

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

***APPLICATION NUMBER:***

**022331Orig1s001**

***Trade Name:*** KAPVAY

***Generic or Proper Name:*** Clonidine hydrochloride

***Sponsor:*** Concordia Pharms Inc.

***Approval Date:*** September 28,2010

***Indication:*** KAPVAY™ is a centrally acting alpha2-adrenergic agonist indicated for the treatment of deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medication.

This extended-release formulation of clonidine hydrochloride is also approved for the treatment of hypertension under the trade name JENLOGA.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 22331Orig1s001

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022331/S-001/S-002

**SUPPLEMENT APPROVAL**

Shionogi Pharma, Inc.  
Attention: Allison Lowry, RAC  
Director, Regulatory Affairs  
Five Concourse Parkway, Suite 1800  
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 29, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kapvay (clonidine hydrochloride) extended-release tablets, 0.1 mg and 0.2 mg.

We acknowledge receipt of your amendments dated August 5, 2010, and September 7, 2010.

The August 5, 2010, submission constituted a complete response to our July 28, 2010, action letter.

These "Prior Approval" supplemental new drug applications provide for the use of Kapvay (clonidine hydrochloride) extended-release tablets for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy (S-001) or as adjunctive therapy to stimulant medications (S-002).

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at



<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on August 5, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “Final Printed Carton and Container Labels for approved NDA 022331/S-001/S-002.” Approval of this submission by FDA is not required before the labeling is used.

### **PROPRIETARY NAME**

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Kapvay, for this product

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 5 years of age because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

- The diagnostic criteria and assessment measures for determining efficacy for the treatment of ADHD in children less than 6 years old are not well defined.
- Pharmaceutical treatment in this age group is uncommon.
- Kapvay is a solid dose, extended-release formulation, available in 0.1 mg and 0.2 mg strengths, and its tablets cannot be subdivided. Since a liquid/rapid-melt form and additional strengths are not available, it is not expected that the product will be prescribed for potential ADHD patients less than 6 years old.

We are deferring submission of the additional pediatric studies for ages 6 to 17 for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected.

A longer-term randomized withdrawal maintenance study of efficacy and safety of clonidine hydrochloride extended-release tablets as monotherapy, or alternatively, as adjunctive therapy, in children and adolescents is required because ADHD is a chronic condition and it is very likely that most patients who respond in short term treatment will be extended for longer-term treatment.

Additionally, a juvenile animal study of clonidine in combination with a stimulant as a postmarketing requirement (as communicated in the minutes of our 3/9/09 meeting) is required.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1676-1                      Deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients ages 6 to 17: A longer-term randomized withdrawal maintenance study of efficacy and safety of clonidine hydrochloride extended-release tablets as monotherapy, or alternatively, as adjunctive therapy, in children and adolescents

Final Protocol Submission:    April 2011  
Study Initiation:                August 2011  
Final Report Submission:      December 2013

1676-2                      Juvenile animal study:  
In order to support safe use of clonidine in combination with stimulants in pediatric patients and to provide additional safety information for labeling, you must conduct a juvenile animal study of clonidine in combination with a stimulant as a postmarketing requirement (as communicated in the minutes of our 3/9/2009 meeting).

Final Protocol Submission:    10/31/2011  
Study Initiation:                01/30/2012  
Final Report Submission:      04/30/2013

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Hiren D. Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
09/28/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**OTHER ACTION LETTERS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022331/S-001/S-002

**COMPLETE RESPONSE**

Shionogi Pharma, Inc.  
Attention: Allison Lowry, RAC  
Director, Regulatory Affairs  
Five Concourse Parkway, Suite 1800  
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your Supplemental New Drug Applications (sNDA) dated September 29, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kapvay (clonidine hydrochloride) extended-release tablets, 0.1 mg and 0.2 mg.

We acknowledge receipt of your amendments dated:

November 3, 2009	January 28, 2010	May 14, 2010
November 5, 2009	February 15, 2010	May 27, 2010
December 8, 2009	March 16, 2010	June 2, 2010
December 10, 2009	March 18, 2010	June 21, 2010
December 18, 2009	March 22, 2010	April 7, 2010
January 7, 2010	March 24, 2010	July 9, 2010
January 8, 2010	April 20, 2010	July 16, 2010
January 18, 2010	April 27, 2010	

These "Prior Approval" supplemental new drug applications provide for the use of Kapvay (clonidine hydrochloride) for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy (S-001) or as adjunctive therapy to stimulant medications (S-002) for the treatment of ADHD.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**LABELING**

We have determined that an extended-release dosage modifier designation is appropriate for this application. Since your product has also been approved under NDA 022331 with the tradename

of Jenloga to treat hypertension, the dosage form modifier must be revised for this product as well. Therefore, please submit a Prior Approval Labeling Supplement to the reference NDA and include revised labeling that supports Jenloga (clonidine hydrochloride) extended-release tablets. Your revised labeling resubmission for Kapvay (clonidine hydrochloride) extended-release tablets should be submitted in parallel to the aforementioned Prior Approval Labeling Supplement for Jenloga.

### **Proprietary Name and Container Label**

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Kapvay, for this product. However, our approval of the proprietary name is tentative based upon the final date of approval for these supplements. If final approval of these applications extends beyond October 2010, the name will be reevaluated by DMEPA.

Additionally, please submit revised container labeling denoting the modifier of extended-release.

### **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Hiren D. Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Content of Labeling



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

/s/

THOMAS P LAUGHREN  
07/28/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KAPVAY safely and effectively. See full prescribing information for KAPVAY.

