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RESEARCH**

APPLICATION NUMBER:

22-331

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

ONDQA (Biopharmaceutics) Review

NDA: 22-331
Submission Date: 03/27/09
Product: CloniBID (Clonidine hydrochloride) tablets, 0.1 mg
Type of Submission: Original NDA (Memo to File: Dissolution Specification Agreement)
Sponsor: Addrenex Pharmaceutical Co., Ltd.
Reviewer: Tapash K. Ghosh, Ph.D.

Background: In the complete response letter (Dec 2008) from FDA, the Agency requested that the sponsor modify the specifications, tightening the range at each time point to meet the FDA guidance of a $\pm 20\%$ range at all time points as mentioned below:

Time (hours)	% Released
1	/
4	
8	
16	

b(4)

In an e-mail correspondence dated September 9, 2009, the sponsor stated that based on their assessment of the process capability defined by the existing dissolution data, Addrenex proposed the specifications below. These differ only in shifting both the 4 and 8 hour time points up by 5%, still keeping the range at $\pm 20\%$.

Time (hours)	% Released
1	/
4	
8	
16	

b(4)

The sponsor claimed that a review of selected primary registration batches/package configurations produced at UPM show that the specification proposed by the FDA above may be problematic, especially the 8 hour time point as tablets age on stability. The CTM batch used in the clinical trials is included for reference. These data are presented below:

UPM Lot	Range from T0 to last stability timepoint (% released)	
	4 hours	8 hours
2007E054A (CTM)		
2007L112A 8ct w/desiccant		
2007L112A 180ct w/desiccant		
2007L113A 180ct w/desiccant		
2007L116A 8ct w/desiccant (Registrat)		
2007L116A 180ct w/desiccant		

b(4)

*Outside of suggested FDA specifications
Values underlined are potentially problematic at future timepoints.

Since the Feb 09 FDA acceptance of Addrenex proposed specifications, work has commenced at another commercial vendor with the plan to transfer manufacturing to this new site with a prior approval manufacturing supplement following approval of the initial NDA.

The new site formulation development was based on the specifications proposed by and agreed to FDA in Feb09. Formulations have been developed and primary stability batches produced utilizing the new specifications.

Reverting to the specifications requested by the agency in the recent email may require the formulation be modified at this late stage of development.

Recommendation: The sponsor was informed about the Agency's decision via t-con held on September 23, 2009 and they accepted the Agency's proposed specification. They were also asked to provide the Agency document that the Agency previously accepted the following specification. However, they did not submit that document.

	% Released			
	2.0	7.0	7.0	7.0
pH				
Time (hr)	1	4	8	16
Sponsor's proposed Spec	<u> </u>	<u> </u>	<u> </u>	<u> </u>

b(4)

The following dissolution specifications have been finalized based on the agreement reached between the Agency and the sponsor via t-con dated September 23, 2009.

Time (hours)	% Released
1	
4	
8	
16	

b(4)

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICA LS INC	JENLOGA
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICA LS INC	JENLOGA

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/s/

TAPASH K GHOSH
09/28/2009

PATRICK J MARROUM
09/28/2009

ONDQA (Biopharmaceutics) Review

NDA: 22-331
Submission Date: 03/27/09
Product: CloniBID (Clonidine hydrochloride) tablets, 0.1 mg
Type of Submission: Original NDA
Sponsor: Addrenex Pharmaceutical Co., Ltd.
Reviewer: Tapash K. Ghosh, Ph.D.

Background: The original New Drug Application (NDA 22-331) is for a sustained-release oral tablet of clonidine hydrochloride and the sponsor proposed the following dissolution specifications:

pH	% Released			
	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Sponsor's proposed Spec	—	—	—	—

b(4)

However, in the previous review of the original NDA, based on the dissolution profiles from three registration (Clinical/bio) batches, the reviewer proposed the following dissolution specification:

pH	% Released			
	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Reviewer's proposed Spec	—	—	—	—

b(4)

In this submission, the sponsor responded that as discussed with the Agency in communications of February 20, 2009, the following dissolution specifications will be adopted.

pH	% Released			
	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Applicant's proposed Spec	—	—	—	—

b(4)

The purpose of this review is to comment on the sponsor's new dissolution specifications for the proposed product.

Recommendation: The Agency's IVIVC guidance on setting dissolution specifications without an IVIVC recommends that the range at any dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Based on that and following revisiting the data, the reviewer still insists that the sponsor follow the Agency's proposed dissolution specification as described below. In case, problems occur in manufacturing batches, the Agency will be willing to look at the data to reconsider modifying the dissolution specifications.

	% Released			
pH	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Reviewer's proposed Spec	—	—	—	—

b(4)

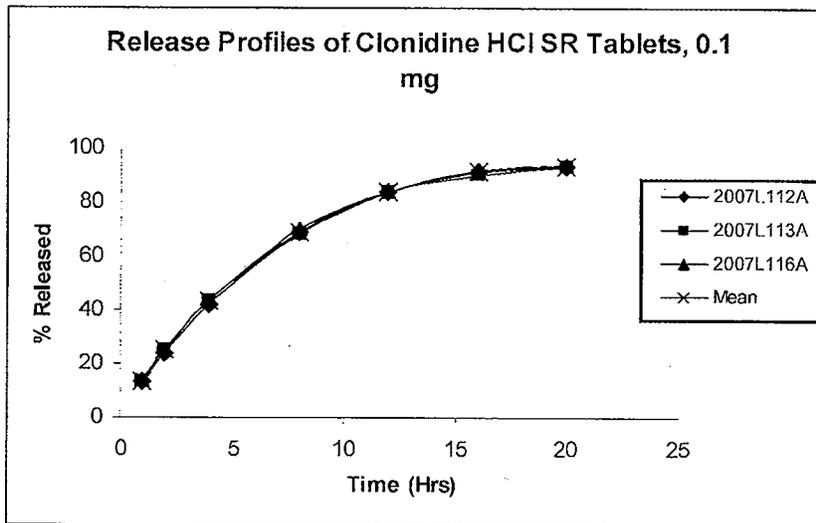
Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

Results: For ready reference, results from the dissolution studies are included here again:

Clonidine Lot#	Purpose	Dissolution Profile % Released at Time in Hours							
		pH 2.0		pH 7.0					
		1	2	4	8	12	16	20	
2007L112A	Registration								
2007L113A	Registration								
2007L116A	Registration								
Average									
SD									
%CV									

b(4)



Dissolution Specification: The Agency's IVIVC guidance on setting dissolution specifications without an IVIVC recommends that the range at any dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Based on that and following revisiting the data, the reviewer still insists that the sponsor follow the Agency's proposed dissolution specification as described below. In case, problems occur in manufacturing batches, the Agency will be willing to look at the data to reconsider modifying the dissolution specifications.

pH	% Released			
	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Reviewer's proposed Spec	—	—	—	—

b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICA LS INC	SYMPRES
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICA LS INC	SYMPRES

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/s/

TAPASH K GHOSH
09/02/2009

PATRICK J MARROUM
09/03/2009

Office of Clinical Pharmacology Review

NDA number:	22-331
Submission type; Code:	BC 006
Applicant name:	Addrenex Pharmaceuticals Ltd.
Submission dates:	11/05/08
Proposed brand name:	Sympres (previously CloniBID, Clonixel)
Generic name:	Clonidine hydrochloride
Dosage form:	Sustained release tablet
Dosage strengths:	0.1 mg
Proposed indication:	Treatment of essential hypertension
OCP division:	DCP1
OND division:	Cardiovascular and renal products
Primary reviewer:	Divya Menon-Andersen, PhD
Secondary reviewer / Team leader:	Robert O. Kumi, PhD

Summary

Addrenex Pharmaceuticals Ltd. is seeking approval via the 505(b) 2 pathway of Sympres (clonidine hydrochloride sustained release tablet) for use in the treatment of mild to moderate hypertension. The potential for alcohol induced dose dumping was not addressed in the original submission (N_000). Subsequently, following the Division's request, Addrenex submitted *in vitro* dissolution data evaluating the potential for alcohol induced dose dumping as an amendment to the original application. This submission is reviewed here, and is an addendum to the original review.

Comments

Ethanol does not appear to affect the release characteristics of Sympres, and there appears to be no potential for alcohol induced dose dumping.

Study AC-MV-119-R0 (Alcohol interaction)

In vitro dissolution testing in alcohol to evaluate the effect of ethanol on the drug release characteristics of Sympres.

Protocol number: AC-MV-119-R0
Investigator: Anthony F. Grigor, Ph.D.
Study site: UPM Pharmaceuticals
6200 Seaforth Street
Baltimore, MD 21224
Study date: 10/08/08

Objective

The objective of the study was to assess via *in vitro* dissolution testing, the impact of ethanol on the release characteristics of Sympres.

Study design

Table 1 presents a summary of the testing conditions employed in the *in vitro* dissolution study.

Table 1: Summary of dissolution testing conditions.

Test group	Media	Other testing conditions
1	0.01N HCl with 0% ethanol	Apparatus: USP II (paddle) Dissolution media volume: 500 mL at 37°C Rotation speed: 50 rpm Sampling times: 0, 60, and 120 minutes Sample volume: 5 mL Number of units tested: 12
2	0.01N HCl with 20% ethanol	
3	0.1N HCl with 0% ethanol	
4	0.1N HCl with 20% ethanol	

Formulation

Sympres 0.1 mg: UPM Pharmaceuticals Ltd., lot number 2007L113A, batch size: —
(commercial batch size)

b(4)

Data analysis

The cumulative amount of clonidine hydrochloride released at each sampling time point was calculated for all four test groups and presented as % label claim (mean ± SD).

Bioanalytical method

Clonidine hydrochloride in the dissolution medium was quantitated using a — HPLC method.

b(4)

Reviewer's comment:

Performance measures for the assay were not provided in the Clinical Pharmacology section of the current submission. Details of the assay method were

presented in the CMC section of the application. The assay was reviewed by the CMC reviewer and found to be acceptable.

Results

The cumulative amount of clonidine released from Sympres at 0, 60, and 120 minutes after start of testing is presented in **Table 2**.

Table 2: Cumulative amount of clonidine released from Sympres expressed as % label claim.

Test group	Tablet weight	Dissolution medium	% label claim released Mean (SD)		
			0 min	60 min	120 min
1	119.37 to 123.3 mg	0.01N HCl with 0% ethanol	0	— (1.0)	— (1.0)
2		0.01N HCl with 20% ethanol	0	— (1.0)	— (1.4)
3		0.1N HCl with 0% ethanol	0	— (0.7)	— (1.1)
4		0.1N HCl with 20% ethanol	0	— (0.9)	— (1.1)

b(4)

As seen in **Table 2**, the cumulative amount of clonidine hydrochloride released from Sympres appears to be the same with and without 20% ethanol in the dissolution media.

Conclusions

Ethanol does not appear to affect the release characteristics of Sympres, and there appears to be no potential for alcohol induced dose dumping.

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/s/

Divya Menon-Andersen
12/17/2008 03:24:52 PM
BIOPHARMACEUTICS

Robert Kumi
12/17/2008 03:29:01 PM
BIOPHARMACEUTICS

ONDQA (Biopharmaceutics) Review

NDA: 22-331
Submission Date: 02/15/08
Product: CloniBID (Clonidine hydrochloride) tablets, 0.1 mg
Type of Submission: Original NDA
Sponsor: Addrenex Pharmaceutical Co., Ltd.
Reviewer: Tapash K. Ghosh, Ph.D.

