

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-331

MEDICAL REVIEW(S)



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-331 (Sympres; clonidine modified release tablets for hypertension)
Sponsor: Addrenex Pharmaceuticals
Review date: 29 September 2009

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-331
HFD-110/Fortney/Karkowsky

This memo conveys the Division's decision for approval of this application for a modified-release formulation of clonidine tablets for treatment of hypertension.

This application has been the subject of reviews of CMC (Mitra; 12 November and 17 December 2008, 25 September 2009), biopharmaceutics (Ghosh; 15 December 2008, 3 September 2009, 28 September 2009), pharmacology (Resnick; 29 August 2008), clinical pharmacology (Menon-Andersen; 7 November and 18 December 2008), and clinical studies (Williams; 22 September 2008).

Most issues have been addressed in Dr. Karkowsky's CDTL memo (16 December 2008) and in my CR memo of 19 December 2009. I summarize very briefly.

"Modified Release" has been omitted from the name, but it appears in several places in the label, which notes that it cannot be expected to give identical response to Catapres.

We appear to have consensus on dissolution specifications. And other CMC issues enumerated in the CR letter of 19 December 2008.

The sponsor still has to fulfill requirements under PREA; this does not delay approval.

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/s/

NORMAN L STOCKBRIDGE
09/29/2009



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-331 (Sympres; clonidine modified release tablets for hypertension)
Sponsor: Addrenex Pharmaceuticals
Review date: 19 December 2008

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-331
HFD-110/Fortney/Karkowsky

This memo conveys the Division's decision for a Complete Response to this application for a modified-release formulation of clonidine tablets for treatment of hypertension.

This application has been the subject of reviews of CMC (Mitra; 12 November and 17 December 2008), dissolution (Ghosh; 15 December 2008), pharmacology (Resnick; 29 August 2008), biopharmaceutics (Menon-Andersen; 7 November and 18 December 2008), and clinical studies (Williams; 22 September 2008).

Most issues have been addressed in Dr. Karkowsky's CDTL memo (16 December 2008). I summarize very briefly.

Clonidine is a well established antihypertensive agent available as a tablet or as a patch. The current tablet formulation is not approvable as a generic drug, because the formulation gives only a little more than half of the C_{max} while producing much the same exposure at the inter-dosing interval.

The development program includes two studies. The first is a single-dose PK study comparing Sympres tablets under fed and fasted conditions with Catapres under fasted conditions. Sympres had no appreciable food effect.

A small 3-week ABPM study developed enough clinical data to establish reasonable instructions for use, and demonstrated relatively low (12%) intra-subject variability in PK. The sponsor's modeling of the PK-PD relationship contributed little.

The formulation did not exhibit dose-dumping with ethanol.

The study demonstrated quite large peak reductions in heart rate (15-20 bpm at doses of 0.4 or 0.6 mg, but given the lower exposure at C_{max}, I reject the idea that this could be worse than with Catapres (which was not used in the multi-dose study).

There is some concern over the use of "Modified Release" in the name. Since the product does not justify a reduction in dosing interval, the extension "Extended Release" is considered inappropriate. If only T_{max} were different, one might consider no extension to the name at all, but C_{max} differences will mean that both blood pressure and adverse effect profiles are likely to be different. Thus, mg-for-mg substitution is not appropriate (one will need to retitrate upon substitution), and some distinction in the name is needed. I think that "Modified Release" is the best choice.

The sponsor requests a waiver for pediatric studies. Neither I nor Dr. Karkowsky find the sponsor's argument persuasive. In particular, their safety concern is largely assuaged by the common use of clonidine to treat ADHD in children.

ONDQA recommends a small modification to the sponsor's proposed dissolution specifications.

The sponsor appears to have provided updated stability data within the past few weeks, but reviewed data support a shelf-life of _____

b(4)

Several additional CMC issues prevent approval. These are enumerated on pages 10-11 of CMC Review #2.

Labeling is not being included in the Complete Response letter, but will need to be close in content to that of Catapres.

The establishment inspection resulted in a "withhold" recommendation.

The various deficiencies are incorporated into the Complete Response letter.

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/s/

Norman Stockbridge
12/19/2008 11:26:56 AM
MEDICAL OFFICER



CLINICAL REVIEW

Application Type NDA
 Submission Number 22-331
 Submission Code 000

Letter Date February 15 2008
 Stamp Date February 19 2008
 PDUFA Goal Date October 21 2008

Reviewer Name A.O. Williams M.D.
 Review Completion Date September 9, 2008

Established Name Clonidine hydrochloride SR
 (Proposed) Trade Name _____ (not yet approved)
 Therapeutic Class alpha-2 adrenergic agonist
 Applicant ADDRENEX

b(4)

Priority Designation S

Formulation Tablets
 Dosing Regimen Individualized (0.1 to 0.6mg)
 Indication Hypertension
 Intended Population Patients with essential hypertension

39 pages, 14 Tables, 11 Figures & 11 References

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1 Recommendations/Risk Benefit Assessment

This reviewer recommends that the study drug, Clonidine HCl, be approved as a sustained release formulation. The properties of a sustained release have been validated by PK and PD data in this NDA and no food effect has been demonstrated.

The justification for recommending approval is as follows:

- 1) The dose dependent reduction of systolic and diastolic blood pressure (relative to baseline) at all three doses, even at the lowest dose of 0.2mg.
- 2) The maintenance of the decrease in mean blood pressure (systolic and diastolic) during the daytime, night time and composite 24 hour period
- 3) Decrease in blood pressure during the 12 hour daytime inter-dosing interval at all doses.
- 4) The lack of a rebound of hypertension following sudden withdrawal of study drug (return to normal baseline BP without overshoot) and
- 5) The possible clinical outcomes expected of drugs that lower blood pressure in general which can be assumed with the observed magnitude of blood pressure decrease from drug exposure even though there are no outcome studies or data on this formulation.
- 6) The tolerability and relative safety of the study drug albeit in a small safety population (n=42).
- 7) See "Conclusions" in Section 10 of this review.

- The data submitted in this NDA show that after administration of the sustained release formulation, peak clonidine concentrations from single doses were lower and occurred at later times than those of CATAPRES.
- The sustained release property of the CLONICEL formulation at steady state was shown from the low C_{max}/C_{min} mean ratios observed for the 3 treatment groups. These mean ratios averaged between 1.4 to 1.5 suggesting a low peak to trough fluctuation.
- The effects of blood pressure was evident by a dose dependent reduction in mean daytime systolic and diastolic blood pressures (relative to baseline) for the 0.2 and 0.4 mg dose levels. For the 0.6 mg dose, there was no significant dose decrease suggesting a plateau effect. The effect on

blood pressure was maintained over the entire 12 hour daytime dosing interval at all dose levels (but more so with 0.4 and 0.6mg) and between 10 and 12 hours after dosing.