### KAPVAY (clonidine hydrochloride) extended-release tablets, oral Initial U.S. Approval: 1974

#### -----INDICATIONS AND USAGE-----

KAPVAY™ is a centrally acting alpha<sub>2</sub>-adrenergic agonist indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medications. (1)

The efficacy of KAPVAY is based on the results of two clinical trials in children and adolescents. (14) Maintenance efficacy has not been systematically evaluated, and patients who are continued on longer-term treatment require periodic reassessment. (1)

This extended-release formulation of clonidine hydrochloride is also approved for the treatment of hypertension under the trade name JENLOGA. (1)

#### -----DOSAGE AND ADMINISTRATION-----

Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime, as depicted below (2.1)

Total Daily Dose	Morning Dose	Bedtime Dose
0.1 mg/day		0.1 mg
0.2 mg/day	0.1 mg	0.1 mg
0.3 mg/day	0.1 mg	0.2 mg
0.4 mg/day	0.2 mg	0.2 mg

- Tablets should not be crushed, chewed or broken before swallowing. (2.1)
- Do not substitute for other clonidine products on a mg-per-mg basis, because of differing pharmacokinetic profiles. (2.1)
- When discontinuing, taper the dose in decrements of no more than 0.1 mg every 3 to 7 days. (2.4)

#### -----DOSAGE FORMS AND STRENGTHS-----

Extended-release tablets: 0.1 mg and 0.2 mg, not scored. (3)

#### -----CONTRAINDICATIONS-----

Clonidine hydrochloride tablets should not be used in patients with known hypersensitivity to clonidine. (4)

#### -----WARNINGS AND PRECAUTIONS-----

- Hypotension/bradycardia: Use KAPVAY with caution in patients at risk for hypotension, bradycardia, and heart block. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Advise patients to avoid becoming dehydrated or overheated. (5.1)
- Somnolence/Sedation: Has been observed with KAPVAY. Consider the potential for additive sedative effects with CNS depressant drugs. Caution

patients against operating heavy equipment or driving until they know how they respond to KAPVAY. (5.2)

- Abrupt Discontinuation: Patients should be instructed not to discontinue KAPVAY therapy without consulting their physician due to the potential risk of withdrawal effects. KAPVAY should be discontinued slowly in decrements of no more than 0.1 mg every 3 to 7 days. (5.3)
- Allergic Reactions: In patients who have developed localized contact sensitization or other allergic reaction to clonidine in a transdermal system, substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash, urticaria, or angioedema. (5.4)
- Use in patients with vascular disease, cardiac conduction disease, or chronic renal failure: Monitor carefully and uptitrate slowly. (5.5)
- Other clonidine containing products: Do not use KAPVAY concomitantly with other products containing clonidine, (e.g. Catapres®). (5.6)

#### -----ADVERSE REACTIONS-----

Common and drug related adverse reactions (incidence at least 5% and twice the rate of placebo) reported with the use of KAPVAY include (6.1):  
Somnolence, fatigue, upper respiratory tract infection (cough, rhinitis, sneezing), irritability, throat pain (sore throat), insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth, and ear pain.

**To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Pharma, Inc. at 1-800-849-9707 ext. 1454 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### -----DRUG INTERACTIONS-----

- Sedating Drugs: Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. (7.1)
- Tricyclic Antidepressants: May reduce the hypotensive effect of clonidine. (7.2)
- Drugs Known to Affect Sinus Node Function or AV Nodal Conduction: Caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers) due to a potential for additive effects such as bradycardia and AV block. (7.3)
- Use with other products containing clonidine: Do not use KAPVAY concomitantly with other products containing clonidine (e.g. Catapres®). (7.4)
- Antihypertensive drugs: Use caution when coadministered with KAPVAY. (7.5)

#### -----USE IN SPECIFIC POPULATIONS-----

- Since clonidine hydrochloride is excreted in human milk, caution should be exercised when KAPVAY is administered to a nursing woman. (8.3)
- KAPVAY has not been studied in children less than 6 years old. (8.4)
- Renal Insufficiency: The dosage of KAPVAY must be adjusted according to the degree of impairment, and patients should be carefully monitored. (8.6)

**See page XX for Patient Counseling Information**

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\*Sections or subsections omitted from the full prescribing information are not listed.

## **FULL PRESCRIBING INFORMATION**

### **1. INDICATIONS AND USAGE**

KAPVAY<sup>™</sup> (clonidine hydrochloride) extended-release is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications.

The efficacy of KAPVAY in the treatment of ADHD is based on two controlled trials (one monotherapy and one adjunctive to stimulant medication) in children and adolescents ages 6-17 who met DSM-IV criteria for ADHD hyperactive or combined hyperactive/inattentive subtypes [see Clinical Studies (14)]. In the adjunctive study, KAPVAY was administered to patients who had been on a stable regimen of either methylphenidate or amphetamine (or their derivatives) and who had not achieved an optimal response. The effectiveness of KAPVAY for longer-term use (more than 5 weeks) has not been systematically evaluated in controlled trials.

A diagnosis of ADHD implies the presence of hyperactive-impulsive and/or inattentive symptoms that cause impairment and were present before the age of 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

#### **Special Diagnostic Considerations**

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV<sup>®</sup> characteristics.

#### **Need for Comprehensive Treatment program**

KAPVAY is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. KAPVAY is not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational/vocational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe KAPVAY will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms and on the level of functional impairment.

NOTE: This extended-release formulation of clonidine hydrochloride is also approved for the treatment of hypertension in adults under the trade name JENLOGA.

### **2. DOSAGE AND ADMINISTRATION**

KAPVAY is an extended-release tablet formulation of clonidine hydrochloride. While it is dosed twice a day, the same as the immediate-release clonidine formulation, it is not to be used interchangeably with the immediate-release formulation.

## 2.1 General Dosing Information

KAPVAY is an extended-release tablet and, therefore, must be swallowed whole and never crushed, cut or chewed. KAPVAY may be taken with or without food.

Due to the lack of controlled clinical trial data and differing pharmacokinetic profiles, substitution of KAPVAY for other clonidine products on a mg-per-mg basis is not recommended.

## 2.2 Dose Selection

The dose of KAPVAY, administered either as monotherapy or as adjunctive therapy to a psychostimulant, should be individualized according to the therapeutic needs and response of the patient. Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime (see Table 1).

**Table 1 KAPVAY Dosing Guidance**

<b>Total Daily Dose</b>	<b>Morning Dose</b>	<b>Bedtime Dose</b>
0.1 mg/day		0.1 mg
0.2 mg/day	0.1 mg	0.1 mg
0.3 mg/day	0.1 mg	0.2 mg
0.4 mg/day	0.2 mg	0.2 mg

Doses of KAPVAY higher than 0.4 mg/day (0.2 mg twice daily) were not evaluated in clinical trials for ADHD and are not recommended.

When KAPVAY is being added-on to a psychostimulant, the dose of the psychostimulant can be adjusted depending on the patient's response to KAPVAY.

## 2.3 Maintenance Treatment

The effectiveness of KAPVAY for longer-term use (more than 5 weeks) has not been systematically evaluated in controlled trials. Therefore the physician electing to use KAPVAY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

## 2.4 Discontinuation

When discontinuing KAPVAY, the total daily dose should be tapered in decrements of no more than 0.1 mg every 3 to 7 days.