Background: The original New Drug Application (NDA 22-331) is for a sustained-release oral tablet of clonidine hydrochloride. Clonidine HCl is a compendial USP product, with the immediate release tablet available commercially in the US. According to the sponsor, the proposed sustained-release formulation will decrease the C_{max} value seen in immediate release tablets which contributes to the side effect profile. The goal of the formulation development was to achieve a minimum of — release at the 16 hour time point in order to achieve a profile with a significantly lower peak plasma level compared to the immediate release preparation, which calls for not less than — (Q) of the labeled amount of clonidine to be dissolved in 30 minutes in 500 ml 0.01 N HCl (pH 2) media. The purpose of this review is to recommend dissolution specifications for the proposed product.

b(4)

Description and Composition of the Drug Product

CloniBID is an oral modified release tablet of clonidine hydrochloride, USP. Sustained release property was achieved by the addition of — to each tablet. Each modified release tablet contains 100 micrograms of clonidine hydrochloride with the formulation described below:

Component	mg/tablet
Clonidine hydrochloride, USP	0.10
Sodium lauryl sulfate, NF	/
Lactose monohydrate, NF	
Hypromellose Type 2208, USP	
Partially gelatinized starch, NF	
Colloidal silicon dioxide, NF	
Magnesium stearate, NF	
Total weight per tablet	120

b(4)

Description of Dissolution Method:

Commercially available immediate release clonidine HCl tablet follows USP monograph for dissolution specification which calls for USP apparatus 2 (paddle method), in 500 ml 0.01 N HCl (pH 2) media at 50 RPM. Dissolution method development involved initial testing at pH 2, switching to pH 7 after 2 hours mimicking transit out of the stomach into the pH of the small intestine. At the 2 hour time point, the 0.01 HCL medium will be decanted from the vessel. The medium will be replaced with a pH 7.0 phosphate buffer (preheated to 37°C) without dislodging the tablet at the bottom of the vessel. The method as described below was developed at UPM Pharmaceuticals and is detailed in their document AM-147.

- a) Apparatus: USP Apparatus 2 at 50 rpm.
- b) Sampling: pH 2.0, 0.01N HCl (1, 2 hours); pH 7.0, phosphate buffer (4, 8, 12, 16 hours); 5 ml dissolution sample is withdrawn.
- c) Dissolution medium: 500 ml of media above.
- d) Assay method: HPLC, Detector: ; Mobile phase, column: same for assay; Flow rate: 1.5 ml/min; Injection volume: 100 µl.

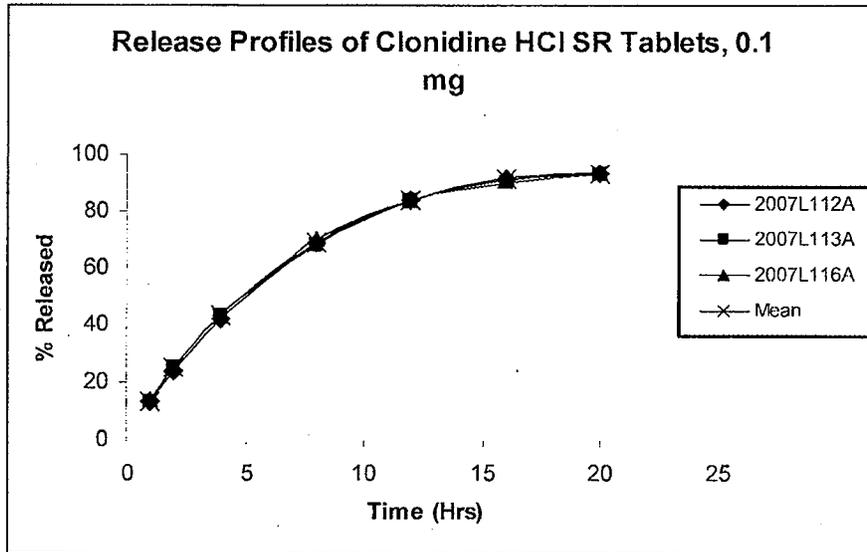
b(4)

Results:

The dissolution profiles from three registration (Clinical/bio) batches are described in the following Table and Figure:

Clonidine Lot#	Purpose	Dissolution Profile						
		% Released at Time in Hours						
		pH 2.0		pH 7.0				
		1	2	4	8	12	16	20
2007L112A	Registration	/	/	/	/	/	/	/
2007L113A	Registration	/	/	/	/	/	/	/
2007L116A	Registration	/	/	/	/	/	/	/
Average		13	25	43	69	84	91	93
SD		0.58	0.58	0.58	1.00	0.00	1.00	0.58
%CV		4.33	2.34	1.35	1.45	0.00	1.10	0.62

b(4)



Dissolution Specification: Based on the above results, modifications have been made in the sponsor's proposed specifications as described below:

pH	% Released			
	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Sponsor's proposed Spec	—	—	—	—
Reviewer's proposed Spec	—	—	—	—

b(4)

Recommendation: The following recommendation for dissolution specification should be conveyed to the sponsor:

pH	% Released			
	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Reviewer's proposed Spec	—	—	—	—

b(4)

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. . _____

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Tapash Ghosh
12/15/2008 10:27:09 AM
BIOPHARMACEUTICS

Patrick Marroum
12/15/2008 10:38:06 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology Review

NDA number:	22-331
Submission type; Code:	Original, N_000
Applicant name:	Addrenex Pharmaceuticals Ltd.
Submission dates:	02/15/08, 08/15/08, 08/28/08 and 09/10/08
Proposed brand name:	Sympres (previously CloniBID, Clonicef)
Generic name:	Clonidine hydrochloride
Dosage form:	Sustained release tablet
Dosage strengths:	0.1 mg
Proposed indication:	Treatment of essential hypertension
OCP division:	DCP1
OND division:	Cardiovascular and renal products
Primary reviewer:	Divya Menon-Andersen, PhD
Secondary reviewer / Team leader:	Robert O. Kumi, PhD

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1 EXECUTIVE SUMMARY

Addrenex Pharmaceuticals Ltd. is seeking approval via the 505(b) 2 pathway of Sympres (clonidine hydrochloride sustained release tablet) for use in the treatment of mild to moderate hypertension. Currently, three dosage forms of clonidine (immediate release (IR) tablet, transdermal patch, and injectable) are approved for marketing in the United States of America. The IR tablet and transdermal patch are approved for use in the treatment of hypertension.

Sympres is formulated by mixing clonidine hydrochloride with [redacted]. Sympres will be marketed as a 0.1 mg tablet for oral administration, twice daily (*bid*). The sponsor proposes a starting dose of 0.1 mg, taken at bedtime and then in the morning (*bid*), which may then be titrated upwards in increments of 0.1 mg/day at weekly intervals, to attain the desired antihypertensive effect. Doses of Sympres above 0.6 mg/day were not evaluated; therefore the maximum proposed dose of Sympres is 0.6 mg/day.

b(4)

The application contains two clinical studies in support of the sponsor's claims of extended release characteristics, systemic exposure, and efficacy. The systemic exposure to clonidine following administration of a single dose of 0.1 mg Sympres and a single dose of 0.1 mg of the IR tablet Catapres was evaluated and compared in the first study (CLON101) conducted in healthy volunteers. The effect of food on systemic exposure to clonidine following administration of a single dose of 0.1 mg of Sympres was also evaluated. In the second study (CLON201), the steady state pharmacokinetics and pharmacodynamics of clonidine following administration of 0.2, 0.4, or 0.6 mg/day of Sympres in patients with mild to moderate hypertension was evaluated.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP1) reviewed NDA 22-331. The NDA is considered acceptable from a clinical pharmacology perspective.

Comments

1. The application met the criteria for bioavailability for an extended release product as specified in the CFR.
 - a. Meets the modified release claim.
 - b. Systemic exposure to clonidine (area under the concentration time curve or AUC) equivalent to the IR tablet.
 - c. Consistent performance between individual dosage units.
 - d. No evidence of food induced dose dumping.
 - e. While the steady state pharmacokinetics of clonidine following administration of Sympres were not compared with that of an approved product, the plasma clonidine concentrations at steady state were within the accepted optimal therapeutic range for clonidine.
2. The potential for alcohol induced dose dumping has not been addressed; this is being assessed via *in vitro* dissolution using aqueous – alcoholic dissolution media. Addrenex indicated that the dissolution results would be submitted to FDA by the end of October, 2008, however, the results are still pending. OCP will

review these dissolution results once submitted, and OCP recommendations will be documented as an amendment to this current OCP review.

1.2 Phase 4 Commitments

There are no recommendations.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Two studies, CLON101 and CLON 201, were conducted to support approval of the proposed clonidine hydrochloride sustained release tablet, Sympres. According to 21 CFR §320.25, an *in vivo* bioavailability study for an extended release product should establish steady state performance equivalent to an approved dosage form, administered according to the dosing regimen in its labeling. In lieu of this the sponsor proposed targeting the accepted optimal therapeutic range for clonidine (200 to 2000 pg/mL). In addition, the sponsor was required to provide evidence of antihypertensive effect following dosing with Sympres, and maintenance of the same throughout the dosing interval. Hence, the sponsor conducted a steady state pharmacokinetic and pharmacodynamic study in patients with mild to moderate hypertension to support their claims of controlled release and antihypertensive effect.

Relative BA / Single dose PK

Systemic exposure (AUC) to clonidine following administration of 0.1 mg Sympres was equivalent to that observed following administration of a single dose of the IR tablet (Catapres 0.1 mg). As presented in **Table 1**, peak plasma concentrations (C_{max}) were significantly lower, and time to C_{max} (t_{max}) was significantly prolonged when compared to Catapres.

Table 1: Summary of pharmacokinetic measures for clonidine following administration of a single dose of 0.1 mg of Sympres and Catapres (Ref: Table 11.4.3.3-4, vol. 10).

	AUC _{0-∞} Mean (SD) (pg h/mL)	C _{max} Mean (SD) (pg/mL)	t _{max} Median (range) (h)
Sympres	6505 (1728)	235 (34.7)	5.03 (5 to 18)
Catapres	7313 (1812)	443 (59.6)	2.0 (1.0 to 2.5)

There was no evidence of dose dumping after administration of Sympres with a high fat meal.

Steady state pharmacokinetics and pharmacodynamics

Steady state pharmacokinetics and pharmacodynamics of clonidine were characterized in patients with mild to moderate hypertension. The patients were randomized to receive 0.2, 0.4 or 0.6 mg daily in two divided doses.

The steady state exposure of clonidine following administration of 0.2, 0.4 or 0.6 mg of Sympres appears to be dose proportional (**Table 2**). The observed mean plasma clonidine concentrations were within the optimal therapeutic range of 200 to 2000 pg/mL.

Table 2: Summary of pharmacokinetic measures for Sympres following dosing to steady state (Ref: Table 11.4.2.3, vol. 13)

Dose		C _{max}	C _{min}	C _{avg}	AUC _τ	C _{max} /C _{min}
0.2 mg/day n=12	Mean	553	407	489	5867	1.38
	SD	157	138	145	1735	0.14
	Range	379-887	233-703	325-430	3902-9535	1.19-1.63
0.4 mg/day n=12	Mean	1060	762	921	11050	1.42
	SD	291	241	266	3196	0.12
	Range	696-1830	468-662	595-860	7141-10320	1.21-1.45
0.6 mg/day n=15	Mean	1980	1380	1680	20130	1.44
	SD	839	568	684	8207	0.12
	Range	907-3800 *	581-2610	702-3020	8423-36230	1.19-1.71

* Four out of the 15 patients in the 0.6 mg/day dose group had plasma clonidine concentrations in the range of 2000 to 3800 pg/mL.