Pharmacokinetic-Pharmacodynamic modeling was conducted using blood pressure response data and the C_{max} , C_{min} and AUC values at day 25. The relationships between effect and exposure were similar for changes in diastolic and systolic blood pressure for each of the 3 exposure parameters. The clonidine concentration required to produce 50 % of the maximal response on systolic blood pressure was 458 pg/ml for C_{max} and 359 pg/ml for C_{min} . Concentrations of this magnitude were consistently achieved in the 0.4 mg and 0.6 mg groups but not in the 0.2mg group. All patients in the 0.4 and 0.6 mg groups achieved >500 pg/ml clonidine concentrations. These conclusions are based on the sigmoidal E max model which may not be a perfect model (Figure 11). CLONICEL administered at doses ranging from 0.2 mg to 0.6 mg / day was well tolerated in this study. The frequency of adverse events increased progressively with increasing doses. The pattern of adverse events was similar to those seen with other alpha-2 agonist active drugs. The frequencies of drowsiness and sedation reported were 33% and 10%, respectively. In contrast the frequencies of these two adverse events with clonidine immediate release were 5% and 0% respectively.

The risk to benefit analysis for this sustained release formulation should be evaluated in the light of significant reduction of blood pressure. Since this is a twice daily administered drug it does not have the advantage that other once a day dosing of sustained release drugs have. In addition two adverse events of dizziness and sedation and the frequent predisposition to bradycardia were observed.

The patients should be warned about the potential risks for these adverse events, particularly drowsiness that was observed in about a third of the patients, albeit a small population.

1.1 Recommendation on Regulatory Action

The reviewer recommends approval of the study drug for the treatment of hypertension based on pharmacodynamic effects manifested by lowering of blood pressure and satisfying the criteria for a 505(b)(2) pathway. This application is based on 505(b)(2) pathway of the FDA and it relies in part on the Agency's previous findings of safety and efficacy for previously approved formulations, namely: "Immediate Release" and "Patch" - Catapres NDA 17-407 in 1974.

The issue of adopting a proprietary name for the study drug requires further clarification. The sponsor refers to the same study drug as CLONICEL and CLONIBID in this submission. The latter has been rejected by DDMAC and two names have been submitted for consideration. The reviewer suggests that the study drug be referred to as Clonidine hydrochloride SR or Sustained Release pending approval of a suitable proprietary name.

1.2 Risk Benefit Assessment

The benefits of a sustained release appear to outweigh the risks of clonidine immediate release which are well known and documented because it is twice daily and the BP lowering effect is evident throughout the interdosing interval. The efficacy benefit is manifested in the ABPM data that showed meaningful decreases in blood pressure (SBP and DBP) and heart rate across all 3 treatment groups. There was a dose-dependent reduction of mean systolic and diastolic BP at the two doses of 0.2 mg (15.5/11.2 mmHg) and 0.4 mg (25/16.6 mmHg) per day. This reduction appeared to plateau at 0.6 mg

(23.3/16.9mm/Hg). Similar BP reduction patterns occurred for daytime, night time and 24 hour measurements of BP which can also be considered as a significant clinical benefit.

The pharmacodynamic effect versus the time data showed that the magnitude of treatment effect of the morning dose on blood pressure in the 0.2 mg group appeared relatively less compared to the 0.4 mg and 0.6 mg doses. Similar effects on BP and heart rate were observed in the interdosing interval for the 0.4 and 0.6 mg dose levels. The duration of the effect on blood pressure was maintained over the entire 12 hour daytime dosing interval at the higher doses.

The maintenance of treatment effect was further investigated at the tail end of the interdosing interval. The differences between the SBP, DBP and HR values at base line and the last two hours of the interdosing interval on day 26 were calculated for each patient and summarized in Table 5 below. The paired t-tests showed statistically significant differences for SBP and DBP at the 0.4 and 0.6 mg dosing levels (Table 5). There were no significant differences in the heart rates between the treatment groups except at hour 11 in the group that received 0.6 mg ($P=0.0029$)

Safety was however assessed on a relatively small population of 33 out of a total of 40 patients. This is grossly inadequate. However, there are several published data on the safety profile of clonidine IR to allay fears or concerns about safety of this drug.

Accumulated safety data and post marketing experience since the introduction of clonidine IR into the market still support relative safety except for a few reports of hypotension, dizziness and sedation.

Decreases in blood pressure were observed for all the patients except for two patients and absent in one patient in the 0.6 mg /day treatment group.

Rebound phenomenon was ascertained by abrupt discontinuation of treatment after the pm dose on day 26. ABPM assessments were continued for 48 hours following this dose.

Both SBP and DBP returned to baseline levels gradually without overshooting the baseline levels even though the drug had been withdrawn abruptly.

The usual adverse events associated with IR clonidine were observed except sedation.

One patient experienced sinus bradycardia two weeks after initiation of study drug and was the only patient discontinued from the study. Other adverse events reported included dryness of mouth, fatigue, dizziness, headache, nausea, somnolence and insomnia.

1.3 Recommendations for Postmarketing Risk Management Activities

Post marketing pharmacovigilance as currently observed for Clonidine IR is recommended. Preliminary studies outside of the USA have shown that SR clonidine is effective and safe in controlling blood pressure but this formulation was never fully developed and marketed in the US.

The sponsor realizes the need for an easily administered clonidine formulation that will retain the efficacy of the current oral formulation but will have an improved safety profile.

Experience from the use of the sustained formulation in countries where this has been approved should be made available and be an integral part of post-approval post marketing database.

1.4 Recommendations for other Post Marketing Study Commitments

Drug-drug interactions were not investigated in this study because enough is known from clonidine IR. Although no other post marketing study commitments are recommended, pharmacovigilance on drug-drug interactions should be evaluated during the post-marketing period.

2 Introduction and Regulatory Background

The purpose of this application is to seek marketing approval for clonidine hydrochloride sustained release for the treatment of hypertension. The proprietary name for this product was originally referred to in this application as CLONICEL. The new proprietary name proposed for marketing is CLONIBID but this has not been approved by the Agency. The two names under consideration are _____ Both suggested names refer to the same sustained release formulation of clonidine HCl.

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The initial intention of the sponsor was to obtain marketing approval for the sustained release formulation by demonstrating bioequivalence with the current transdermal patch. The Division was agreeable to the bioequivalence route but that a demonstration of bioequivalence alone was unlikely to succeed. Instead the Agency proposed a PK/PD route for approval with measurements of steady state plasma concentration levels and blood pressure through 24 hr. ABPM measurements. There was no need for additional efficacy clinical studies.