## 3. DOSAGE FORM AND STRENGTHS

KAPVAY tablets are available in two strengths, 0.1 mg and 0.2 mg as an extended-release formulation. Both the 0.1 mg and 0.2 mg tablets are white, non-scored, standard convex with debossing on one side. The 0.1 mg tablets are round and the 0.2 mg tablets are oval. KAPVAY tablets must be swallowed whole and never crushed, cut or chewed.

## 4. CONTRAINDICATIONS

KAPVAY should not be used in patients with known hypersensitivity to clonidine.

## **5. WARNINGS AND PRECAUTIONS**

### **5.1 Hypotension/Bradycardia**

Treatment with KAPVAY can cause dose related decreases in blood pressure and heart rate. In patients that completed 5 weeks of treatment in a controlled, fixed-dose monotherapy study in pediatric patients, during the treatment period the maximum placebo-subtracted mean change in systolic blood pressure was -4.0 mmHg on KAPVAY 0.2 mg/day and -8.8 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in diastolic blood pressure was -4.0 mmHg on KAPVAY 0.2 mg/day and -7.3 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in heart rate was -4.0 beats per minute on KAPVAY 0.2 mg/day and -7.7 beats per minute on KAPVAY 0.4 mg/day.

During the taper period of the fixed-dose monotherapy study the maximum placebo-subtracted mean change in systolic blood pressure was +3.4 mmHg on KAPVAY 0.2 mg/day and -5.6 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in diastolic blood pressure was +3.3 mmHg on KAPVAY 0.2 mg/day and -5.4 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in heart rate was -0.6 beats per minute on KAPVAY 0.2 mg/day and -3.0 beats per minute on KAPVAY 0.4 mg/day.

Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Use KAPVAY with caution in patients with a history of hypotension, heart block, bradycardia, or cardiovascular disease, because it can decrease blood pressure and heart rate. Use caution in treating patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Use KAPVAY with caution in patients treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope. Advise patients to avoid becoming dehydrated or overheated.

### **5.2 Sedation and Somnolence**

Somnolence and sedation were commonly reported adverse reactions in clinical studies. In patients that completed 5 weeks of therapy in a controlled fixed dose pediatric monotherapy study, 31% of patients treated with 0.4 mg/day and 38% treated with 0.2 mg/day vs 7% of placebo treated patients reported somnolence as an adverse event. In patients that completed 5 weeks of therapy in a controlled flexible dose pediatric adjunctive to stimulants study, 19% of patients treated with KAPVAY+stimulant vs 8% treated with placebo+stimulant reported somnolence. Before using KAPVAY with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), consider the potential for additive sedative effects. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with KAPVAY. Advise patients to avoid use with alcohol.

### **5.3 Abrupt Discontinuation**

No studies evaluating abrupt discontinuation of KAPVAY in children with ADHD have been conducted. In children and adolescents with ADHD, physicians should gradually reduce the dose of KAPVAY in decrements of no more than 0.1 mg every 3 to 7 days. Patients should be instructed not to discontinue KAPVAY therapy without consulting their physician due to the potential risk of withdrawal effects.

In adults with hypertension, sudden cessation of clonidine hydrochloride extended-release formulation treatment in the 0.2 to 0.6 mg/day range resulted in reports of headache, tachycardia, nausea, flushing, warm feeling, brief lightheadedness, tightness in chest, and anxiety.

In adults with hypertension, sudden cessation of treatment with immediate-release clonidine has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor

accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

## 5.4 Allergic Reactions

In patients who have developed localized contact sensitization to clonidine transdermal system, continuation of clonidine transdermal system or substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash.

In patients who develop an allergic reaction from clonidine transdermal system, substitution of oral clonidine hydrochloride may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

## 5.5 Patients with Vascular Disease, Cardiac Conduction Disease, or Renal Failure

Clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

## 5.6 Other Clonidine-Containing Products

Clonidine, the active ingredient in KAPVAY, is also approved as an antihypertensive. Do not use KAPVAY in patients concomitantly taking other clonidine-containing products, (e.g. Catapres®).

# 6. ADVERSE REACTIONS

## 6.1 Clinical Trial Experience

Two KAPVAY ADHD clinical studies evaluated 256 patients who received active therapy, in one of the two placebo-controlled studies (Studies 1 and 2) with primary efficacy end-points at 5-weeks.

### Study 1: Fixed-dose KAPVAY Monotherapy

Study 1 was a multi-center, randomized, double-blind, placebo-controlled study with primary efficacy endpoint at 5 weeks, of two fixed doses (0.2 mg/day or 0.4 mg/day) of KAPVAY in children and adolescents (6 to 17 years of age) who met DSM-IV criteria for ADHD hyperactive or combined inattentive/hyperactive subtypes.

Commonly observed adverse reactions (incidence of  $\geq 2\%$  in either active treatment group and greater than the rate on placebo) during the treatment period are listed in Table 2.

**Table 2 Common Adverse Reactions in the Fixed-Dose Monotherapy Trial- Treatment period (Study 1)**

Preferred Term	Percentage of Patients Reporting Event		
	KAPVAY 0.4 mg/day N=78	KAPVAY 0.2 mg/day N=76	Placebo (N=76)
Somnolence <sup>1</sup>	31%	38%	5%
Headache	19%	29%	18%
Upper Abdominal Pain	13%	20%	17%
Fatigue <sup>2</sup>	13%	16%	1%
Upper Respiratory Tract Infection	6%	11%	4%
Irritability	6%	9%	3%



**Table 2 Common Adverse Reactions in the Fixed-Dose Monotherapy Trial- Treatment period (Study 1)**

Throat Pain	6%	8%	3%
Nausea	8%	5%	4%
Nightmare	9%	3%	0
Dizziness	3%	7%	5%
Insomnia	6%	4%	1%
Emotional Disorder	5%	4%	1%
Constipation	6%	1%	0
Dry Mouth	5%	0	1%
Nasal Congestion	5%	3%	1%
Body Temperature Increased	1%	5%	3%
Gastrointestinal Viral	0%	7%	4%
Diarrhea	1%	4%	3%
Ear Pain	0	5%	1%
Nasopharyngitis	3%	3%	1%
Abnormal Sleep-Related Event	1%	3%	0
Aggression	1%	3%	1%
Asthma	1%	3%	1%
Bradycardia	4%	0	0
Enuresis	4%	0	0
Influenza like Illness	3%	1%	1%
Tearfulness	3%	1%	0
Thirst	3%	1%	0
Tremor	3%	1%	0
Epistaxis	0	3%	0
Lower Respiratory Tract Infection	0	3%	1%
Pollakiuria	0	3%	0
Sleep Terror	0	3%	0

1. Somnolence includes the terms “somnolence” and “sedation”.
2. Fatigue includes the terms “fatigue” and “lethargy”.

Commonly observed adverse reactions (incidence of  $\geq 2\%$  in either active treatment group and greater than the rate on placebo) during the taper period are listed in Table 3.