Also, as seen in Table 3 there appears to be no change in the clearance of clonidine between single dose in healthy volunteers and at steady state in patients with mild to moderate hypertension.

Table 3: Clearance estimates obtained from non-compartmental analysis for clonidine following dosing with Sympres (Ref: Table 14.2.2.1, vol. 13).

	Single dose	Steady state					
	0.1 mg	0.2 mg		0.4 mg		0.6 mg	
	Day 1	Day 23	Day 25	Day 23	Day 25	Day 23	Day 25
CL/F	16.2 (3.4)	18.3 (4.7)	19.1 (5.1)	19.3 (4.6)	19.8 (3.2)	17.5 (7.7)	17.5 (6.6)

Inter - subject variability in clearance ranged from 20 to 40%. Average intra - subject variability for the three treatment groups ranged from 10 to 12%. Average fluctuation (C_{max}/C_{min}) for the three treatment groups ranged from 1.38 to 1.52.

The primary pharmacodynamic endpoint in this study was the mean change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP). As seen in Table 4, mean difference in SBP and DBP between day 1 (baseline) and day 26 of the study was statistically significant at the 0.4 and 0.6 mg dose levels throughout the dosing interval. Further, overall there appears to be no change in heart rate (HR).

Table 4: Mean difference from baseline (day 1) in daytime blood pressure on study day 26 at the tail end of the dosing interval (Ref: Tables 11.4.3.2 and 14.2.4, vol.13).

Time post dose	Treatment groups	SBP		DBP		HR	
		Mean difference	p-value	Mean difference	p-value	Mean difference	p-value
Hour 11	0.2 mg/day	10.82	0.0308	6.27	0.1037	2.55	0.4468
	0.4 mg/day	21.29	0.0023	10.64	0.0052	7.73	0.1052
	0.6 mg/day	19.57	0.0053	17.00	0.0003	18.14	0.0029
Hour 12	0.2 mg/day	6.50	0.0676	8.50	0.0120	-5.33	0.0762
	0.4 mg/day	16.90	0.0054	7.27	0.0103	0.64	0.8924
	0.6 mg/day	19.33	0.0044	9.80	0.0341	7.67	0.1392

Systolic and diastolic blood pressure was monitored for 48 hours after the abrupt withdrawal of Sympres for the occurrence of rebound hypertension. However, the duration of observation was insufficient. Therefore valid conclusions regarding the absence of rebound hypertension cannot be made.

Clinical Pharmacology Briefing

A required inter - division level briefing was held on October 30, 2008; and attended by Immo Zdrojewski, Mike Pacanowski, Ritesh Jain, Ramana Uppoor, Norman Stockbridge, Mehul Mehta, John Lazor, Ting Eng Ong, Islam Younis, Russell Fortney, Lillian Zhang, Lily Mulugeta, Angelica Dorantes, Robert Kumi, and Divya Menon-Andersen.

Divya Menon-Andersen, PhD
Reviewer, Division of Clinical Pharmacology 1

Date: October 30, 2008

Robert O. Kumi, PhD
Secondary reviewer / Team leader (Acting), Cardio – renal products
Division of Clinical Pharmacology 1

Cc: KumiR, UppoorR, MehulM

2 QUESTION BASED REVIEW

This is an abridged version of the question based review.

2.1 General Attributes of the Drug

Clonidine is a centrally acting antihypertensive agent approved for marketing in the US in 1979. The usual dose range for clonidine is 0.1 - 0.8 mg/day, given in two divided doses and titrated to effect (Chobanian AV, et al., 2003). The concentration - response relationships for clonidine have been evaluated in several anecdotal studies (Davies DS, et al., 1977; Frisk-Holmberg M, et al., 1984; Wing LM, et al., 1977; Lowenthal DT, et al., 1988). The consensus finding was that within the concentration range of 200 – 2000 pg/mL, the observed antihypertensive effect of clonidine is directly proportional to its plasma concentration. *In vivo* bioavailability requirements as specified in 21 CFR §320.25 for an extended release dosage form requires establishing steady state performance equivalent to an approved dosage form, administered according to the dosing regimen in its labeling. As an alternative to this, the sponsor proposed targeting the accepted optimal therapeutic range for clonidine. The Division of Cardio-renal Products agreed to this proposal in a meeting held on January 22, 2008.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

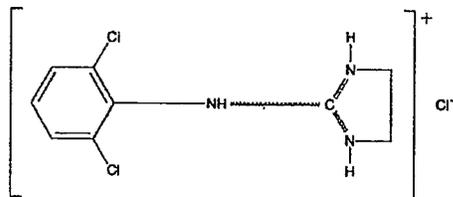
Description: White, crystalline powder, odorless, and bitter to taste.

Chemical name: 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride

Molecular formula: C₉H₉Cl₂N₃.HCl

Molecular weight: 266.56

Structural formula:



Solubility: Soluble in water and alcohol.

Formulation:

Sympres is a modified* release tablet, formulated by mixing clonidine with [redacted]

[redacted] resulting in slow release over a prolonged duration when compared to the IR dosage form. The composition of the tablet is presented in Table 5.

*Note: Designation of Sympres as a sustained or extended release tablet may be misleading, since the proposed dose and dosing frequency is the same as that of the IR tablet. The term 'modified' is better suited to indicate that while the concentration-time profile of clonidine following dosing with Sympres is different from that of the IR tablet; it does not provide prolonged plasma clonidine levels.

Table 5: Composition of Sympres tablets.

Component	Weight in mg	Function
Clonidine hydrochloride, USP	0.10	Active ingredient
Sodium lauryl sulfate, NF		
Lactose monohydrate, NF		
Hypromellose type 2208, USP		
Partially pregelatinized starch, NF		
Colloidal silicon dioxide, NF		
Magnesium stearate, NF		

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2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Clonidine is a centrally acting α -2 adrenergic receptor agonist. Stimulation of the α -2 adrenergic receptors cause decreased sympathetic outflow from the central nervous system. This ultimately results in a decrease in peripheral resistance, renal vascular resistance, heart rate, and arterial blood pressure.

Clonidine is currently approved as an IR tablet (hydrochloride salt), and a transdermal patch (free base) for use in the treatment of hypertension. A parenteral dosage form for epidural administration is approved for use in combination with opiates in the management of severe pain in cancer patients. Sympres is indicated in the treatment of hypertension, and was formulated to provide systemic clonidine levels comparable to that following administration of the immediate release tablet, Catapres, but with a reduced 'peak to valley' effect (fluctuation - C_{max}/C_{min}).

2.1.3 What are the proposed dosages and routes of administration?

A starting dose of 0.1 mg, taken at bedtime and then in the morning (*bid*), is proposed for Sympres in the treatment of hypertension. The dose may be titrated upwards to attain the desired antihypertensive effect in increments of 0.1 mg/day at weekly intervals. Total doses above 0.6 mg / day are not recommended, because they have not been evaluated in clinical studies.

Sympres tablets are formulated in a single strength of 0.1 mg for oral administration.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

Two clinical studies were conducted with Sympres to support dosing and claims. Both studies were reviewed and the individual study reports are presented in section 4.2.

Table 6: Key design features of the clinical studies conducted with Sympres.

Study number	Design	Study population	Treatments	Endpoint
CLON 101 Relative BA / Food effect	Single center, 3 sequence, 3 period, randomized, crossover design	Healthy volunteers	Single dose of 0.1 mg Sympres fed or fasted or 0.1 mg Catapres n = 15	PK
CLON 201 Steady state PK and PD	Multi-center, double blind, randomized, parallel design	Subjects with mild to moderate hypertension	Multiple dose, 0.2 mg, n = 12 Multiple dose, 0.4 mg, n = 12 Multiple dose, 0.6 mg, n = 15	PK on days 23 and 25 of study; Systolic and diastolic blood pressure on day 26 of study.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Change from baseline in systolic and diastolic blood pressure on day 26 of the study was the primary pharmacodynamic endpoint in the steady state pharmacokinetics and pharmacodynamics study, CLON 201. This study was conducted in patients with mild to moderate essential hypertension.

Clonidine is a centrally acting antihypertensive agent; therefore a change in blood pressure is an appropriate measure of its efficacy. Blood pressure was measured using an ambulatory blood pressure monitor.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Clonidine is the only active moiety. Please refer to section 2.6 for details of the bioanalytical method.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationship for efficacy?

Exposure – response data are available from the steady state pharmacokinetics and pharmacodynamics study, CLON 201. In study CLON 201, the antihypertensive effect of three doses of Sympres, 0.2, 0.4 and 0.6 mg/day, were evaluated in patients with mild to moderate hypertension. The dose range was selected based on prior exposure - response data for previously approved clonidine IR tablets and transdermal patches. Historically, maximum benefit of dosing with clonidine has been observed within the concentration range of 200 to 2000 pg/mL. The antihypertensive effect is attenuated at concentrations above 2000 pg/mL, with no further antihypertensive effect observed at concentrations

above 4000 pg/mL (Summary basis of Approval -NDA 18891, 1985; Lowenthal DT, et al., 1988).

2.2.4.1.1 Does administration of Sympres (0.2 to 0.6 mg/day) achieve optimal therapeutic concentrations?

The primary objectives of CLON 201 were to evaluate the steady state pharmacokinetics and pharmacodynamics of clonidine. **Table 7** presents a summary of pharmacokinetic measures for clonidine following dosing of Sympres. As seen in **Table 7**, the observed mean plasma clonidine concentrations were within 200 to 2000 pg/mL.

Table 7: Steady state pharmacokinetic measures for clonidine following administration of 0.2, 0.4 or 0.6 mg of Sympres (Ref: Table 11.4.2.3, vol.13).

Dose		C _{max}	C _{min}	C _{avg}	AUC _τ	C _{max} /C _{min}
0.2 mg/day n=12	Mean	553	407	489	5867	1.38
	SD	157	138	145	1735	0.14
	Range	379-887	233-703	325-430	3902-9535	1.19-1.63
0.4 mg/day n=12	Mean	1060	762	921	11050	1.42
	SD	291	241	266	3196	0.12
	Range	696-1830	468-662	595-860	7141-10320	1.21-1.45
0.6 mg/day n=12	Mean	1980	1380	1680	20130	1.44
	SD	839	568	684	8207	0.12
	Range	907-3800*	581-2610	702-3020	8423-36230	1.19-1.71

* Four out of the 15 patients in the 0.6 mg/day dose group had plasma clonidine concentrations in the range of 2000 to 3800 pg/mL.

Figure 2 shows a graphical representation of the data. As seen in **Figure 2**, on study day 23, four of the 15 subjects who received 0.6 mg/day of Sympres, exhibited plasma concentrations above 2000 pg/mL, but below 4000 pg/mL (range: 2000 to 3800 pg/mL).