The sponsor was requested to demonstrate the following for drug approval:

- properties of a sustained release
- conduct a food effect study to rule out dose dumping, and
- demonstrate consistent PK performance between individual units.

The sponsor realizes the need for an easily administered clonidine formulation that will retain the efficacy of the current oral formulation but will have an improved safety profile. Preliminary studies have shown that SR clonidine is effective and safe in controlling blood pressure but this formulation was never fully developed and marketed in the US.

For this NDA the following clinical pharmacology studies were carried out and they form the basis of this review.

- Study on Pharmacodynamics
- Study on steady state pharmacokinetics
- Study on bioequivalence and food effect

The objectives of the clinical pharmacology studies included the following:

- To determine the steady state pharmacokinetics of clonidine from 3 dosing regimens of CLONICEL: 0.2; 0.4; 0.6mg / day administered in divided doses every 12 hours.
- To determine intra-patient variability in steady state pharmacokinetics of clonidine from these 3 dosing regimens of CLONICEL.
- To evaluate the steady-state pharmacodynamic effects of these three dosing regimens of CLONICEL on ABPM and safety measurements.

The objectives and strategy of this clinical review are to evaluate the pharmacodynamic effects of the new formulation and to evaluate safety.

2.1 Product Information

Clonigel is a patented, oral dose, sustained release formulation of the widely available generic drug, clonidine hydrochloride USP. This drug is a centrally acting α_2 adrenergic

agonist that has been used effectively for more than 3 decades to treat mild-to-moderate hypertension. Clonidine is currently approved in the US in 3 formulations: immediate release, transdermal patch, and epidural injection. Several studies have shown the efficacy and safety of orally administered and transdermal clonidine in the treatment of hypertension.

2.2-Table of currently available treatments for hypertension

Table 1: Examples of Currently available treatments for hypertension reviewed by Reviewer

Name of Drug	Mode of action	Immediate or Sustained Release
Irbesartan	AII inhibitor	IR
Irbesartan and HCTZ	AII inhibitor	IR
Olmesartan	AII inhibitor	IR
Caduet (Amlodipine and Avorstatin)	Dihydropyridine component and statin	IR
Azor (Amlodipine and Olmesartan)	AII inhibitor and Dihydropyridine	IR
Perindopril	ACE inhibitor	IR
Valsartan and HCTZ	AII inhibitor	IR
Accupril (Quinapril/HCTZ)	ACE inhibitor	IR
Clonidine	Alpha 2 adrenergic agonist	SR
Toprol XL	Adrenergic Beta blocker	SR

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients for this drug are available in the United States.

2.4 Important Safety Issues with consideration to related drugs

The most important safety issue related to this study drug is symptomatic sinus bradycardia. Other safety issues include headache, fatigue, nausea, dizziness and insomnia (See section 7 of this review).

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The Division was agreeable to the bioequivalence route but that a demonstration of bioequivalence alone was unlikely to lead to approval of the new formulation. The Agency suggested and recommended that a PK/PD route might be appropriate for approval with measurements of steady state plasma concentration levels and blood pressure through 24 hr. ABPM measurements. There was however no need for additional pivotal efficacy clinical studies.

The sponsor was requested to demonstrate the following:

- properties of a sustained release
- conduct a food effect study to rule out dose dumping, and
- demonstrate consistent PK performance between individual units.

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 : Acceptable

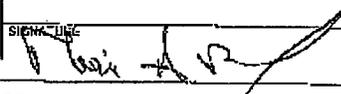
3.2 Compliance with Good Clinical Practices

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.

3.3 Financial Disclosures

The certificate for financial interest is reproduced below in Figure 1. There is no evidence of conflict of interest by any of the investigators based on this certification.

Figure 1: Financial disclosure certificate

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: OMB No. 0810-0086 Expiration Date: April 30, 2009
TO BE COMPLETED BY APPLICANT	
<p>With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)); submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).</p>	
Please mark the applicable checkbox.	
<p><input checked="" type="checkbox"/> (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).</p> <div style="border: 1px solid black; height: 40px; width: 100%;"></div>	
<p><input type="checkbox"/> (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).</p>	
<p><input type="checkbox"/> (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and if was not possible to do so, the reason why this information could not be obtained is attached.</p>	
NAME Moise A. Khayat, Ph.D.	TITLE President and CEO
FIRM/ORGANIZATION Adrenex Pharmaceuticals, Inc.	
SIGNATURE 	DATE 02/08/2008
<p>Paperwork Reduction Act Statement An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Service, Paperwork Project (0810-0086), Washington, DC 20543-0001.</p>	

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Not applicable

4.1 Chemistry Manufacturing and Controls

Not applicable

4.2 Clinical Microbiology

Not relevant

4.3 Preclinical Pharmacology/Toxicology

Not relevant

4.4 Clinical Pharmacology

See Clinical Pharmacology review by Dr Divya Menon-Andersen

4.4.1 Mechanism of Action

This drug is a centrally acting α_2 -adrenergic agonist that has been used effectively for more than 3 decades to treat mild to moderate hypertension. Clonidine is currently approved in the US in 3 formulations: immediate release, transdermal patch, and epidural injection.

4.4.2 Pharmacodynamics

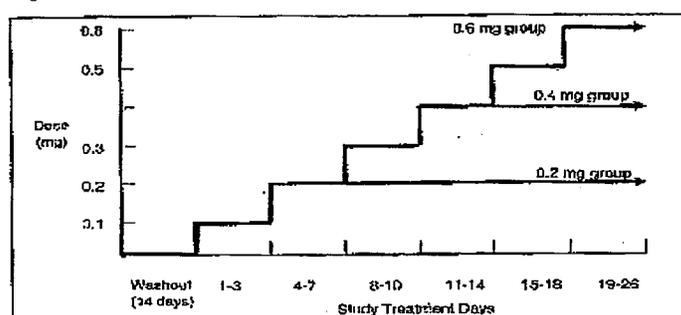
Study CLON 201 was carried out for pharmacodynamic effects of the sustained release.

Protocol -CLON-201: Title: A double blind, dose ranging study of the PK and PD of clonidine following administration of CLONICEL (SR) in patients with mild to moderate essential hypertension.

This was a 4-week, double blind, multicenter, randomized, parallel group study of the steady state PK and PD of 42 patients with mild to moderate hypertension. Following a 2 week wash out period of previous antihypertensive medications, patients were randomized and titrated to 0.2, 0.4 or 0.6 mg per day in twice daily dosing regimens for 26 days.