**Table 3 Common Adverse Reactions in the Fixed-Dose Monotherapy Trial- Taper period\* (Study 1)**

Preferred Term	Percentage of Patients Reporting Event		
	KAPVAY 0.4 mg/day N=78	KAPVAY 0.2 mg/day N=76	Placebo (N=76)
Abdominal Pain Upper	6%	0	3%
Headache	2%	5%	3%
Gastrointestinal Viral	5%	0	0
Somnolence	3%	2%	0
Heart Rate Increased	3%	0	0
Otitis Media Acute	0	3%	0

\*Taper Period: 0.2 mg dose, week 8; 0.4 mg dose, weeks 6-8; Placebo dose, weeks 6-8

### **Study 2: Flexible-dose KAPVAY as Adjunctive Therapy to Psychostimulants**

Study 2 was a multi-center, randomized, double-blind, placebo-controlled study, with primary efficacy endpoint at 5 weeks, of a flexible dose of KAPVAY as adjunctive therapy to a psychostimulant in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD hyperactive or combined

inattentive/hyperactive subtypes. KAPVAY was initiated at 0.1 mg/day and titrated up to 0.4 mg/day over a 3-week period. Most KAPVAY treated patients (75.5%) were escalated to the maximum dose of 0.4 mg/day.

Commonly observed adverse reactions (incidence of  $\geq 2\%$  in the treatment group and greater than the rate on placebo) during the treatment period are listed in Table 4.

**Table 4 Common Adverse Reactions in the Flexible-Dose Adjunctive to Stimulant Therapy Trial- Treatment Period (Study 2)**

Preferred Term	Percentage of Patients Reporting Event	
	KAPVAY+STM (N=102)	PBO+STM (N=96)
Somnolence <sup>1</sup>	19%	8%
Fatigue <sup>2</sup>	16%	4%
Abdominal Pain Upper	12%	7%
Nasal Congestion	6%	5%
Throat Pain	6%	3%
Decreased Appetite	5%	4%
Body Temperature Increased	4%	2%
Dizziness	4%	2%
Insomnia	4%	2%
Epistaxis	3%	0
Rhinorrhea	3%	0
Abdominal Pain	2%	1%
Anxiety	2%	0
Pain in Extremity	2%	0

1. Somnolence includes the terms: "somnolence" and "sedation".
2. Fatigue includes the terms "fatigue" and "lethargy".

Commonly observed adverse reactions (incidence of  $\geq 2\%$  in the treatment group and greater than the rate on placebo) during the taper period are listed in Table 5.

**Table 5 Common Adverse Reactions in the Flexible-Dose Adjunctive to Stimulant Therapy Trial- Taper Period\* (Study 2)**

Preferred Term	Percentage of Patients Reporting Event	
	KAPVAY+STM (N=102)	PBO+STM (N=96)
Nasal Congestion	4%	2%
Headache	3%	1%
Irritability	3%	2%
Throat Pain	3%	1%
Gastroenteritis Viral	2%	0
Rash	2%	0

\*Taper Period: weeks 6-8

Most common adverse reactions, defined as events that were reported in at least 5% of drug-treated patients and at least twice the rate as in placebo patients, during the treatment period were somnolence, fatigue, upper respiratory tract infection, irritability, throat pain, insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth, and ear pain. The most common adverse reactions that were reported during the taper phase were upper abdominal pain and gastrointestinal virus.

## **Adverse Reactions Leading to Discontinuation**

Thirteen percent (13%) of patients receiving KAPVAY discontinued from the pediatric monotherapy study due to adverse events, compared to 1% in the placebo group. The most common adverse reactions leading to discontinuation of KAPVAY monotherapy treated patients were from somnolence/sedation (5%) and fatigue (4%). Less common adverse reactions leading to discontinuation (occurring in approximately 1% of patients) included: formication, vomiting, prolonged QT, increased heart rate, and rash. In the pediatric adjunctive treatment to stimulants study, one patient discontinued from KAPVAY + stimulant group because of bradyphrenia.

## **Effects on Laboratory Tests, Vital Signs, and Electrocardiograms**

KAPVAY treatment was not associated with any clinically important effects on any laboratory parameters in either of the placebo-controlled studies.

Mean decreases in blood pressure and heart rate were seen [see Warnings and Precautions (5.1)].

There were no changes on ECGs to suggest a drug-related effect.

## **7. DRUG INTERACTIONS**

No drug interaction studies have been conducted with KAPVAY in children. The following have been reported with other oral immediate release formulations of clonidine.

### **7.1 Interactions with CNS-depressant Drugs**

Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs.

### **7.2 Interactions with Tricyclic Antidepressants**

If a patient is receiving clonidine hydrochloride and also taking tricyclic antidepressants the hypotensive effects of clonidine may be reduced.

### **7.3 Interactions with Drugs Known to Affect Sinus Node Function or AV Nodal Conduction**

Due to a potential for additive effects such as bradycardia and AV block, caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers).

### **7.4 Use with other products containing clonidine**

Do not use KAPVAY concomitantly with other products containing clonidine (e.g. Catapres®).

### **7.5 Antihypertensive Drugs**

Use caution when KAPVAY is administered concomitantly with antihypertensive drugs, due to the potential for additive pharmacodynamic effects (e.g., hypotension, syncope) [see *Warnings and Precautions* (5.2)].