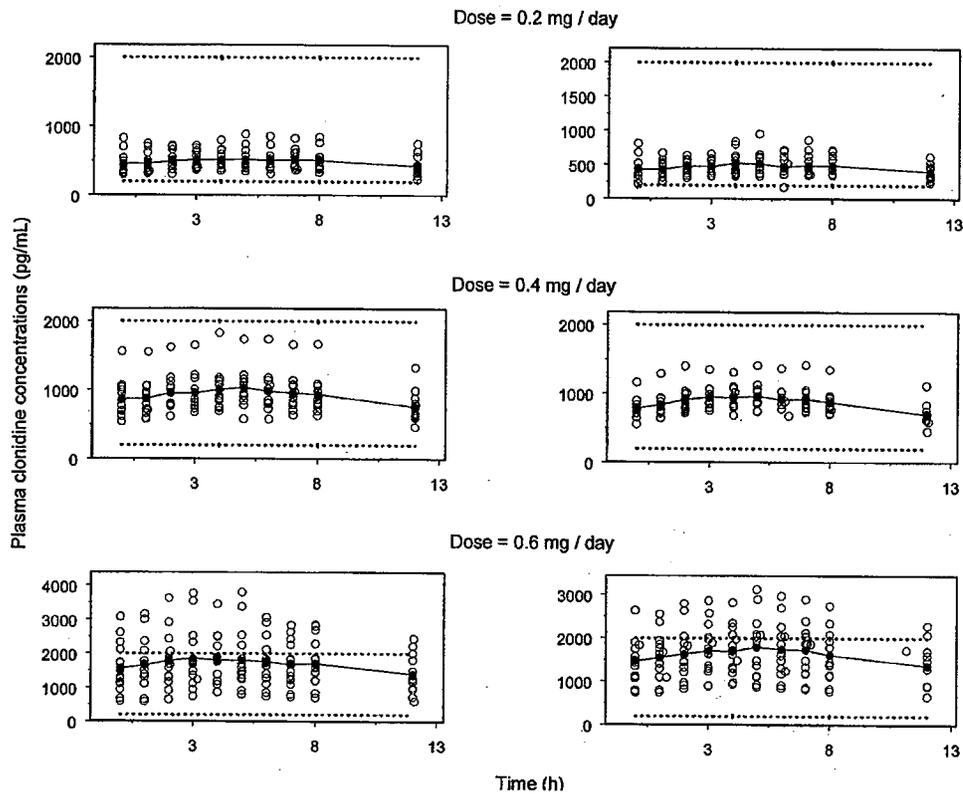


Figure 2: Plasma clonidine concentration versus time plots at steady state following administration of 0.2 (n=12), 0.4 (n=12) or 0.6 (n=15) mg of Sympres. Plasma profiles from day 23 are presented in the left panel and those from day 25 are presented in the right panel. The open circles represent the individual observations, and the line and closed circles represent the mean. The broken lines mark the optimal therapeutic range of 200 to 2000 pg/mL.

2.2.4.1.2 Is there a dose response relationship for clonidine following administration of Sympres?

The observed mean change in blood pressure from baseline values increased with dose in the 0.2 and 0.4 mg dose groups (Table 8). No further decrease in blood pressure was observed in patients who received 0.6 mg/day of Sympres.

Table 8: Mean daytime blood pressure at baseline, and on study days 26, 27 and 28 (Ref: Table 14.4.3.1, vol 13).

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

2.2.4.1.3 *Is the antihypertensive effect following the administration of Sympres maintained throughout the inter-dosing interval?*

The antihypertensive effect of Sympres was maintained at the tail end of the dosing interval (11 and 12 h post dosing) only at the 0.4 and 0.6 mg/day dose levels.

Table 9 presents a comparison of mean change from baseline in SBP and DBP by dose groups at 11 and 12 hours post dosing. As seen from Table 9, the mean change from baseline in systolic and diastolic blood pressure is statistically significant at the end of the dosing interval in 0.4 and 0.6 mg/day treatment groups, indicating that the antihypertensive effect was maintained throughout the dosing interval.

Table 9: Mean difference from baseline (day 1) in daytime blood pressure on study day 26 at the tail end of the dosing interval (Ref: Tables 11.4.3.2 and 14.2.4, vol.13).

Time post dose	Treatment groups	SBP		DBP	
		Mean difference	p-value	Mean difference	p-value
Hour 11	0.2 mg/day	10.82	0.0308	6.27	0.1037
	0.4 mg/day	21.29	0.0023	10.64	0.0052
	0.6 mg/day	19.57	0.0053	17.00	0.0003
Hour 12	0.2 mg/day	6.50	0.0676	8.50	0.0120
	0.4 mg/day	16.90	0.0054	7.27	0.0103
	0.6 mg/day	19.33	0.0044	9.80	0.0341

2.2.4.1.4 *Does rebound hypertension occur following the abrupt withdrawal of Sympres?*

Systolic and diastolic blood pressure was monitored for 48 hours after the abrupt withdrawal of Sympres for the occurrence of rebound hypertension. SBP and DBP appeared to return to baseline by 48 h. Historical data suggests that rebound hypertension following abrupt discontinuation of clonidine is observed between 24 to 72 hours post withdrawal of the drug. The duration of observation in this study appears to be insufficient. Therefore valid conclusions cannot be made.

2.2.4.1.5 What were the features and limitations of the sponsor's exposure-response relationships?

Valid and reliable conclusions regarding exposure-response relationships cannot be made from the exposure – response analysis presented in this application. Additionally, the analysis is irrelevant to the objectives of the study.

As part of the data analysis effort, the sponsor attempted to develop an exposure - response relationship for efficacy. A sigmoid E_{max} model was used to describe the relationship between observed C_{max} , C_{min} and AUC_{τ} , and the change from baseline in the area under the effect curve (AUEC) for systolic and diastolic blood pressure. The model predicted parameters and a representative model fit are presented in Table 10 and Figure 3, respectively.

Table 10: Parameter estimates of the PK/PD model (Ref: Table 11.4.3.3, vol.13).

Parameter		Systolic BP	Diastolic BP
C_{max}	E_{max} (Δ BP)	24.3	16.7
	EC_{50} (pg/mL)	458	431
	EC_{90} (pg/mL)	646	561
	Shape Factor (γ)	6.39	8.29
C_{min}	E_{max} (Δ BP)	24.4	16.8
	EC_{50} (pg/mL)	359	341
	EC_{90} (pg/mL)	532	461
	Shape Factor (γ)	5.56	7.31
AUC_{τ}	E_{max} (Δ BP)	24.3	16.8
	EC_{50} (h*pg/mL)	4702	4401
	EC_{90} (pg/mL)	6692	5921
	Shape Factor (γ)	6.26	7.42

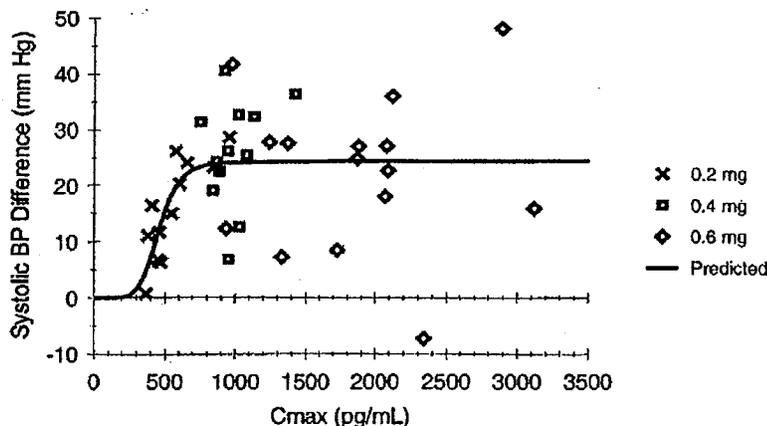


Figure 3: Plot of observed and predicted change from baseline SBP versus C_{max} . The solid line represents the model fit.

The exposure – response analysis presented is unacceptable for the following reasons.

- The objectives of the analysis were not stated.

- The methods used and the process of model development were not described.
- The results presented were incomplete. Model parameter estimates were presented without any measure of precision.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

Exposure – response relationships for safety were not evaluated. Instead, the study relied on attaining and staying within the accepted optimal therapeutic range for clonidine. Additionally, the controlled release tablet was designed to minimize ‘peak to trough’ effect (fluctuation - C_{max}/C_{min}) that is observed on repeat dosing with the IR tablet. Peak plasma clonidine levels have been associated with adverse events such as sedation, and trough levels with rebound hypertension.

Based on the bioavailability data presented in NDA 18-891 (Catapres-TTS), plasma clonidine concentrations attained following administration of 0.6 mg/day are expected to be similar to that observed following administration of a 0.3 mg/day transdermal patch. Doses of up to two patches (2 x 0.3 mg/day) are recommended for use in the treatment of hypertension; therefore supporting the safety of Sympres at doses up to 0.6 mg/day.

2.2.4.3 Does this drug prolong QT/QTc Interval?

The effect of clonidine on QT interval following administration of Sympres was not evaluated.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

Yes, the dose and dosing regimen are consistent with known exposure – response relationships for clonidine.

According to historical data, the antihypertensive effect of clonidine increases with increasing concentrations over a range of 200 to 2000 pg/mL. The antihypertensive effect is attenuated at concentrations above 2000 pg/mL, with no further reduction in blood pressure occurring at concentrations above 4000 pg/mL. The proposed dose range (up to 0.6 mg/day) and the dosing regimen (*bid*) for Sympres will provide average clonidine plasma concentrations within of 200 to 2000 pg/mL.

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 What are the single and multiple dose PK parameters?

Single dose PK

The pharmacokinetics of clonidine were evaluated in study CLON 101 under fed and fasted conditions, following administration of single oral doses of 0.1 mg Sympres, and 0.1 mg Catapres (fasted). **Figure 4** presents the plasma clonidine concentration versus time plot and the pharmacokinetic measures estimated via non - compartmental methods are presented in **Table 11**.

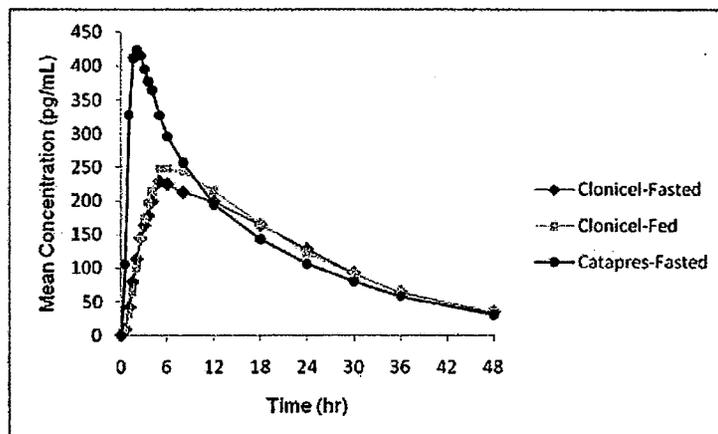


Figure 4: Plot of average plasma clonidine concentration versus time following administration of Sympres 0.1 mg fasted (A), Sympres 0.1 mg fed (B), and Catapres 0.1 mg fasted (C).

Table 11: Summary of pharmacokinetic measures for clonidine following administration of a single dose of 0.1 mg Sympres (Ref: Table 11.4.3.2, vol. 10)

Parameter	Treatment A: CLONICEL-Fasted				Treatment B: CLONICEL-Fed				Treatment C: CATAPRES-Fasted			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	15	6.80	3.61	53.05	14	6.50	1.23	18.88	15	2.07	0.50	23.96
C_{max} (pg/mL)	15	235	34.7	14.76	14	258	33.3	12.89	15	443	59.6	13.45
AUC_{last} (hr*pg/mL)	15	5790	1167	20.16	14	5985	1112	18.57	15	6698	1415	21.12
AUC_{inf} (hr*pg/mL)	15	6505	1728	26.56	14	6729	1650	24.52	15	7313	1812	24.78
$AUC_{E_{trapp}}$ (%)	15	9.95	5.88	59.09	14	9.98	5.75	57.61	15	7.66	4.62	60.35
λ_z (hr ⁻¹)	15	0.0585	0.0142	24.23	14	0.0579	0.0126	21.76	15	0.0584	0.0134	22.95
$T_{1/2}$ (hr)	15	12.67	3.76	29.66	14	12.65	3.56	28.12	15	12.52	3.11	24.83
T_{last} (hr)	15	48.01	0.03	0.06	14	47.16	3.21	6.81	15	48.00	0.00	0.00
C_{last} (pg/mL)	15	34.6	19.2	55.48	14	36.3	18.6	51.30	15	30.6	18.3	59.69

Multiple dose PK

In study CLON 201, the PK of clonidine at steady state (study days 23 and 25) were evaluated in patients with mild to moderate hypertension, following oral administration of 0.2, 0.4 or 0.6 mg/day. Figure 2 presents plots of plasma clonidine concentration versus time following administration of Sympres. The PK parameters estimated using non – compartmental methods are presented in Table 7.