The chosen doses were known to be associated with known therapeutic effects in hypertensive patients (0.2 to 2 ng / ml). Upon completion of baseline ABP measurements, an escalation titration schedule was implemented to achieve the target assigned dose (Figure) Patients were dispensed study medication with instructions to take their morning dose at 8.00 am (± 2 hours) and their evening dose at 8.00 pm (± 2 hours) . Safety measurements were conducted at each study visit.

Figure 2: Dose escalation schedule



In summary, ABPM was performed at baseline prior to dosing and on the last day of dosing (day 26). All major PK and PD parameters were assessed during week 4 (days 22 – 28).

Ten blood samples were collected for measurement of steady state plasma concentrations of clonidine for a period of 12 hours following the morning dose on each of Days 23 and 25.

Patients were discontinued from study medication immediately after completion of day 26 day dosing period, although they were sequestered for 48 hours for evaluation of rebound hypertension and safety.

The primary pharmacodynamic endpoint was change in ABPM data between baseline and study day 26. The relationship between dose and PD effects was evaluated.

PK/PD analyses were performed using differences in ABPM data on Day 0 and study day 26. PK parameters included AUC, Cmax, and Cmin, and were evaluated using the sigmoidal E max model. For safety, data from 42 patients enrolled were analyzed. These included collected adverse events, physical examination, vital signs, ECG and clinical laboratory examination,

Table 2: Patient disposition

Category	0.2mg	0.4mg	0.6mg	Total
Enrolled				71
Safety Population	12	15	15	42
PK Population	12	12	15	39
Number completed	12	12	15	39
Enrolled - Site 100				22
Safety Population	3	4	4	11
PK Population	3	4	4	11
Number completed	3	4	4	11
Enrolled - Site 200				21
Safety Population	5	6	7	18
PK Population	5	4	7	16
Number completed	5	4	7	16
Enrolled - Site 300				28
Safety Population	4	5	4	13
PK Population	4	4	4	12
Number completed	4	4	4	12

Table 3: Summary of Patients terminated prematurely*

No of patients	0.2	0.4	0.6	Total
Enrolled				71
Randomized	13	15	15	43
Safety population	12	12	15	42
Completers	12	12	15	39
Terminated prematurely	0	3	0	3
Reason for premature T,				
Adverse event	0	1	0	1
Violation in Criteria	0	2	0	2

* See table 14.

Table 4: Summary of Demographics - Safety

Variable	Stats	0.2mg	0.4mg	0.6mg	Total
Age (years)	n	12	15	15	42
	Mean	44.0	44.8	49.2	46.1
Gender					
Male	n	10	13	12	35
Female	n	2	2	3	7
Ethnicity					
Hispanic or Latino	n	5	2	1	8
Not Hispanic or Latino	n	7	13	14	34
Race					
American Indian	n	1	0	0	1
Black Or African American	n	2	4	5	11
Native Hawaiian	n	0	0	0	0
Asian	n	0	1	0	1
White	n	9	10	10	29
Height (cm)	n	12	15	15	42
	mean	173.68	176	177.25	175.86
Weight (kg)	n	12	15	15	42
	mean	83.61	90.46	91.96	89.04
BMI (kg/m²)	n	12	15	15	42
	mean	27.77	29.09	29.18	28.74

There are no significant changes in the demographics of the PK/PD population compared to the safety population in Table 4 above.

Table 5: Summary of Demographics - PK/PD population

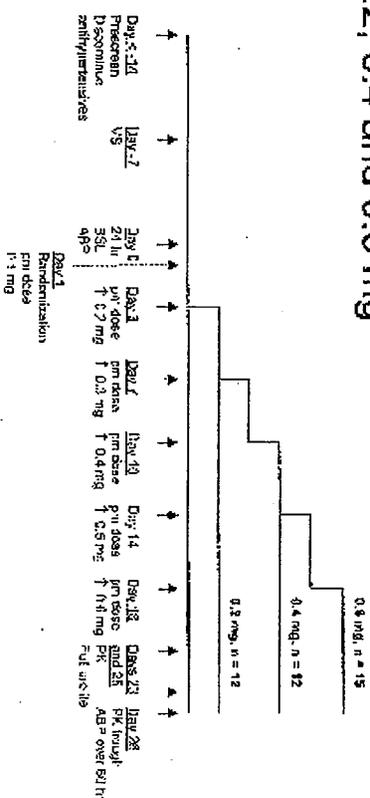
Variable	Stats	0.2mg	0.4mg	0.6mg	Total
Age (years)	n	12	12	15	39
	Mean	44	46	49.2	45.6
Gender					
Male	n	10	11	12	33
Female	n	2	1	3	6
Ethnicity					
Hispanic or Latino	n	5	2	1	8
Not Hispanic or Latino	n	7	10	14	31
Race					
American Indian	n	1	0	0	1
Black Or African American	n	2	2	5	9
Native Hawaiian	n	0	0	0	0
Asian	n	0	1	0	1
White	n	9	9	10	28
Height (cm)	n	12	12	15	39
	mean	173.68	176.43	177.25	175.90
Weight (kg)	n	12	12	15	39
	mean	83.61	90.14	91.96	88.83
BMI (kg/m ²)	n	12	12	15	39
	mean	27.77	28.92	29.18	28.66

Figure 1 below shows the exposure -response in the randomized study of a total 91 patients screened. Of these, 45 patients were assigned randomly to the study treatments. Three were withdrawn before taking any study drug leaving 42 patients who received at least one dose.