## **8. USE IN SPECIFIC POPULATIONS**

## **8.1 Pregnancy**

**Pregnancy Category C:** Oral administration of clonidine hydrochloride to pregnant rabbits during the period of embryo/fetal organogenesis at doses of up to 80 mcg/kg/day (approximately 3 times the oral maximum recommended daily dose [MRHD] of 0.4 mg/day on a mg/m<sup>2</sup> basis) produced no evidence of teratogenic or embryotoxic potential. In pregnant rats, however, doses as low as 15 mcg/kg/day (1/3 the MRHD on a mg/m<sup>2</sup> basis) were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating and throughout gestation. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the MRHD) when treatment of the dams was restricted to gestation days 6-15. Increases in resorptions were observed in both rats and mice at 500 mcg/kg/day (10 and 5 times the MRHD in rats and mice, respectively) or higher when the animals were treated on gestation days 1-14; 500 mcg/kg/day was the lowest dose employed in this study. No adequate and well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless clearly needed.

## **8.3 Nursing Mothers**

Since clonidine hydrochloride is excreted in human milk, caution should be exercised when KAPVAY is administered to a nursing woman.

## **8.4 Pediatric Use**

A study was conducted in which young rats were treated orally with clonidine hydrochloride from day 21 of age to adulthood at doses of up to 300 mcg/kg/day, which is approximately 3 times the maximum recommended human dose (MRHD) of 0.4 mg/day on a mg/m<sup>2</sup> basis. A slight delay in onset of preputial separation was seen in males treated with the highest dose (with a no-effect dose of 100 mcg/kg/day, which is approximately equal to the MRHD), but there were no drug effects on fertility or on other measures of sexual or neurobehavioral development.

KAPVAY has not been studied in children with ADHD less than 6 years old.

## **8.6 Patients with Renal Impairment**

The impact of renal impairment on the pharmacokinetics of clonidine in children has not been assessed. The initial dosage of KAPVAY should be based on degree of impairment. Monitor patients carefully for hypotension and bradycardia, and titrate to higher doses cautiously. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental KAPVAY following dialysis.

## **8.7 Adult Use in ADHD**

KAPVAY has not been studied in adult patients with ADHD.

## **9.0 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

KAPVAY is not a controlled substance and has no known potential for abuse or dependence.

## 10. OVERDOSAGE

### Symptoms

**Clonidine overdose:** hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in children than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure.

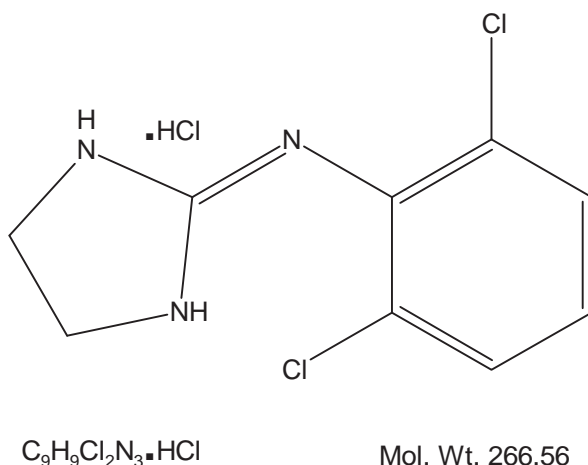
### Treatment

Consult with a Certified Poison Control Center for up-to-date guidance and advice.

## 11. DESCRIPTION

KAPVAY (clonidine hydrochloride) extended-release is a centrally acting  $\alpha_2$ -adrenergic agonist available as 0.1 mg or 0.2 mg extended-release tablets for oral administration. Each 0.1 mg and 0.2 mg tablet is equivalent to 0.087 mg and 0.174 mg, respectively, of the free base.

The inactive ingredients are sodium lauryl sulfate, lactose monohydrate, hypromellose type 2208, partially pregelatinized starch, colloidal silicon dioxide, and magnesium stearate. The formulation is designed to delay the absorption of active drug in order to decrease peak to trough plasma concentration differences. Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The following is the structural formula:



Clonidine hydrochloride is an odorless, bitter, white, crystalline substance soluble in water and alcohol.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Clonidine stimulates  $\alpha_2$ -adrenergic receptors in the brain. Clonidine is not a central nervous system stimulant. The mechanism of action of clonidine in ADHD is not known.

## 12.2 Pharmacodynamics

Clonidine is a known antihypertensive agent. By stimulating  $\alpha_2$ -adrenergic receptors in the brain stem, clonidine reduces sympathetic outflow from the central nervous system and decreases peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

## 12.3 Pharmacokinetics

### Single-dose Pharmacokinetics in Adults

Immediate-release clonidine hydrochloride and KAPVAY have different pharmacokinetic characteristics; dose substitution on a milligram for milligram basis will result in differences in exposure. A comparison across studies suggests that the C<sub>max</sub> is 50% lower for KAPVAY compared to immediate-release clonidine hydrochloride.

Following oral administration of an immediate release formulation, plasma clonidine concentration peaks in approximately 3 to 5 hours and the plasma half-life ranges from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Following oral administration about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver. Although studies of the effect of renal impairment and studies of clonidine excretion have not been performed with KAPVAY, results are likely to be similar to those of the immediate release formulation.

The pharmacokinetic profile of KAPVAY administration was evaluated in an open-label, three-period, randomized, crossover study of 15 healthy adult subjects who received three single dose regimens of clonidine: 0.1 mg of KAPVAY under fasted conditions, 0.1 mg of KAPVAY following a high fat meal, and 0.1 mg of clonidine immediate-release (Catapres®) under fasted conditions. Treatments were separated by one-week washout periods.