2.2.5.2 How do the PK of the drug and its major metabolites in healthy adults compare to that in patients?

Clearance (CL/F) of clonidine in healthy volunteers following administration of a single dose, and patients with mild to moderate hypertension are similar.

Table 12: Clearance estimates obtained from non-compartmental analysis for clonidine following dosing with Sympres (Ref: Table 14.2.2.1, vol. 13).

	Single dose CLON 101	Steady state CLON 201					
	0.1 mg	0.2 mg		0.4 mg		0.6 mg	
	Day 1	Day 23	Day 25	Day 23	Day 25	Day 23	Day 25
CL/F	16.2 (3.4)	18.3 (4.7)	19.1 (5.1)	19.3 (4.6)	19.8 (3.2)	17.5 (7.7)	17.5 (6.6)

2.2.5.3 What are the characteristics of drug absorption?

Following oral administration of Sympres, peak plasma clonidine levels are observed within 5 to 6 hours of dosing in most subjects. At steady state, C_{max} increased proportionately with dose (Table 7).

In comparison, peak plasma clonidine concentrations were attained within 2 hours post dosing with the IR formulation.

2.2.5.4 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

As assessed from the steady state data presented in Table 7, systemic exposure metrics (AUC , C_{max} , and C_{min}) for clonidine increased proportionately with dose.

2.2.5.5 How do the PK parameters change following chronic dosing?

As seen in Table 12 clearance (CL/F) does not change between single dose (CLON 101) and steady state (CLON 201).

2.2.5.6 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?

The inter-subject variability in clearance ranged from 20 to 40 % in patients with mild to moderate hypertension. The average intra-subject variability as judged from trough concentrations for the three dose groups ranged from 10 to 12 %.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of intrinsic factors on exposure or response was not evaluated.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Influence of food on systemic exposure to clonidine following administration of a single oral dose of 0.1 mg Sympres was evaluated in study CLON 101. Food did not affect the

AUC or C_{max} of clonidine. **Table 13** presents the results of the statistical analysis of the food effect study.

Table 13: Statistical analysis of log-transformed AUC and C_{max} of Sympres 0.1 mg fed (test) and Sympres 0.1 mg fasted (Reference) (Ref: Table 11.4.3.4, vol.10).

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % confidence interval	
	Test	Ref		Lower	Upper
C_{max}	255.32	232.51	109.81	104.21	115.71
AUC_{last}	5846.41	5677.28	102.98	96.13	110.32
AUC_{inf}	6495.50	6322.56	102.74	94.14	112.12

2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the immediate release formulation?

The relative bioavailability of Sympres when compared with Catapres is 86.56% (BE limits: 81.51 to 91.93%), as assessed from the single dose study CLON 101. **Table 14** presents the results of the statistical analysis of the relative BA study.

Table 14: Statistical analysis of log-transformed AUC and C_{max} of Sympres 0.1 mg fasted (test) and Catapres 0.1 mg fasted (Reference) (Ref: Table 11.4.3.3, vol.10)

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % confidence interval	
	Test	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

2.5.2 What is the effect of food on the bioavailability of the drug from the dosage form?

Food does not affect the bioavailability of clonidine, as assessed from the single dose study CLON 101 (**Table 13**). CLON 101 was a single center, open label, randomized, three period, three sequence, crossover study in healthy volunteers. Sympres was administered under fasting conditions and following a high fat breakfast (meal was approximately equivalent to 150, 250 and 500 calories from protein, carbohydrate and fat, respectively).

There was no evidence of dose dumping when Sympres was administered with the high fat breakfast.

2.5.3 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Currently, the responsibility for evaluation of dissolution conditions and specifications lies with ONDQA. However, OCP will evaluate the dissolution results submitted as part of an *in vitro* alcohol interaction study that addresses the potential for alcohol induced dose dumping.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma?

Plasma concentrations of clonidine were determined using a validated HPLC/MS/MS method.

2.6.2 For all moieties measured, is free, bound, or total measured?

The total concentration of clonidine was measured.

2.6.3 What bioanalytical methods are used to assess concentrations?

Table 15 provides the details of the bioanalytical method used to support the pharmacokinetic studies. The method satisfied all criteria for 'method validation' and 'application to routine analysis' set by the Bioanalytical Guidance, and was therefore acceptable.

Table 15: Assay validation results for clonidine (Ref: Section 16.6, vol 17).

Standard curve range *	Linear in the range 4 to 1500 pg/mL (weighted $1/x^2$, $r = 0.9982$)
Precision (%CV)	QC samples (12, 150, 602, 1200 pg/mL): Within run → 0.6 to 14.2 % Between run → 2.0 to 12.8 % Very High QC (7500 pg/mL): Within run → 1.3% At LLOQ (4 pg/mL): Within run → 5.7 to 12.1 % Between run → 16.3 %
Accuracy (Bias)	QC samples (12, 150, 602, 1200 pg/mL): Within run → -7.5 to 11.7 % Between run → -2.5 to 5.8 % Very High QC (7500 pg/mL): Within run → 0.8% At LLOQ (4 pg/mL): Within run → -20.0 to 9.3 % Between run → -2.3 %
Internal standard	Clonidine -D ₄ source: _____, Lot number H278P9
Reference standard	Clonidine source: _____ Lot number 126K1291, purity: 99.0% source: _____ Lot number 066K1621, purity: 99.0%
Specificity	No interference
Recovery	Clonidine: 70.5 to 76.9% Clonidine -D ₄ : 70.3 %
Matrix	K ₂ - EDTA human plasma
Stability (in human plasma)	Benchtop: 25 hours Freeze-thaw: Following 5 FT cycles Long term: 127 days at -20°C Extract: 47 hrs at 22°C Run injection: 124 hrs at 22°C

* The assay was fully validated in the range 8 to 1500 pg/mL. The range was subsequently extended to 4 to 1500 pg/mL, and a partial validation was performed.

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3 DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for Sympres, and finds it acceptable pending the following revisions listed below. The electronic version of the label cannot be edited (PDF image).

1. Section 5.1: Risk of withdrawal

“None of the patients who reported these events, however, evidenced a pattern suggestive of rebound hypertension as assessed by ambulatory blood pressure monitoring (ABPM) for 48 hours after dosing compared with baseline assessments.”

This statement may be misleading. Based on the data submitted, mean BP values approach baseline 48 h post withdrawal.

2. Section 10: Description

“The formulation is designed to delay the absorption of active drug in order to decrease peak to trough plasma concentration differences.”

The formulation plays no role in absorption per se. The slow release of clonidine over a prolonged period, when compared with the IR tablet, results in a slower rate of absorption. Also, this implies modified release as opposed to sustained release. Instead, the sentence above should read as -

“The formulation is designed to slowly release the active drug in order to decrease peak to trough plasma concentration differences.”

3. Section 11.3: Pharmacokinetics

Should include the pharmacokinetic information presented under sections 13.1.

4. Section 13: Clinical studies

- Details regarding the conduct of the studies are not required.
- Figure 2 displaying mean plasma profiles at steady state should be deleted.
- Heading for Table 2 should read “Table 2: Mean and SD Noncompartmental Pharmacokinetic measures on Day 25”.
- Table 3 and Figure 3 under the sub-section ‘Pharmacodynamics’ are misleading.

4 APPENDICES

4.1 Proposed Labeling

14 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4.2 Individual Study Reviews

4.2.1 Study CLON – 101 (Bioequivalence, food effect)

Single dose pharmacokinetics of clonidine following administration of Sympres under fasted and fed conditions, and of Catapres under fasted conditions in healthy volunteers.

Protocol number: CLON – 101

Investigator: _____

Study site: _____

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Study dates: 05/24/07 to 06/09/07

4.2.1.1 Objectives

The objectives of this study were to assess bioequivalence of Sympres 0.1 mg extended release tablets to Catapres 0.1 mg immediate release tablet, and to determine the effect of food on the pharmacokinetics of Sympres 0.1 mg extended release tablets.

4.2.1.2 Study design

This was a single center, open label, randomized, three period, three sequence, crossover study. The treatment periods were separated by a washout period of a minimum of 7 days. Each of the subjects was randomized to receive the following:

1. Sympres 0.1 mg under fasted conditions (treatment A).
2. Sympres 0.1 mg within 30 minutes of a high calorie breakfast. The high calorie breakfast (meal was approximately equivalent to 150, 250 and 500 calories from protein, carbohydrate and fat, respectively) consisted of the following: 2 eggs cooked in butter, 2 strips of bacon, 2 slices of toast with 2 pats of butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk (treatment B).
3. Catapres 0.1 mg under fasted conditions (treatment C).

Reviewer's comment:

The composition and calorie content of the high fat meal follows the BA/BE guidance and is acceptable.

4.2.1.2.1 Formulation

1. Sympres 0.1 mg: UPM Pharmaceuticals, Lot number 2007E054A, Batch size: _____, manufacturing date: May 2007
2. Catapres 0.1 mg: Promeco S.A. de C.V./ (Boehringer Ingelheim-Mexico), Lot number 653615, expiration date: August 2009

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4.2.1.2.2 Pharmacokinetic sampling

Blood samples were collected at pre-dose and at 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h, 18h, 24h, 30h, 36h, and 48h post dose.

4.2.1.2.3 Pharmacokinetic data analysis

Using noncompartmental methods, the following pharmacokinetic measures were determined for all three treatments.

C_{max} , AUC_{last} , AUC_{inf} , T_{max} , λ_z and $t_{1/2}$

4.2.1.2.4 Statistical data analysis

Log transformed pharmacokinetic measures of systemic exposure (C_{max} , AUC) were analyzed using ANOVA linear mixed effects model with sequence, period and treatment as fixed effects, and subject within sequence as a random effect. Point estimates and associated 90 % confidence intervals were determined for the differences of the adjusted treatment means. These were then back transformed to the original scale to give the point estimate and 90% confidence interval for the ratios of the treatment means. T_{max} was compared using the Wilcoxon signed rank test.

4.2.1.3 Safety assessments

Physical examination and clinical laboratory tests were performed and evaluated to assess subject safety.

4.2.1.4 Bioanalytical method

Plasma clonidine was measured using a validated HPLC/MS/MS method. The performance measures of the assay are presented in **Table 1**.

Table 1: Performance measures of clonidine assay in study CLON 101 (Ref: Section 16.5; vol.11)

Linearity	Linear in the range 4 to 752 pg/mL (weighted $1/x^2$, $r = 0.9966$)
Precision (%CV)	QC samples: Interrun \rightarrow 3.8 to 115.6 % * (precision of the qualifying QCs was < 15%)
Accuracy (Bias)	QC samples: Interrun \rightarrow -6.0 to 39.2 % * (Accuracy of the qualifying QCs was < 15%)
Specificity	No interference

* QCs that failed to qualify were included in the calculation. A calculated concentration of 105 pg/mL (nominal value: 12.0 pg/mL) was reported for one of the failed QCs.