Figure 3: Exposure Response in Randomized study-CLON201

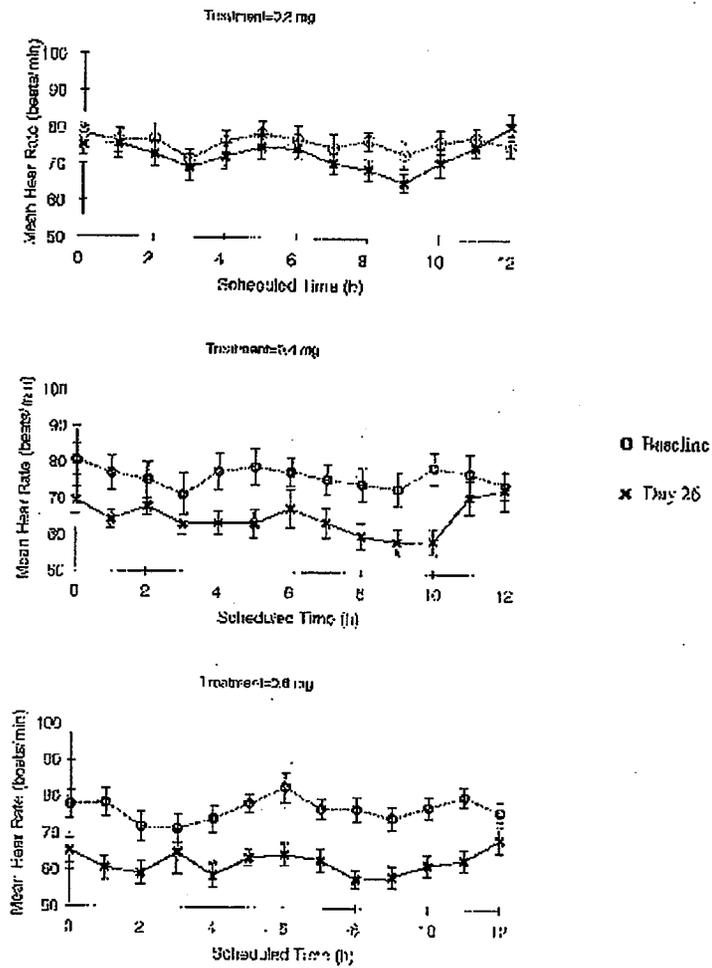
CLON 201 - Exposure - response

- Double blind, multicenter, randomized study
- 0.2, 0.4 and 0.6 mg



- PK samples: Days 23 and 25 - predose, 1, 2, 3, 4, 5, 6, 7, 8, and 12h post dose
- Single trough on Day 26
- PD samples: Baseline and Day 26

Figure 4: Mean Heart rate profiles by treatment – 0.2mg -Baseline and Day 26

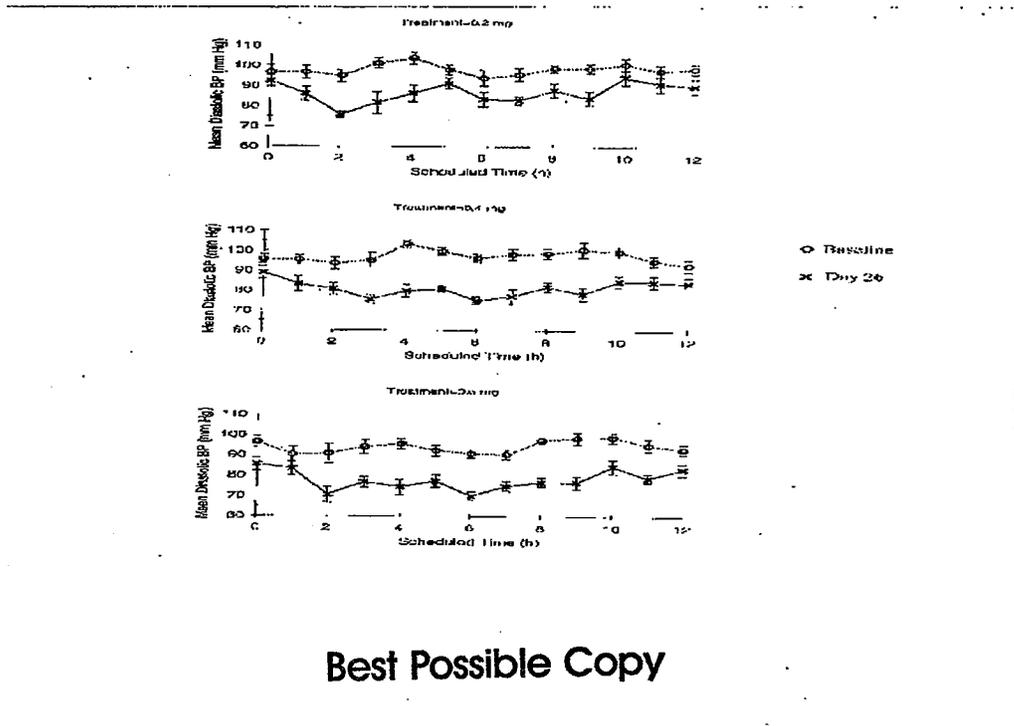


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Table 6: Mean daytime blood pressure at baseline and days 26 to 28

Treatment group (mg/day)	SBP (mmHg)				DBP (mmHg)			
	Day 0	Day 26	Day 27	Day 28	Day 0	Day 26	Day 27	Day 28
0.2 (n=12)	146.7	131.2	135.7	142.9	98.3	87.1	89.1	95.6
0.4 (n=12)	149.1	124.1	130.0	143.9	97.9	81.3	84.3	94.7
0.6 (n=15)	147.5	124.2	134.0	150.4	95.0	78.1	83.7	95.5
Groups combined (N=39)	147.7	126.7	133.3	146.1	97.0	81.9	85.5	95.3

Figure 5: Mean Diastolic BP profiles by treatment –Baseline and Day 26



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Figure 6 Mean Systolic BP profiles by treatment –Baseline and Day 26