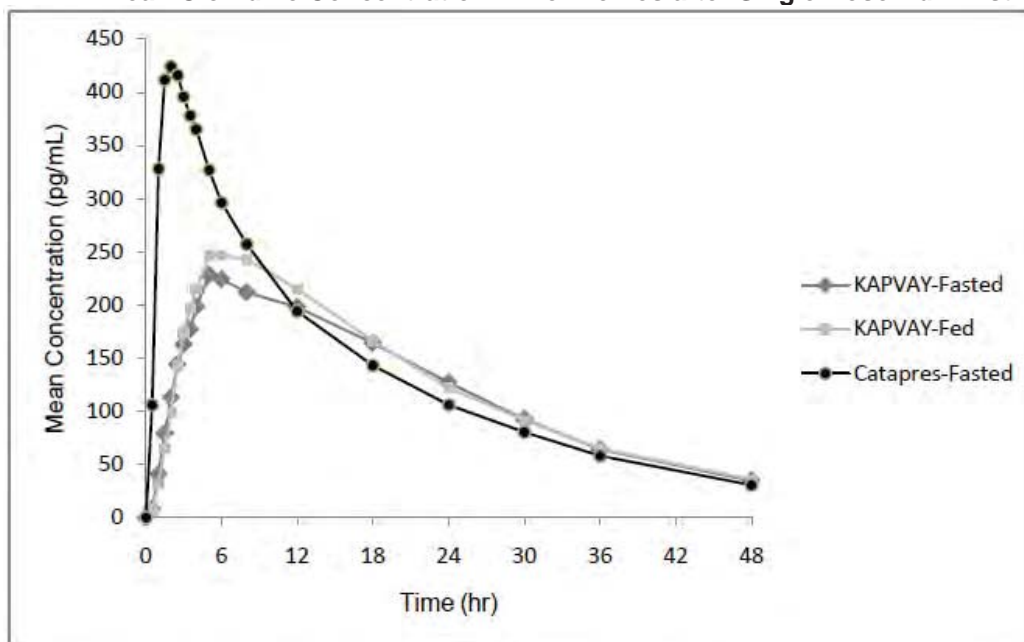
Mean concentration-time data from the 3 treatments are shown in Table 6 and Figure 1. After administration of KAPVAY, maximum clonidine concentrations were approximately 50% of the Catapres maximum concentrations and occurred approximately 5 hours later relative to Catapres. Similar elimination half-lives were observed and total systemic bioavailability following KAPVAY was approximately 89% of that following Catapres.

Food had no effect on plasma concentrations, bioavailability, or elimination half-life.

**Table 6 Pharmacokinetic Parameters of Clonidine in Healthy Adult Volunteers**

Parameter	CATAPRES-Fasted n=15		KAPVAY-Fed n=15		KAPVAY-Fasted n=14	
	Mean	SD	Mean	SD	MEAN	SD
C <sub>max</sub> (pg/mL)	443	59.6	235	34.7	258	33.3
AUC <sub>inf</sub> (hr*pg/mL)	7313	1812	6505	1728	6729	1650
hT <sub>max</sub> (hr)	2.07	0.5	6.80	3.61	6.50	1.23
T <sub>1/2</sub> (hr)	12.57	3.11	12.67	3.76	12.65	3.56

**Figure 1 Mean Clonidine Concentration-Time Profiles after Single Dose Administration**



### **Multiple-dose Pharmacokinetics in Children and Adolescents**

Plasma clonidine concentrations in children and adolescents (0.1 mg bid and 0.2 mg bid) with ADHD are greater than those of adults with hypertension with children and adolescents receiving higher doses on a mg/kg basis. Body weight normalized clearance (CL/F) in children and adolescents was higher than CL/F observed in adults with hypertension. Clonidine concentrations in plasma increased with increases in dose over the dose range of 0.2 to 0.4 mg/day. Clonidine CL/F was independent of dose administered over the 0.2 to 0.4 mg/day dose range. Clonidine CL/F appeared to decrease slightly with increases in age over the range of 6 to 17 years, and females had a 23% lower CL/F than males. The incidence of “sedation-like” AEs (somnolence and fatigue) appeared to be independent of clonidine dose or concentration within the studied dose range in the titration study. Results from the add-on study showed that clonidine CL/F was 11% higher in patients who were receiving methylphenidate and 44% lower in those receiving amphetamine compared to subjects not on adjunctive therapy.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility**

Clonidine HCl was not carcinogenic when administered in the diet of rats (for up to 132 weeks) or mice (for up to 78 weeks) at doses of up to 1620 (male rats), 2040 (female rats), or 2500 (mice) mcg/kg/day. These doses are approximately 20, 25, and 15 times, respectively, the maximum recommended human dose (MRHD) of 0.4 mg/day on a mg/m<sup>2</sup> basis.

There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Fertility of male or female rats was unaffected by clonidine HCl doses as high as 150 mcg/kg/day (approximately 3 times the MRDHD on a mg/m<sup>2</sup> basis). In a separate experiment, fertility of female rats appeared to be adversely affected at dose levels of 500 and 2000 mcg/kg/day (10 and 40 times the MRHD on a mg/m<sup>2</sup> basis).



### **13.2 Ocular Toxicity**

In several studies with oral clonidine hydrochloride, a dose-dependent increase in the incidence and severity of spontaneous retinal degeneration was seen in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys showed a concentration of clonidine in the choroid. In combination with amitriptyline, clonidine hydrochloride administration led to the development of corneal lesions in rats within 5 days.

In view of the retinal degeneration seen in rats, eye examinations were performed during clinical trials in 908 adult patients before, and periodically after, the start of clonidine therapy for hypertension. In 353 of these 908 patients, the eye examinations were carried out over periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmological findings were recorded and, according to specialized tests such as electroretinography and macular dazzle, retinal function was unchanged.

## **14. CLINICAL STUDIES**

The efficacy of KAPVAY in the treatment of ADHD was established in 2 (one monotherapy and one adjunctive therapy) placebo-controlled trials in pediatric patients aged 6 to 17, who met DSM-IV criteria of ADHD hyperactive or combined hyperactive/inattentive subtypes. Signs and symptoms of ADHD were evaluated using the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS-IV) total score including hyperactive/impulsivity and inattentive subscales.

Study 1 was an 8-week randomized, double-blind, placebo-controlled, fixed dose study of children and adolescents aged 6 to 17 (N=236) with a 5-week primary efficacy endpoint. Patients were randomly assigned to one of the following three treatment groups: KAPVAY (CLON) 0.2 mg/day (N=78), KAPVAY 0.4 mg/day (N=80), or placebo (N=78). Dosing for the KAPVAY groups started at 0.1 mg/day and was titrated in increments of 0.1 mg/week to their respective dose (as divided doses). Patients were maintained at their dose for a minimum of 2 weeks before being gradually tapered down to 0.1 mg/day at the last week of treatment. At both doses, improvements in ADHD symptoms were statistically significantly superior in KAPVAY-treated patients compared with placebo-treated patients at the end of 5 weeks as measured by the ADHDRS-IV total score.

Study 2 was an 8-week randomized, double-blind, placebo-controlled, flexible dose study in children and adolescents aged 6 to 17 (N=198) with a 5-week primary efficacy end point. Patients had been treated with a psychostimulant (methylphenidate or amphetamine) for four weeks with inadequate response. Patients were randomly assigned to one of two treatment groups: KAPVAY adjunct to a psychostimulant (N=102) or psychostimulant alone (N=96). The KAPVAY dose was initiated at 0.1 mg/day and doses were titrated in increments of 0.1 mg/week up to 0.4 mg/day, as divided doses, over a 3-week period based on tolerability and clinical response. The dose was maintained for a minimum of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. ADHD symptoms were statistically significantly improved in KAPVAY plus stimulant group compared with the stimulant alone group at the end of 5 weeks as measured by the ADHDRS-IV total score.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

KAPVAY extended-release tablets are white, non-scored, standard convex with debossing ("651" for 0.1 mg and "652" for 0.2 mg) on one side.