4.2.1.5 Study Results

4.2.1.5.1 Subject demographics

Fifteen subjects were enrolled in the study and fourteen subjects completed all three periods. One subject tested positive for drug substance prior to the beginning of the third period of the study and was withdrawn from the study. **Table 2** presents the summary subject demographics.

Table 2: Summary subject demographics for CLN – 101 (Ref: Table 14.1.1, vol. 10)

Group	Parameter	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m ²)	Gender
All enrolled subjects n = 15	Median	30	74.5	173.5	26.2	3F/12 M
	Mean	32.1	74.7	173.2	25.0	
	Range	55.6 – 94.4	19 – 50.4	153.5-194.5	18.5 -29.8	

4.2.1.5.2 Pharmacokinetic results

One subject (# 507) was excluded from the study at the beginning of period 3 (treatment B) of the study. So for treatment B, pharmacokinetic data were available for analysis from only 14 healthy subjects.

Plots of average plasma clonidine concentrations versus time following administration of Sympres 0.1 mg fasted (treatment A), Sympres 0.1 mg fed (treatment B) and Catapres 0.1 mg fasted are presented in **Figure 1**.

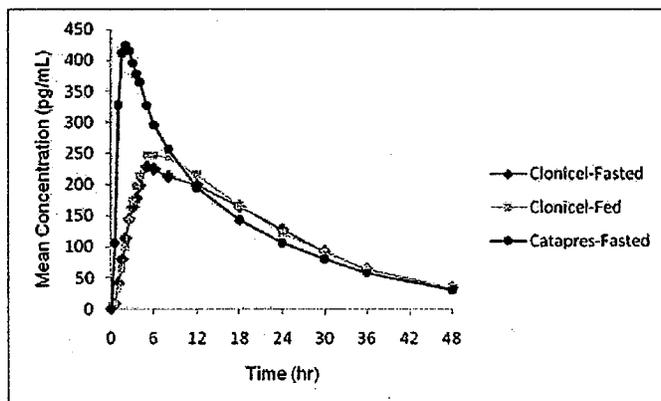


Figure 1: Plot of average plasma clonidine concentration versus time following administration of Sympres 0.1 mg fasted (A), Sympres 0.1 mg fed (B), and Catapres 0.1 mg fasted (C).

As seen in **Table 3**, exposure (AUC) to clonidine following administration of a single oral dose of Sympres 0.1 mg was comparable to that following administration of a single oral dose of Catapres 0.1 mg. The average peak plasma clonidine concentration attained following dosing with Sympres 0.1 mg was delayed and nearly half of that observed on dosing with Catapres 0.1 mg. The elimination half lives for the two products were similar.

Table 3: Summary of pharmacokinetic measures for Sympres and Catapres (Ref: Table 11.4.3.2, vol. 10)

Parameter	Treatment A: CLONICEL-Fasted				Treatment B: CLONICEL-Fed				Treatment C: CATAPRES-Fasted			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	6.80	3.61	53.05	14	6.50	1.23	18.88	15	2.07	0.50	23.96
C _{max} (pg/mL)	15	235	34.7	14.76	14	258	33.3	12.89	15	443	59.6	13.45
AUC _{last} (hr*pg/mL)	15	5790	1167	20.16	14	5985	1112	18.57	15	6698	1415	21.12
AUC _{inf} (hr*pg/mL)	15	6505	1728	26.56	14	6729	1650	24.52	15	7313	1812	24.78
AUC _{Extrap} (%)	15	9.95	5.88	59.09	14	9.98	5.75	57.61	15	7.66	4.62	60.35
λ _z (hr ⁻¹)	15	0.0585	0.0142	24.23	14	0.0579	0.0126	21.76	15	0.0584	0.0134	22.95
T _{1/2} (hr)	15	12.67	3.76	29.66	14	12.65	3.56	28.12	15	12.52	3.11	24.83
T _{last} (hr)	15	48.01	0.03	0.06	14	47.16	3.21	6.81	15	48.00	0.00	0.00
C _{last} (pg/mL)	15	34.6	19.2	55.48	14	36.3	18.6	51.30	15	30.6	18.3	59.69

Tables 4a and 4b present the results of the statistical analysis of pharmacokinetic exposure measures. As seen in Table 5, the 90% CI of the ratio (AUC_{test}/AUC_{ref}) lies within 80 to 125%, and therefore do not significantly differ in the extent of exposure. As expected, the two formulations differed significantly in their C_{max}. T_{max} for Sympres 0.1 mg fasted (median = 5.03 h) was also significantly longer when compared to Catapres 0.1 mg fasted (median = 2.00 h) (p<0.0001, Wilcoxon signed rank test).

Table 4a: Statistical analysis of log-transformed AUC and C_{max} of Sympres 0.1 mg fasted (test) and Catapres 0.1 mg fasted (Reference) (Ref: Table 11.4.3.3, vol.10)

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % confidence interval	
	Test	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

As shown in Table 4b, food does not significantly affect the disposition of clonidine.

Table 4b: Statistical analysis of log-transformed AUC and C_{max} of Sympres 0.1 mg fed (test) and Sympres 0.1 mg fasted (Reference) (Ref: Table 11.4.3.4, vol.10).

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % confidence interval	
	Test	Ref		Lower	Upper
C _{max}	255.32	232.51	109.81	104.21	115.71
AUC _{last}	5846.41	5677.28	102.98	96.13	110.32
AUC _{inf}	6495.50	6322.56	102.74	94.14	112.12

4.2.1.5.3 Safety results

Nine of the 15 subjects enrolled in the study experienced adverse events. A total of 15 AEs were reported, of which the investigators consider 10 AEs related to the study drug. Drowsiness and dizziness were the most commonly reported side effects.

4.2.1.6 Conclusions

1. The total systemic exposure (AUC) to clonidine following administration of a single dose of Sympres 0.1 mg is not significantly different from that following

administration of a single dose of Catapres 0.1 mg. Compared to Catapres, C_{max} was significantly lower (about 52 %) and t_{max} was significantly longer (about twice as long).

2. Food had no effect on the disposition of clonidine following administration of Sympres 0.1 mg.

4.2.2 Study CLON 201 (Steady state pharmacokinetics and pharmacodynamics)

A double-blind, dose ranging study of the pharmacokinetics and pharmacodynamics of clonidine following administration of Sympres in patients with mild to moderate essential hypertension.

Protocol number: CLON – 201

Investigators:

Study dates: 08/15/07 to 10/19/07

Study site: This study was conducted at three centers in the US

b(4)

b(4)

4.2.2.1 Objectives

The objectives of this study were the following.

1. To evaluate the steady-state pharmacokinetics and pharmacodynamics of clonidine following administration of 0.2 mg, 0.4 mg or 0.6 mg / day of Sympres, given in 2 divided doses.
2. To evaluate the intra-individual variability in the pharmacokinetics of clonidine at steady-state following administration of 0.2, 0.4 or 0.6 mg /day of Sympres.

4.2.2.2 Study Design

This was a multicenter, double blind, randomized study, evaluating the pharmacokinetics and pharmacodynamics of clonidine following administration of three different doses of Sympres. Following a washout period of 14 days, subjects meeting the inclusion criteria for the study were randomized to receive 0.2 mg, 0.4 mg or 0.6 mg of Sympres, given *bid*. A schematic of the study design is presented in **Figure 1**.

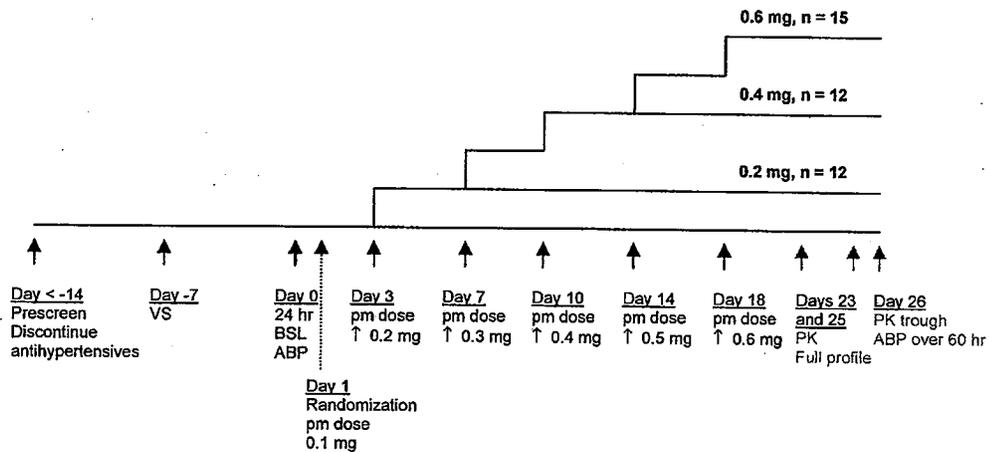


Figure 1: Schematic of the study design for CLON 201 (Ref: Tables 9.4.1 and 9.5.1).

As seen in **Figure 1**, all subjects were started at a dose of 0.1 mg. The dose was then escalated in 0.1 mg increments at 3 to 4 day intervals, to reach the target dose. All subjects were supplied with a blister pack containing Sympres and matching placebo tablets, and were instructed to take three tablets twice daily (8:00 am / 8:00 pm). **Table 1** provides details of the dosing schedule. The evening dose on day 26 was the last dose of the study.

Table 1: Dosing schedule for CLON 201 (Ref: Table 9.4.1, vol. 13)

Treatment Group	Days	No. of tablets (morning)		No. of tablets (evening)	
		Active	Placebo	Active	Placebo
0.2 mg	1-3	0	3	1	2
	4-26	1	2	1	2
0.4 mg	1-3	0	3	1	2
	4-7	1	2	1	2
	8-10	1	2	2	1
	11-26	2	1	2	1
0.6 mg	1-3	0	3	1	2
	4-7	1	2	1	2
	8-10	1	2	2	1
	11-14	2	1	2	1
	15-18	2	1	3	0
	19-26	3	0	3	0

Reviewer's comment:

While all patients in the study were at PK and PD steady state at the time of ABPM on study day 26, they had received the study medication for varying durations. Patients in the 0.2, 0.4, and 0.6 mg/day group received Sympres for 22 days, 16, and 8 days, respectively.

4.2.2.2.1 Formulation

3. Sympres 0.1 mg : UPM Pharmaceuticals, Lot number 2007E054A, Batch size: _____, manufacturing date: May 2007
4. Matching placebo: UPM Pharmaceuticals, Lot number 2007E059A.

b(4)

4.2.2.2.2 Pharmacokinetic measurements

Blood samples were collected at pre-dose and at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, and 12h post dose (morning dose) on days 23 and 25 of the study. A single blood sample was collected on day 26 prior to the scheduled morning dose.

4.2.2.2.3 Pharmacodynamic measurements

Ambulatory blood pressure monitor (ABPM) measurements were made on days 0 and 26 of the study. Baseline blood pressure was measured on day 0 of the study. Subjects were fitted with ABP monitors around 8:00 am in the morning and blood pressure measurements were recorded at 1 hr interval during the day and at 2 hr intervals during the night for the next 24 hours. On day 26 of the study, subjects were fitted with the ABP monitors prior to the scheduled morning dose, following which, blood pressure measurements were recorded at 1 hr intervals during the day and at 2 hr intervals at night over the next 60 hours.