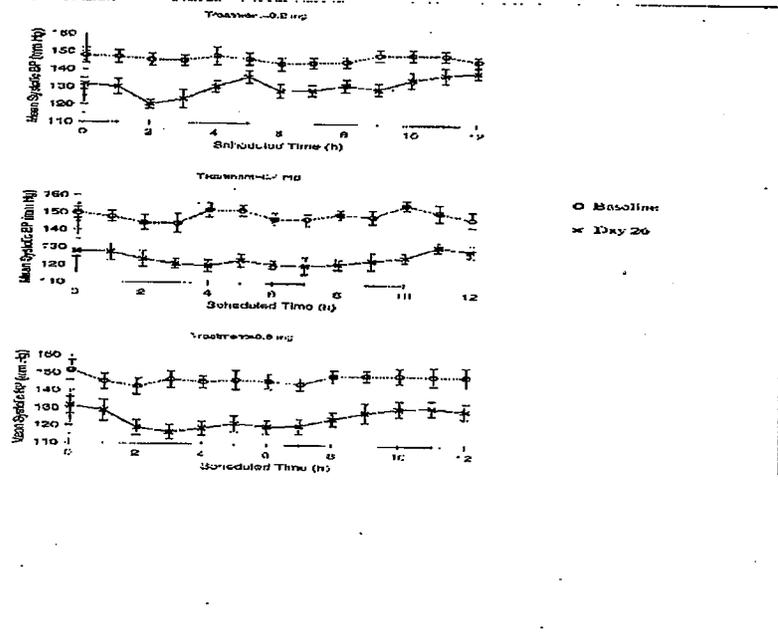
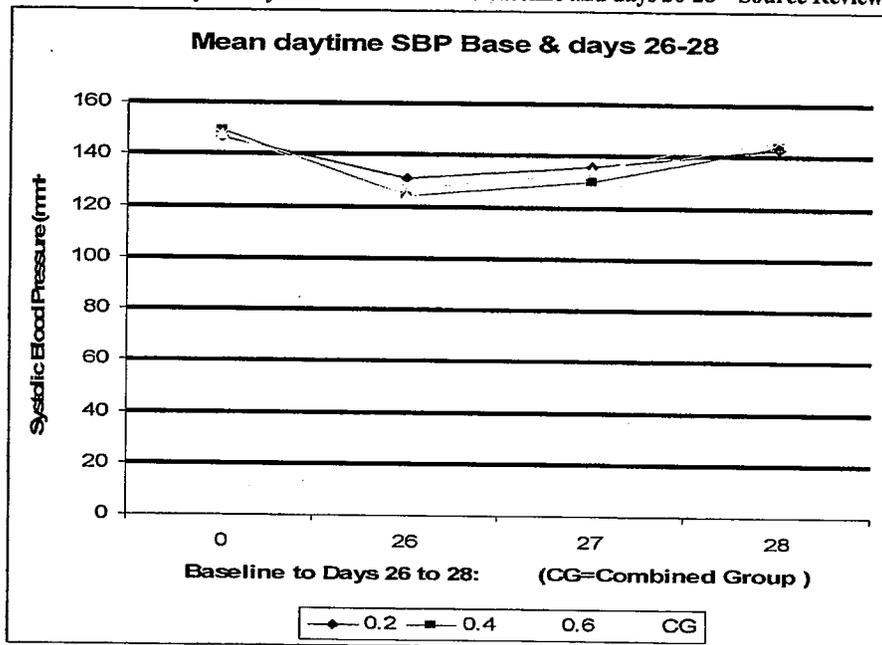
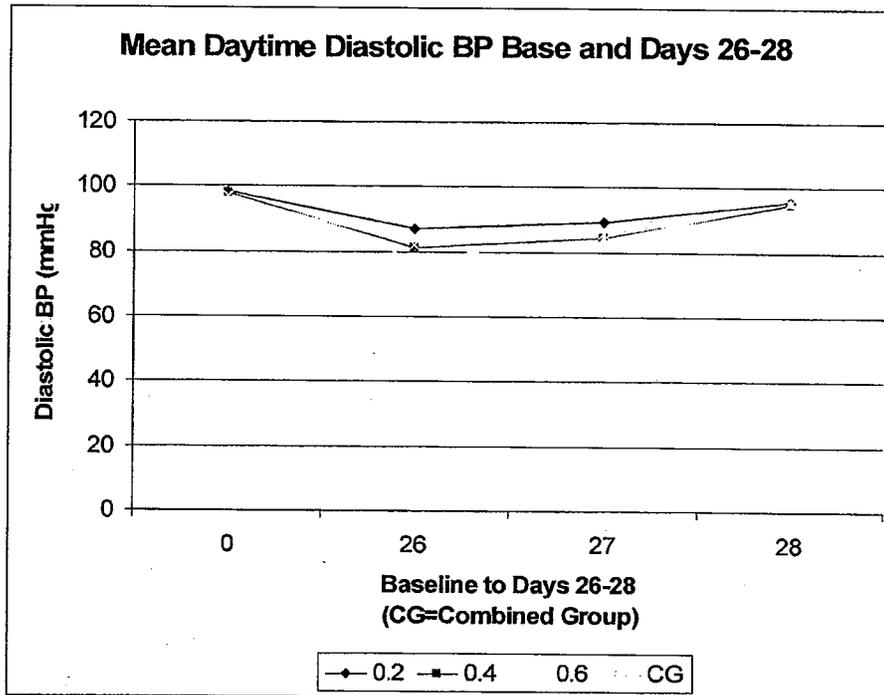


Figure 7: Mean daytime Systolic Blood Pressure baseline and days 26-28 – Source Reviewer



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Figure 8: Mean daytime Diastolic Blood Pressure baseline and days 26-28 – Source Reviewer



The maintenance of treatment effect was investigated at the tail end of the interdosing interval. The differences between the SBP, DBP and HR values at base line and the last two hours of the interdosing interval on day 26 were calculated for each patient and summarized in Table 6 below. The paired t-tests showed statistically significant differences for SBP and DBP at the 0.4 and 0.6 mg dosing levels (Table 5) . There were no significant differences in the heart rates between the treatment groups except at hour 11 in the group that received 0.6mg.(P=0.0029)

Table 7: Mean differences in BP from baseline at 11 and 12 hours Post dosing-CLON 201

Parameter	Tmt group	Hour 11		Hour 12	
		Mean - diff	p-value	Mean - diff	p-value
Systolic Blood Pressure	0.2	10.82	0.0308	6.50	0.0676
	0.4mg	21.91	0.0023	18.25	0.0021
	0.6mg	19.57	0.0053	19.33	0.0044
Diastolic Blood Pressure	0.2	6.27	0.1037	8.500	0.0120
	0.4mg	10.64	0.0052	9.000	0.0070
	0.6mg	17.00	0.0003	19.33	0.0044
Heart Rate	0.2	2.54	0.4468	-5.333	0.0762
	0.4mg	7.72	0.1052	12.50	0.7731
	0.6mg	18.14	0.0029	7.667	0.1392

4.4.3 Pharmacokinetics

PK sampling was performed from 8:00 AM to 8:00 PM on days 23 and 25 and ABPM was reformed for 24 hours just prior to initial dosing, for 24 hours during the final day (Day 26) of dosing and for 48 hours after the abrupt cessation of dosing. Periodic safety assessments including physical exams, vital signs ECGs clinical laboratories and assessment of adverse events were performed throughout the study.

Title of Protocol 101: Single dose PK of clonidine following administration of CLONICEL under fasted and fed conditions and of CATAPRES under fasted condition in healthy volunteers.

Table 6 shows PK parameters measured at day 25.

Table 8: Mean and SD Non-compartmental PK parameters on Day 25-Study 101

group		Cmax	Tmax	Cmin	Cmax/Cmin	AUC t
0.2 mg	Mean	560	4.25	375	1.52	5627
	SD	183	1.65	119	0.26	1594
0.4 mg	Mean	986	4.67	709	1.4	10410
	SD	173	1.15	147	0.14	2007
0.6mg	Mean	1870	5.02	1320	1.43	19310
	SD	636	1.52	451	0.18	6561

Table 9: Single dose PK parameters of clonidine – Study 101

Figure 9: PK showing mean clonidine concentrations as function of time.