The 0.1 mg are round tablets supplied in bottles containing 60 (NDC 59630-658-60) or 180 tablets (NDC 59630-658-18).

The 0.2 mg are oval tablets supplied in bottles containing 60 (NDC 59630-659-60) or 180 tablets (NDC 59630-659-18).



Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].  
Dispense in a tight, light-resistant container.

## **17 PATIENT COUNSELING INFORMATION**

*See FDA-approved Patient Labeling*

### **17.1 General Information**

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with KAPVAY and should counsel them in its appropriate use. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Patient Information and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Patient Information and to obtain answers to any questions they may have. The complete text of the Patient Information is attached to the package insert.

### **17.2 Abrupt Discontinuation**

Patients should be advised not to discontinue KAPVAY abruptly. In order to minimize potential withdrawal effects (see Warnings and Precautions), when discontinuing KAPVAY therapy, patients should be instructed to decrease their total daily dose of KAPVAY in decrements of no more than 0.1 mg every 3 to 7 days.

### **17.3 Allergic Reactions**

In patients who have developed an allergic reaction from clonidine transdermal system, substitution of oral clonidine hydrochloride may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

### **17.4 Dosing**

If the total daily dose of KAPVAY does not allow equal doses to be given in the morning and at bedtime (e.g., if the total daily dose is 0.3 mg/day), the higher of the two doses should be taken at bedtime (e.g., in a patient on 0.3 mg/day, a 0.1 mg dose should be taken in the morning and a 0.2 mg dose should be taken at bedtime). KAPVAY must be swallowed whole and never crushed, cut, or chewed.

### **17.5 Pregnancy**

Patients should be instructed to consult a physician if they are nursing, pregnant, or thinking of becoming pregnant while taking KAPVAY.

### **17.6 Food**

Patients may take KAPVAY with or without food.

### **17.7 Missed Dose**

If patients miss a dose of KAPVAY, they should skip the dose and take the next dose as scheduled. Do not take more than the prescribed total daily amount of KAPVAY in any 24-hour period.

### **17.8 Impairment in Ability to Operate Machinery or Vehicles**

No evaluation of the effects of KAPVAY on the ability to drive or operate machinery was performed during the development program. However, given the observed incidence of somnolence with KAPVAY, patients should be instructed to use caution when driving a car or operating hazardous machinery until they know how they will respond to treatment with KAPVAY.

## Patient Information

### **KAPVAY™ (KAP-vay) (clonidine hydrochloride) Extended-Release Tablets**

Read the Patient Information that comes with KAPVAY before you start taking it and each time you get a refill. There may be new information. This Patient Information leaflet does not take the place of talking to your doctor about your medical condition or treatment.

#### **What is KAPVAY?**

KAPVAY is a prescription medicine used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Your doctor may prescribe KAPVAY alone or together with certain other ADHD medicines.

- KAPVAY is not a central nervous system (CNS) stimulant.
- KAPVAY should be used as part of a total treatment program for ADHD that may include counseling or other therapies.

#### **Who should not take KAPVAY?**

- Do not take KAPVAY if you are allergic to clonidine in KAPVAY. See the end of this leaflet for a complete list of ingredients in KAPVAY.

#### **What should I tell my doctor before taking KAPVAY?**

Before you take KAPVAY, tell your doctor if you:

- have kidney problems
- have low or high blood pressure
- have a history of passing out (syncope)
- have heart problems, including history of heart attack
- have had a stroke or have stroke symptoms
- had a skin reaction (such as a rash) after taking clonidine in a transdermal form (skin patch)
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if KAPVAY will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. KAPVAY can pass into your breast milk. Talk to your doctor about the best way to feed your baby if you take KAPVAY.

Tell your doctor about all of the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

KAPVAY and certain other medicines may affect each other causing serious side effects. Sometimes the doses of other medicines may need to be changed while taking KAPVAY.

#### **Especially tell your doctor if you take:**

- anti-depression medicines
- heart or blood pressure medicine
- other medicines that contain clonidine
- a medicine that makes you sleepy (sedation)

Ask your doctor or pharmacist for a list of these medicines, if you are not sure if your medicine is listed above.

Know the medicines that you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

### How should I take KAPVAY?

- Take KAPVAY exactly as your doctor tells you to take it.
- Your doctor will tell you how many KAPVAY tablets to take and when to take them. Your doctor may change your dose of KAPVAY. Do not change your dose of KAPVAY without talking to your doctor.
- Do not stop taking KAPVAY without talking to your doctor.
- KAPVAY can be taken with or without food
- KAPVAY should be taken 2 times a day (in the morning and at bedtime).
- If you miss a dose of KAPVAY, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time.
- Take KAPVAY tablets whole. Do not chew, crush or break KAPVAY tablets. Tell your doctor if you cannot swallow KAPVAY tablets whole. You may need a different medicine.
- If you take too much KAPVAY, call your Poison Control Center or go to the nearest hospital emergency room right away.

### What should I avoid while taking KAPVAY?

- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking KAPVAY until you talk with your doctor. KAPVAY taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive, operate heavy machinery or do other dangerous activities until you know how KAPVAY will affect you.
- Avoid becoming dehydrated or overheated.

### What are possible side effects of KAPVAY?

**KAPVAY may cause serious side effects, including:**

- **Low blood pressure and low heart rate.** Your doctor should check your heart rate and blood pressure before starting treatment and regularly during treatment with KAPVAY.
- Sleepiness.
- Withdrawal symptoms. Suddenly stopping KAPVAY may cause withdrawal symptoms including: increased blood pressure, headache, increased heart rate, lightheadedness, tightness in your chest and nervousness.

The most common side effects of KAPVAY include:

- sleepiness
- tiredness
- upper respiratory tract infection, symptoms may include:
  - cough
  - runny nose
  - sneezing
- irritability
- sore throat
- trouble sleeping (insomnia)
- nightmares
- change in mood
- constipation

- stuffy nose
- increased body temperature
- dry mouth
- ear pain

Tell your doctor if you have any side effects that bother you or that does not go away.