4.2.2.2.4 Sample size determination

A minimum of 12 subjects per treatment group were required to detect a change in blood pressure of 5 mm Hg, given a standard deviation of 5 mm Hg, and $\alpha = 0.05$ and $\beta = 0.8$. In addition, based on clinical judgement, this number was also considered to be sufficient to provide meaningful data on the steady state pharmacokinetics of clonidine.

Reviewer's comment:

The study was not powered for inferential analysis on safety.

4.2.2.3 Data Analysis

The study population was classified as (1) safety and (2) PK and PD populations. The safety population consisted of all subjects who received at least one dose of Sympres. All subjects who received study medication and had valid PK data were included in the PK population, and all subjects who received medication and had at least 12 ABP measurements from any one of the three measurement durations (12 h daytime, 12 h night time, 24 h BP measurement) were included in the PD population.

4.2.2.3.1 Pharmacokinetic data analysis

Using non-compartmental methods, the following pharmacokinetic measures were determined for all three dosing regimens:

C_{max} , C_{min} , C_{avg} , $AUC_{0-\tau}$, T_{max} , CL/F_{ss} , and fluctuation ratio (C_{max}/C_{min}).

4.2.2.3.2 Pharmacodynamic and pharmacokinetic / pharmacodynamic data analysis

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and change from baseline BP were summarized and graphed for each of the treatment groups. Change in the area under the effect curve (AUEC) from baseline upon treatment was calculated for all 3 dose groups and used as the PD metric. A sigmoid E_{max} model was used to describe the relationship between exposure metrics (AUC, C_{max} , C_{min}) and the antihypertensive effect ($\Delta AUEC$).

Reviewer's comment:

The pharmacodynamic measure (ABPM) employed is acceptable.

4.2.2.3.3 Statistical data analysis

Pharmacokinetic measures:

1. Trough concentrations measured on days 23, 25 and 26 were compared using independent repeated measures ANOVA.

Pharmacodynamic measures:

1. Change from baseline in SBP and DBP on day 26 was considered as the primary PD endpoint. No statistical testing was performed.
2. Change from baseline in SBP and DBP at 11 and 12 h post dosing on day 26 was compared using a pairwise t-test.

4.2.2.4 Safety assessments

Physical examination, vital signs (SBP and DBP, heart rate, and oral temperature), clinical laboratory tests, and ECG assessments were performed and evaluated to assess subject safety. In addition, adverse events volunteered by the patient were recorded and evaluated.

4.2.2.5 Bioanalytical method

Plasma clonidine was measured using a validated HPLC/MS/MS method. The performance measures of the assay are presented in **Table 2**.

Table 2: Performance measures of clonidine assay in study CLON 201 (Ref: Section 16.5, vol.16)

Linearity	Linear in the range 8 to 1500 pg/mL (weighted $1/x^2$, $r = 0.9950$)
Precision (%CV)	QC samples (24 to 1200 pg/mL) Interrun \rightarrow 4.4 to 8.4 % (precision of the qualifying QCs was < 15%)
Accuracy (Bias)	QC samples (24 to 1200 pg/mL) Interrun \rightarrow -10.3 to -2.0 % (Accuracy of the qualifying QCs was < 15%)
Specificity	No interference

Reviewer's comment:

- Samples above the ULOQ
Clonidine plasma concentrations were above the ULOQ (1500 pg/mL) in 8 out of the 15 patients in the 0.6 mg treatment group. Although these samples were re-analyzed following dilution with the matrix, there was no comment on the dilution procedure employed in the study report. According to additional information provided by the sponsor at the division's request, study samples analyzed in the repeat analysis run # 7 were diluted 2X, while the rest of the samples re analyzed were diluted 10X.
- The bioanalytical method employed in this study meets the criteria set by the Bioanalytical Guidance and is acceptable.

4.2.2.6 Study results

4.2.2.6.1 Subject demographics

Forty two subjects were enrolled in the study and received at least one dose of the study medication (safety population). Thirty nine subjects completed the study and provided evaluable PK and PD data (PK/PD population). Two patients (subjects 240 and 252) were enrolled erroneously and were withdrawn from the study after receiving 2 doses of the study medication, while the third subject (subject 335) withdrew from the study due to a serious adverse event. **Table 3** presents the summary subject demographics.

Table 3: Summary subject demographics for CLON – 201, PK/PD population (Ref: Table 14.1.3.2, vol. 13)

Group	Parameter	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m ²)	Gender
Sympres 0.2 mg n = 12	Median	45.5	83.2	172.75	28.55	10M/2F
	Mean	44.0	83.61	173.68	27.77	
	Range	34 – 54	74.3 – 98.3	160.5 – 189.5	23.8 – 31.1	
Sympres 0.4 mg n = 12	Median	47.5	89.7	176.25	28.45	11M/1F
	Mean	46	90.14	176.43	28.92	
	Range	26 – 60	75.9 – 110.9	163.7 – 197.0	26.7 – 31.7	
Sympres 0.6 mg n = 15	Median	50.0	90.7	177.50	29.9	12M/3F
	Mean	49.2	91.96	177.25	29.18	
	Range	28 - 64	61.5 – 111.1	154.0 – 193.3	22.1 -34.5	

4.2.2.6.2 Pharmacokinetic results

Figure 2 presents plasma clonidine concentration versus time plots on days 23 and 25 of the study, following administration of 0.2, 0.4 or 0.6 mg of Sympres.

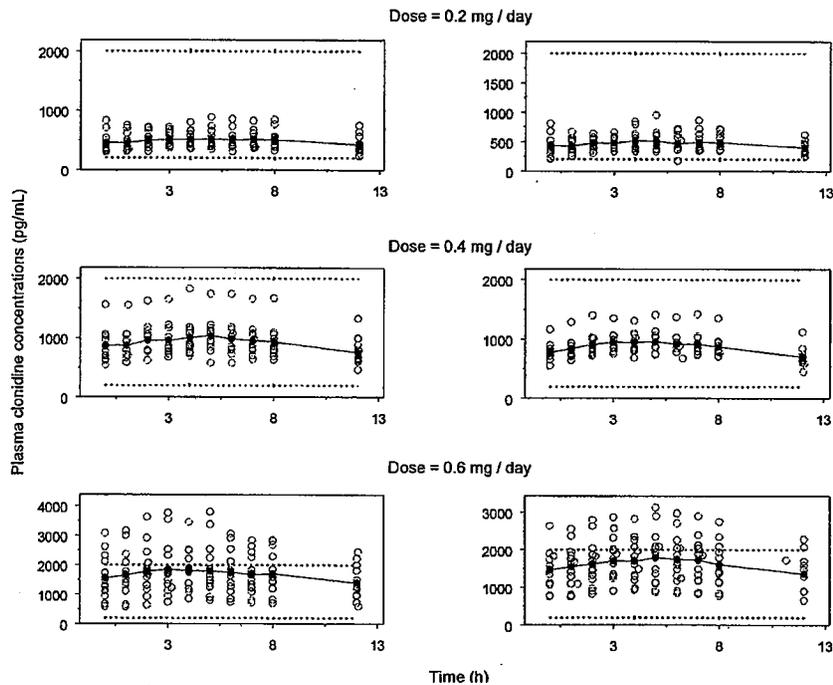


Figure 2: Plasma clonidine concentration versus time plots at steady state following administration of 0.2 (n=12), 0.4 (n=12) or 0.6 (n=15) mg of Sympres. Plasma profiles from day 23 are presented in the left panel and those from day 25 are presented in the right panel. The open circles represent the individual observations while the line and closed circles represent the mean. The broken lines mark the therapeutic range of 200 to 2000 pg/mL.

As seen from the plots, the observed plasma concentration profiles were similar on days 23 and 25 for all three dose groups. The concentrations increased proportionately with increasing doses. **Table 4** presents the results of the non-compartmental PK analysis at steady state. Similar to the results observed in the single dose study, on an average, peak plasma concentrations were attained within 4 to 6 hours of dosing. Inter-subject variability (%CV) in the derived PK measures was estimated to be in the range of 18 to 42%, with higher variability being observed in the 0.6 mg group. As seen from the results presented in **Table 4**, fluctuation (C_{max}/C_{min}) at steady state ranged from 1.38 to 1.52, indicating a favorable peak to trough ratio when compared to the IR formulation (fluctuation (mean \pm SD) = 2.1 ± 0.49 , (FDA, 1985)).

Table 4: Summary of pharmacokinetic measures for Sympres (Ref: Tables 11.4.2.3 and 14.2.2.1, vol. 13)

Dose	Study day		C _{max}	C _{min}	C _{avg}	AUC _t	C _{max} /C _{min}	t _{max}
0.2	23	Mean	553	407	489	5867	1.38	5.0
		SD	157	138	145	1735	0.14	2.09
		Range	379-887	233-703	325-430	3902-9535	1.19-1.63	2.0-8.0
	25	Mean	560	375	469	5627	1.52	4.25
		SD	183	119	133	1594	0.26	1.65
		Range	367-954	172-588	315-433	3777-8158	1.32-2.22	2.05-8.0
0.4	23	Mean	1060	762	921	11050	1.42	4.42
		SD	291	241	266	3196	0.12	1.16
		Range	696-1830	468-662	595-860	7141-10320	1.21-1.45	2.0-6.0
	25	Mean	986	709	868	10410	1.4	4.67
		SD	173	147	167	2007	0.14	1.15
		Range	753-1420	551-1120	668-1310	8018-15750	1.19-1.74	3.0-7.0
0.6	23	Mean	1980	1380	1680	20130	1.44	4.47
		SD	839	568	684	8207	0.12	1.81
		Range	907-3800*	581-2610	702-3020	8423-36230	1.19-1.71	2.0-8.0
	25	Mean	1870	1320	1610	19310	1.43	5.02
		SD	636	451	547	6561	0.18	1.52
		Range	933-3120*	650-2280	800-2730	9604-32730	1.2-1.97	2.0-7.08

* Four out of the 15 patients in the 0.6 mg/day dose group had plasma clonidine concentrations in the range of 2000 to 3800 pg/mL.

Mean (\pm SD) trough concentrations (C_{trough}) on days 23, 25 and 26 are presented in **Figure 3**. Trough concentrations on days 23, 25 and 26 were not significantly different ($p > 0.05$, ANOVA) from one another, confirming attainment of PK steady state.

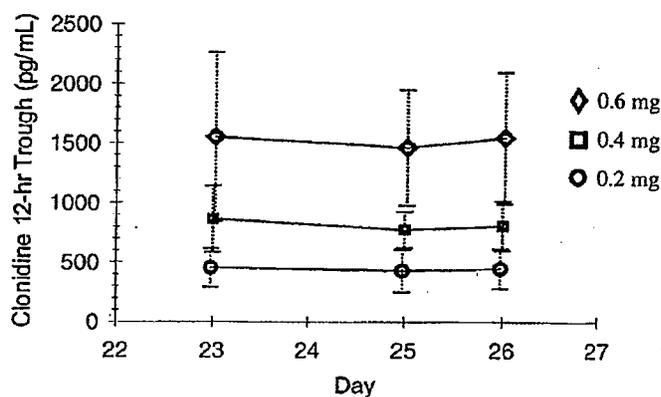


Figure 3: Plot of mean (\pm SD) trough clonidine plasma concentrations at steady state.

Mean intra subject variability for the 3 dose groups, as judged from C_{trough} (5 trough samples), was estimated to be about 10 to 12% for the 3 treatment groups.

