are no untoward surprises in the heart rate or blood pressure data.

In summary, the blood pressure and heart rate data are limited but consistent with pharmacokinetic findings and published literature.

7.1.3. Other efficacy studies

None.

7.1.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary medical reviewer recommended approval contingent on resolution of outstanding chemistry issues and an agreement on labeling. This reviewer concurs with Dr. Xu's recommendation.

7.1.5. Pediatric use/PREA waivers/deferrals:

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7.1.6. Discussion of notable efficacy issues: None outstanding.

7.2. Safety

7.2.1. General safety considerations

Studies 3317, 3390 and 3391 included 84 subjects. Study 7010 was a pilot study of 12 healthy subjects. Hence, the safety database comprised ninety-six subjects/patients with short-term exposure (up to 8 days in study 3317) to these formulations.

All studies were open-label; therefore, one cannot exclude bias in collection of adverse events. In addition, patients with significant cardiovascular disease (other than hypertension) were excluded from study 1003317.

7.2.2. Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

There were no deaths or serious adverse events reported in patients receiving the ER formulations. In the medical review, one serious AE (symptomatic bradycardia/contusion) was noted in a patient in the 0.3 mg BID IR clonidine group (study 3317). According to the sponsor, no serious adverse events were reported in any of the clonidine trials; however, the sponsor reports one case of withdrawal in the IR clonidine group due to symptomatic hypotension (study 3317, patient 722).

One healthy volunteer in the single-dose study (3390) using ER suspension developed hypotension and orthostatic symptoms at Tmax after receiving clonidine ER suspension 0.2 mg (both fed and fasting). This phenomenon was not related to higher clonidine plasma levels. Clonidine is labeled for orthostatic symptoms; one cannot rule out some sensitivity in some to the ER formulation unrelated to plasma levels. In addition, there may be other characteristics (such as position, fluid balance, baseline pressures) that differed between treatment arms and confounded the events. Other than this one subject, there are no data (see adverse events, medical review) to suggest an imbalance between clonidine ER and IR formulations.

There were no adverse event-related discontinuations in patients receiving clonidine ER in the four trials.

A similar incidence of bradycardia (nadir HR < 40 regardless of symptoms) was observed by the primary medical reviewer in both 0.6 mg ER and 0.3 mg BID IR clonidine groups (3 patients per group).

The most common adverse events in the multiple-dose study in hypertensive patients (see primary medical review) are consistent with approved clonidine labeling. Given the small sample size and sampling variability, no gross imbalances are observed between the IR and ER formulations and no dose-relationship is observed.

No adverse events related abnormal laboratory evaluations were observed.

- 7.2.3. Safety update N/A
- 7.2.4. Immunogenicity, where pertinent N/A
- 7.2.5. Special safety concerns: None
- 7.2.6. Discussion of primary reviewer's comments and conclusions

The primary medical reviewer concluded that, based on the limited data, the safety profile for the ER formulations in the tested dose range (0.2-0.6 mg) was similar to IR clonidine. Despite small sample sizes, the extensive safety experience with IR clonidine offered reassurance concerning unexpected adverse events.

The medical reviewer additionally found an incidence of severe bradycardia (HR < 40 bpm regardless of symptoms) of 19% (study 3317) in both IR and ER clonidine, higher than the current IR label (bradycardia 5 in 1000). However, bradycardia in the IR label might have been defined differently (e.g., as a reported adverse event rather than an outlier analysis). In addition, study 3317 has a small sample size, with 16 patients respectively receiving ER 0.6 mg versus IR 0.3 mg BID at the first randomized treatment period, and any single adverse event may lead to a large change in incidence; in this case, three bradycardia events translated into an incidence of 19%.

Using Stata software, the 95% confidence intervals for a sample size of 16 and incidence of 19% are 4% to 45%; an incidence of 0.5% (per the label) would fall outside this range.

- 7.2.7. Pre-Approval Safety Conference (If an NME that will be approved) (If a Post marketing Safety Conference was not held, explain why). N/A.
- 7.2.8. Discussion of notable safety issues (*resolved or outstanding*). None

8. Advisory Committee Meeting

This application did not go to an advisory committee.

9. Other Relevant Regulatory Issues

None

10. Financial Disclosure There is no evidence of financial conflicts.

11. Labeling

11.1. Proprietary name

According to the November 16, 2009 letter from the Division of Medication Error Prevention and Analysis, the sponsor's proposed name of _____ is unacceptable because of its resemblance, with similar product characteristics, to the established name Clonidine tablets, raising the potential of confusion or product substitution with immediate release clonidine. b(4)

11.2. Physician labeling

Briefly highlighted are recommendations by the pharmacology, clinical pharmacology and medical reviewers:

- The pharmacology reviewer recommended modifications to the Pregnancy and Carcinogenicity sections of the label, and combining two paragraphs in the Animal Toxicology section (see Dr. Resnicks' review for details). This reviewer concurs.
- The clinical pharmacology reviewer (Dr. Kumi) recommended language in the Warnings and Precautions and Drug Interactions section concerning excessive alcohol consumption and dose dumping. However, the simulations by Dr. Madabushi lead one to conclude that clinically meaningful dose dumping is unlikely.

This reviewer therefore does not concur with placing "dose dumping" in labeling, but feels that it is reasonable to add pharmacokinetic information concerning interactions with alcohol.

- The medical reviewer recommended:
 - Limiting dosing to 0.6 mg per day maximum (as higher doses were not studied);
 - Adding information about switching clonidine formulations and dosing in renal insufficiency;
 - Modifying the Mechanism of Action section, adding that the maximum blood pressure decrease occurred within 6-8 hours;
 - Adding information to the adverse event section and Drug Interaction section (regarding bradycardia with clonidine and calcium channel blockers)

This reviewer concurs with the recommendations from the medical reviewer.

11.4 Patient labeling/Medication guide N/A

12. DSI Audits None.

13. Conclusions and Recommendations

13.1. Recommended regulatory action:

This reviewer recommends approval of the clonidine ER formulations pending resolution of CMC issues and agreement on labeling.

There are no safety concerns or Risk Minimization Action Plans.

13.2. Postmarketing studies, voluntary or required (e.g., under PREA, Subpart H):

The sponsor should perform appropriate pediatric efficacy, safety and pharmacokinetic studies under PREA.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22499

ORIG-1

TRIS PHARMA INC

CLONIDINE
ORAL SUSPENSION

ER

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/s/

SHARI L TARGUM

11/24/2009