Pharmacokinetics

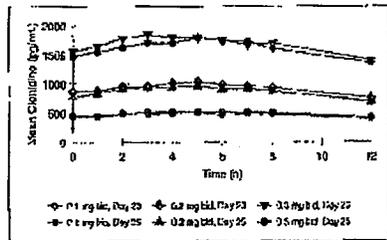


Figure 2: Plot of average clonidine plasma concentrations versus time at steady state.

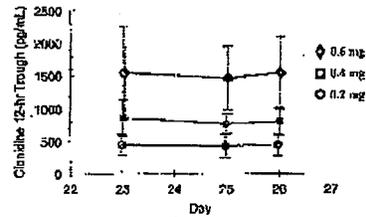


Figure 3: Plot of average (SD) trough clonidine plasma concentrations at steady state.

- Dose proportional PK
- Fluctuation (C_{max}/C_{min})
 - 1.4 to 1.5
- Intrasubject variability
 - 10 to 12% (determined from 5 trough samples)

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Food effect

The plasma concentration time profile of CLONICEL was delayed and more sustained than that of CATAPRES under fasted conditions, although the total systemic exposure and elimination half life of clonidine are similar between the two formulations and furthermore the rate and extent of absorption and elimination half life of clonidine from the CLONICEL formulation remained the same and unaffected by food (Table 8).

Figure 10: Bioequivalence /Food effect

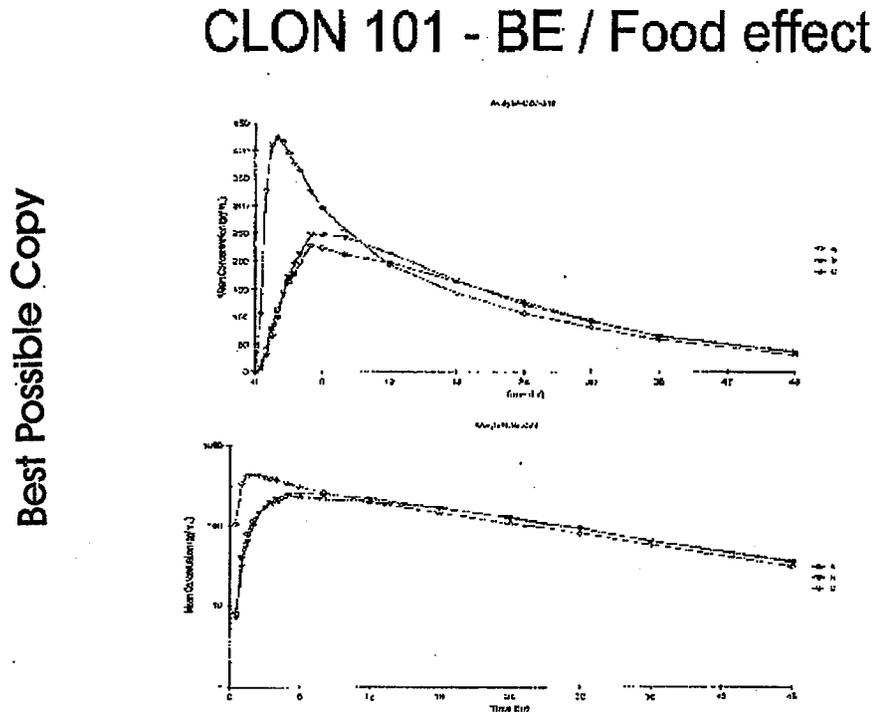
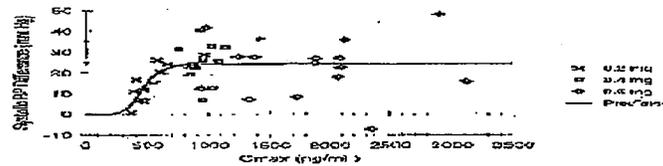


Figure 1: Plot of average plasma clonidine concentration versus time following administration of Clonical ER 0.1 mg fasted (A), Clonical ER 0.1 mg fed (B), and Catapres 0.1 mg IR fasted (C).

The sigmoidal E max model was used with the assumption that there is no pharmacological effect at zero drug concentration.

The relationships between effect and exposure were similar for changes in diastolic and systolic blood pressure for each of the 3 exposure parameters. A representative plot of the observed data identified by CLONICEL dose level is shown in Figure 11 below. The slope of the concentration-response is quite steep at the low concentrations provided by the administration of the 0.2 mg daily dose of Clonidel. Figure 11.

Figure 11: Relationship between effects of clonidine SR on systolic BP and clonidine Cmax
 Sigmoidal Emax relationship between effect on systolic blood pressure



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5 Sources of Clinical Data

The main source of data was from NDA 22331 study report on PK / PD ABPM data.

5.1 Tables of Clinical Studies

There are only two clinical pharm studies. No pivotal clinical studies were carried out.
 Not applicable

5.2 Review Strategy

The strategy for this review is to ascertain and validate the sustained release property of the drug and to evaluate the safety profile of this sustained release formulation.

5.3 Discussion of Individual Studies

- Study on Pharmacodynamics
- Study on steady state pharmacokinetics
- Study on bioequivalence and food effect

There are two clinical pharmacology studies. One study CLON 201 was a double blind, randomized, parallel group design study of 42 patients with mild to moderate hypertension. Following a 2 week wash out period of previous antihypertensive medications, patients were randomized and titrated to 0.2, 0.4 or 0.6 mg per day in twice daily dosing regimens for 26 days. The chosen doses were known to be associated with known therapeutic effects in hypertensive patients (0.2 to 2 ng / ml) .

The second study, CLON 101, evaluated the effect of food on administration of the study drug. The study design was a three period, three sequence, crossover

Treatment sequence: (A) Clonice ER 0.1 mg, fasted; (B) Clonice ER 0.1 mg, fed and (C) Catapres IR 0.1 mg, fasted. The results are illustrated in Figure ///.

Compared to Catapres, the C_{max} was lower, the T_{max} was longer and they both had similar AUC. There was no food effect.

The statistical analysis of bioequivalence is summarized in Table 10 below:

Table 10: Statistical analysis of data for bioequivalence

PK parameter	Geometric Mean		Ratio (%) (Test/Ref)	90% CI	
	Clonice (test)	Catapres (Ref)		Lower	Upper
C _{max}	232.63	439.50	52.93	50.26	55.74
AUC last	5690.04	6573.25	86.56	81.51	91.93
AUC inf	6332.29	7126.93	88.85	83.04	95.06

Table 11: Statistical analysis of data from food effect study

PK parameter	Geometric Mean		Ratio (%) (Test/Ref)	90% CI	
	Fed (test)	Fasted (Ref)		Lower	Upper
Cmax	255.32	232.51	109.81	104.21	115.71
AUC last	5846.41	5677.77	102.98	96.13	110.32
AUC inf	6495.50	6322.56	102.74	94.14	112.12

NDA 22-331

- Bioequivalence / Food effect
 - Assess BE compared to Catapres IR 0.1 mg
 - Effect of food on the bioavailability of Clonidel ER 0.1 mg
- Exposure – response
 - Steady state pharmacokinetics (PK) and pharmacodynamics (PD)
 - Intra-individual variability in PK

6 Review of Efficacy

6.1 Indication

Treatment of essential hypertension.