4.2.2.6.3 Pharmacodynamic results

A dose dependent decrease from baseline blood pressure was observed in most of the subjects following administration of 0.2 and 0.4 mg of Sympres. The observed mean

antihypertensive effect at the 0.6 mg/day level was similar to that seen with the 0.4 mg/day dose level. The antihypertensive effect was negligible or absent in two of the patients (# 245, 0.2 mg/day and # 136, 0.6 mg/day). The reason for this finding is unclear. Mean (\pm SD) blood pressure versus time plots, comparing profiles obtained at baseline and on day 26 are presented **Figure 4**.

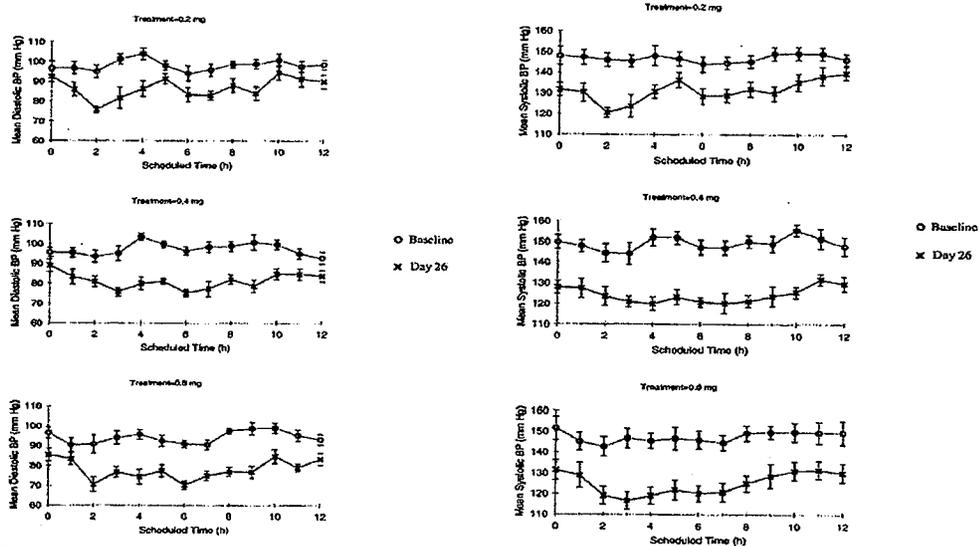


Figure 4: Mean (\pm SE) blood pressure versus time plots at baseline and at day 26, following dosing with 0.2, 0.4 or 0.6 mg Sympres. The left panel presents DBP and the right panel presents SBP.

Mean blood pressure values at baseline and on day 26 of the study are presented in **Table 5**. Further, a plot of the primary PD endpoint, change from baseline SBP and DBP on day 26 is presented in **Figure 5**.

Table 5: Mean daytime blood pressure at baseline and on days 26 to 28 (Ref: Table 11.4.3.1, vol. 13).

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

As seen from **Table 5** and **Figure 5**, patients who received 0.6 mg of Sympres showed no further decrease in BP compared to patients who received 0.4 mg Sympres.

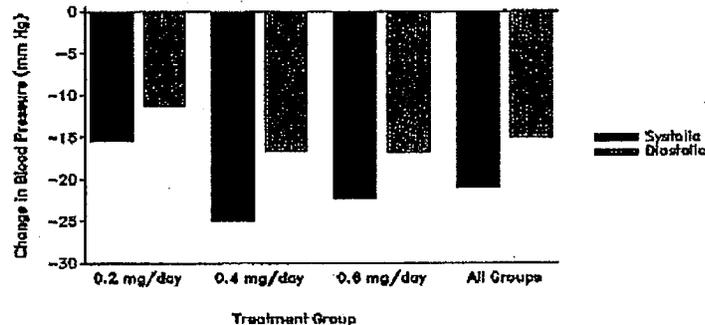


Figure 5: Change in blood pressure from baseline on day 26 of the study for all three dose groups.

Figure 6 presents a plot of the mean SBP and DBP plotted against the study day. Sympres was discontinued without tapering on study day 26 in all dose groups.

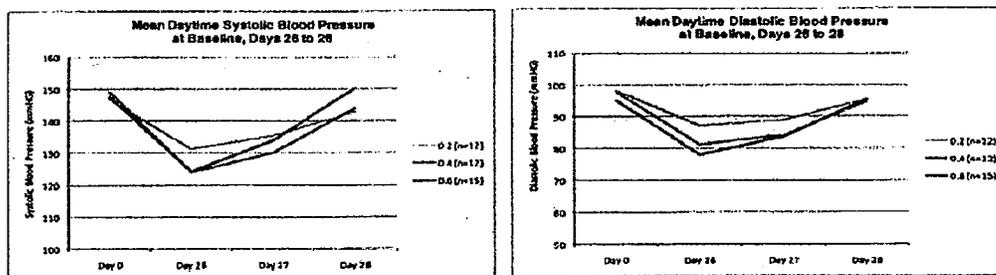


Figure 6: Plot of mean systolic and diastolic blood pressure at baseline and 48 hours after discontinuation of medication on day 26.

As seen in **Figure 6**, the mean SBP and DBP gradually return toward baseline within 48 hours of withdrawal of Sympres. The sponsor considers this as evidence for the absence of a rebound hypertension following the abrupt withdrawal of Sympres.

Reviewer's comment:

Historical data suggests that rebound hypertension following abrupt discontinuation of clonidine is observed between 24 to 72 hours post withdrawal of the drug. The mean SBP and DBP as shown in **Figure 6** do not appear to have returned to baseline values at 48 h post drug withdrawal.

Table 6 presents a comparison of mean change from baseline in SBP, DBP and HR by dose groups at 11 and 12 hours post dosing. As seen from the **Table 6**, the mean change from baseline in systolic and diastolic blood pressure is statistically significant at the end of the dosing interval in 0.4 and 0.6 mg/day treatment groups, indicating that the antihypertensive effect was maintained throughout the dosing interval. There was no significant change in heart rate.

Table 6: Mean difference from baseline in SBP, DBP and HR at 11 and 12 hours post dosing on day 26 (Ref: Tables 11.4.3.2 and 14.2.4, vol.13).

Time post dose	Treatment groups	SBP		DBP		HR	
		Mean difference	p-value	Mean difference	p-value	Mean difference	p-value
Hour 11	0.2 mg/day	10.82	0.0308	6.273	0.1037	2.545	0.4468
	0.4 mg/day	21.29	0.0023	10.64	0.0052	7.727	0.1052
	0.6 mg/day	19.57	0.0053	17.00	0.0003	18.14	0.0029
Hour 12	0.2 mg/day	6.5	0.0676	8.5	0.0120	-5.333	0.0762
	0.4 mg/day	16.9	0.0054	7.27	0.0103	0.636	0.8924
	0.6 mg/day	19.33	0.0044	9.8	0.0341	7.667	0.1392

Reviewer's comment:

As presented by the sponsor, the mean change from baseline in SBP and DBP at the 0.6 mg/day dose level, and the corresponding p-values were identical. This was an error. Mean difference in SBP, DBP, and HR, and associated p-values were recalculated and are presented in Table 6. The numbers in italics were different from the sponsor reported values. However, these changes do not alter the conclusions.

4.2.2.6.4 Pharmacokinetic / Pharmacodynamic analysis results

A sigmoid E_{max} model was used to describe the relationship between observed C_{max} , C_{min} and AUC_{τ} and the change from baseline in the AUEC for SBP and DBP. Table 7 presents the point estimates of the model parameters and a representative plot of the model fit is presented in Figure 7.

Table 7: Parameter estimates of the PK/PD model (Ref: Table 11.4.3.3, vol.13)

Parameter		Systolic BP	Diastolic BP
C_{max}	E_{max} (Δ BP)	24.3	16.7
	EC_{50} (pg/mL)	458	431
	EC_{90} (pg/mL)	646	561
	Shape Factor (γ)	6.39	8.29
C_{min}	E_{max} (Δ BP)	24.4	16.8
	EC_{50} (pg/mL)	359	341
	EC_{90} (pg/mL)	532	461
	Shape Factor (γ)	5.56	7.31
AUC_{τ}	E_{max} (Δ BP)	24.3	16.8
	EC_{50} (h*pg/mL)	4702	4401
	EC_{90} (pg/mL)	6692	5921
	Shape Factor (γ)	6.26	7.42

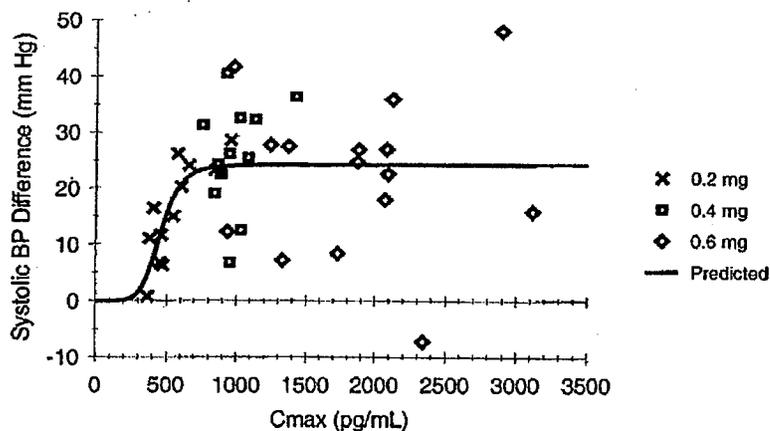


Figure 7: Plot of observed and predicted change from baseline SBP versus C_{max} . The solid line represents the model fit.

Based on the results of the exposure – response (PK/PD) analysis, the sponsor concludes that administration of 0.4 or 0.6 mg of Sympres ER will result in plasma clonidine concentrations above the estimated EC_{50} (C_{min} and C_{max}). Therefore these two doses are more effective than the 0.2 mg dose. In addition, based on the shape of the exposure-response relationship curve, doses over 0.4 mg/day are not expected to provide increased antihypertensive effect.

Reviewer’s comments:

Study CLON 201 does not evaluate a sufficiently wide dose range to allow determination of a meaningful exposure - response relationships. Instead, doses were selected, based on historical data, to provide plasma concentrations within the established therapeutic range of clonidine (200 to 2000 pg/mL). The exposure – response analysis therefore is irrelevant to the objectives of this study. Overall, the exposure – response analysis presented is unacceptable for the following reasons.

- The objectives of the analysis were not stated.
- The methods used and the process of model development were not described.
- The results presented were incomplete. Model parameter estimates were presented without any measure of precision.
- The final model was not evaluated for its predictive ability.

4.2.2.7 Conclusions

1. The pharmacokinetics of clonidine following administration of 0.2, 0.4 or 0.6 mg of Sympres are linear.
2. At steady state, the observed mean fluctuation ranged from 1.38 to 1.52, comparing well with that observed following application of the clonidine transdermal patch (Catapres TTS (mean±SD): 1.33 ± 0.16 , (FDA, 1985)).
3. The mean intra-individual variability ranged between 10 to 12 % for the 3 treatment groups, demonstrating consistent performance between individual units.
4. The inter - individual variability in clearance ranged from 18 to 42%.

5. A dose related antihypertensive effect was observed in SBP and DBP at the 0.2 and 0.4 mg/day level. No further increase in the antihypertensive effect was observed with the 0.6 mg/day dose. However, the observed decrease in BP was maintained throughout the dosing interval (12h) for the 0.4 and 0.6 mg/day dose groups.
6. Systolic and diastolic blood pressure was monitored for 48 hours after the abrupt withdrawal of Sympres for the occurrence of rebound hypertension. However, the duration of observation was insufficient. Therefore valid conclusions cannot be made. A longer duration of measurement (eg. 72 h post withdrawal of Sympres) would enable better assessment of the rebound effect.

Reference List

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