6.1.1 Methods

Analysis of ABPM data illustrated in Figures 3 to 6.

6.1.2 Demographics

See Table 3 to 6

6.1.3 Patient Disposition

See Table 2 above

6.1.4 Analysis of Primary Endpoint(s)

Not applicable

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

Not applicable

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the E max model (Figure 9) clonidine concentrations less than 500 pg/ml were achieved using 0.2 mg. This may explain the relative ineffectiveness of 0.2 mg using the ABPM data.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable on a long term basis because it was not studied. However efficacy was demonstrated during the interdosing interval.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable

7 Review of Safety

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

CLON 101 and CLON 201

7.1.2 Adequacy of Data

Data are inadequate because a total of only 42 patients was enrolled out of which only 33 completed the study. The study database for safety was based on 42 patients who received one dose of the study drug.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable

7.2 Adequacy of Safety Assessments

Not adequate for reasons given above.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

There is adequate experience with clonidine IR which has been marketed for decades.

7.2.2 Explorations for Dose Response

See Figure 1 and

See Figure 9 showing the E max model.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Not applicable

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

7.3 Major Safety Results

Table 12: Safety Summary

	Overall N (%)
Number of patients dosed	42 (100)
Number of patients with at least one AE	27
Number of severe or moderate AEs	17
Number of severe AEs	4
Number of AEs probably related to study drug	31
Number of Patients with an SAE	1
Number of patients with an SAE probably related to study drug	1
Number of patients who discontinued study drug due to AEs	1

7.3.1 Deaths

No deaths

7.3.2 Nonfatal Serious Adverse Events

None

7.3.3 Dropouts and/or Discontinuations

One patient discontinued the study drug due to AEs. See table below.

Table 13: Safety Summary

	Overall N (%)
Number of patients dosed	42 (100)
Number of patients with at least one AE	27
Number of severe or moderate AEs	17
Number of severe AEs	4
Number of AEs probably related to study drug	31
Number of Patients with an SAE	1
Number of patients with an SAE probably related to study drug	1
Number of patients who discontinued study drug due to AEs	1

Table 14: Reasons for premature termination

No of patients	0.2mg	0.4mg	0.6mg	Total
Enrolled				71
Randomized	13	15	15	43
Safety population	12	12	15	42
Completers	12	12	15	39

No of patients	0.2mg	0.4mg	0.6mg	Total
Terminated prematurely	0	3	0	3
Reason for premature T,				
Adverse event	0	1	0	1
Violation in Criteria	0	2	0	2

7.3.4 Significant Adverse Events

The only significant adverse event was symptomatic Bradycardia two weeks after initiating study drug. This was the only severe event that led to discontinuation of study drug.

7.3.5 Submission Specific Primary Safety Concerns

Symptomatic sinus bradycardia

7.4 Supportive Safety Results

Not applicable

7.4.1 Common Adverse Events

Treatment emergent adverse events of moderate to severe intensity occurred in 6 patients and included two patients each with insomnia and dry mouth. The most common adverse events were dry mouth (38% of patients), fatigue (24% of patients), dizziness (12%) headache (9.5%), nausea (7% of patients and somnolence and insomnia (4.8% each). The frequency of the adverse events increased with increasing doses and was least observed with 0.2mg /day compared to 0.4 mg / day and 0.6mg /day.

7.4.2 Laboratory Findings

No significant findings. There were no changes in mean or individual clinical laboratory tests to suggest study drug effect.

7.4.3 Vital Signs

No significant findings. Review of individual patient vital signs revealed no suggestion of study drug effects apart from the expected decrease in blood pressure and moderate decrease in heart rate.

7.4.4. Electrocardiograms (ECGs)

There were no changes to suggest drug induced effects on mean PR, QRS, QT or QTc intervals.

7.4.5 Special Safety Studies

Not required

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

Only 7 of the 42 patients (17%) were females. Two females each reported both fatigue and headache. Eleven of the 42 patients (26%) were black (all but one of the others were white). Five of the eleven blacks (45%) reported one or more TAEAs; two blacks reported dry mouth. The small number of patients and the relatively narrow range of the ages (26 -64) does not allow meaningful analysis of age and frequency of AEs.

7.5.1 Dose Dependency for Adverse Events

The frequency of the adverse events increased with increasing doses and was least observed with 0.2mg /day compared to 0.4 mg / day and 0.6mg /day.

7.5.2 Time Dependency for Adverse Events

No significant findings.

7.5.3 Drug-Demographic Interactions

No significant findings.

7.5.4 Drug-Disease Interactions

No significant findings

7.5.5 Drug-Drug Interactions

No significant findings

7.6 Additional Safety Explorations

Not applicable

7.6.1 Human Carcinogenicity

Not applicable

7.6.2 Human Reproduction and Pregnancy Data

No significant findings

7.6.3 Pediatrics and Effect on Growth

Not relevant

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Same as for Clonidine IR. No rebound after withdrawal. See Figures 5 and 7

7.7 Additional Submissions

Not applicable

8 Postmarketing Experience

Database from countries where the sustained release formulation has been approved.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

To be discussed at the Divisional labeling meeting.

9.3 Advisory Committee Meeting

Not required and not recommended.

10 Conclusions

- A sustained release profile for Clonidine sustained release has been confirmed by a delayed T max, reduced C max, prolonged concentrations of clonidine over the 12 hour dosing interval and low fluctuation of the plasma clonidine concentrations over the dosing interval.
- Significant decreases of blood pressure were observed at all dose levels with dose related decreases at 0.2 and 0.4 mg per day with no significant decrease at 0.6mg /day.
- PK/PD modeling indicated a relationship between blood pressure and heart rate effects on one hand and steady state PK parameters (AUC, C max, C min) at optimal dosing level of 0.4 mg/day.
- CloniceL was well tolerated at doses ranging from 0.2 to 0.6 mg although adverse events increased progressively with increasing doses.
- Labeling will in essence be similar to Clonidine insert with additional information derived from PK / PD data in this NDA submission.
- The sustained release formulation of Clonidine is therefore recommended for approval.

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