These are not all of the possible side effects of KAPVAY. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store KAPVAY?**

- Store KAPVAY between 68°-77°F (20°-25°C).
- Keep KAPVAY in a tightly closed container and keep KAPVAY out of the light.

**Keep KAPVAY and all medicines out of the reach of children.**

#### **General information about the safe and effective use of KAPVAY**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KAPVAY for a condition for which it was not prescribed. Do not give KAPVAY to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about KAPVAY. If you would like more information, talk with your doctor. You can also ask your doctor or pharmacist for information about KAPVAY that is written for healthcare professionals.

For more information about KAPVAY, go to [www.KAPVAY.com](http://www.KAPVAY.com) or call 1-800-849-9707 ext. 1454.

#### **What are the ingredients in KAPVAY?**

- Active Ingredient: clonidine hydrochloride
- Inactive Ingredients: sodium lauryl sulfate, lactose monohydrate, hypromellose type 2208, partially pregelatinized starch, colloidal silicon dioxide, and magnesium stearate

Issued: xx/2010

Distributed by:  
Shionogi Pharma, Inc.  
Atlanta, GA 30328

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**SUMMARY REVIEW**

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:** 24 September 2010

**FROM:** Mitchell V. Mathis, M.D.  
Deputy Director  
Division of Psychiatry Products, HFD-130

**TO:** File NDA 022331 S-1 S-2

**SUBJECT:** Approval recommendation for Kapvay [clonidine hydrochloride] extended-release tablets for the treatment of ADHD in children and adolescents (ages 6-17) both as monotherapy and as adjunctive therapy to stimulants

**UPDATE TO FILE: COMPLETE RESPONSE**

Shionogi Pharma had originally submitted adequate safety and efficacy data to support the approval of Kapvay for use as monotherapy and as adjunctive (to stimulants) therapy in children and adolescents with ADHD (see file, this NDA). The Division reviewed the application and issued a Complete Response Letter to the sponsor secondary to required labeling negotiation, which included an FDA-required change in the established name of the product.

Kapvay is an extended-release (ER) formulation of clonidine hydrochloride, yet it is to be dosed twice daily, the same as the already-marketed immediate release (IR) formulation of clonidine hydrochloride. However, the pharmacokinetic properties of Kapvay are potentially clinically significantly different from the IR formulation (maximum concentration of Kapvay is about half of the IR formulation). Therefore, the Division asked for labeling changes to reflect the extended-release properties of the drug in the established name.

The sponsor submitted labeling with the Division's recommended changes and I have reviewed the labeling along with the clinical team. The most recently negotiated label indicates that the formulation is extended-release in the established name, and throughout both Highlights and Full Prescribing Information. We have also included a figure in the Pharmacokinetics section of labeling depicting mean clonidine concentration-time profile differences between Kapvay and immediate release clonidine. In addition, the carton-container label reflects the established name of clonidine hydrochloride extended-release tablets and also has a statement that the drug should not be substituted for other formulations of clonidine.

These changes are adequate to ensure the safe use of the drug with regard to the differences between this formulation and those formulations already marketed, and my recommendation to the Director is that this product with the updated labeling and carton-container labels be approved.

The Division of Cardio-Renal Drug Products (DCRDP) is responsible for the primary NDA for clonidine hydrochloride extended-release tablets (tradenname: Jenloga) for the treatment of hypertension. DCRDP is in agreement with our division regarding the need to differentiate the IR and ER formulations of clonidine hydrochloride in labeling and on carton-container labels. DCRDP has worked with our review team to implement similar changes to their product labeling and will soon issue a labeling supplement approving the extended-release modifier as part of the established name. This action in DCRDP should precede our approval because our application is a supplement to their NDA.



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MITCHELL V Mathis  
09/24/2010

**MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** July 28, 2010

**FROM:** Thomas P. Laughren, M.D.  
Director, Division of Psychiatry Products  
HFD-130

**SUBJECT:** Recommendation for complete response action for clonidine hydrochloride extended release tablets for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents (ages 6-17).

**TO:** File NDA 22-331/S-001/S-002

[Note: This overview should be filed with the 9-30-09 original submission of these supplemental NDAs.]

## **1.0 BACKGROUND**

Clonidine is a centrally acting alpha-2 adrenergic agonist that has been available in an immediate release formulation for the treatment of hypertension since 1973. This drug has been used off-label for decades as an adjunctive treatment for ADHD. The sponsor of these supplements has developed a modified release formulation of clonidine and received an approval for this formulation (Jenloga) for the treatment of hypertension on 9-29-09. Although this is a modified release formulation, it is still dosed twice daily, and therefore, the sponsor had not been permitted to name this product as an extended release formulation. These supplements provide data in support of the efficacy and safety of clonidine both as monotherapy and as adjunctive therapy in the treatment of ADHD in children and adolescents. The studies in support of this application were conducted under IND 76144.

The primary clinical reviewer for this application was Dr. Maju Mathews and the primary statistical reviewer was Dr. Eiji Ishida. A secondary review of this application was conducted by Dr. Jing Zhang.

## **2.0 CHEMISTRY**

There were no CMC issues that required review as part of this supplement other than consideration for categorical exclusion. All labeling issues have been resolved and the CMC group recommended approval, including the issue of the established name. For the Jenloga application, the label refers to this as “clonidine hydrochloride tablets”. We have had a number of discussions regarding the desirability of giving this product a different name since it does have a different pk profile than the immediate release clonidine hydrochloride. It turns out that

USP does not in fact object to giving a product such as this the “extended release” name, even though the dosing frequency is not changed. Consequently, we will name this “clonidine hydrochloride extended release tablet”. The sponsor will need to supplement the Jenloga application with a name change for that product as well.

### **3.0 PHARMACOLOGY**

The only pharm/tox issue that required review as part of this supplement other than the new labeling format was a juvenile rat study. The findings of this study will be described in labeling, and the sponsor has agreed to conduct an adjunctive juvenile rat study post-approval. All labeling issues have been resolved and the pharm/tox group also recommended approval.

### **4.0 BIOPHARMACEUTICS**

The main differences in pk for immediate release clonidine and the new modified release products are a 50% lower C<sub>max</sub> for the new formulation and a longer T<sub>max</sub> (6 hrs vs 2 hrs). AUC for the new formulation is slightly lower. Co-administered methylphenidate increased clonidine clearance by 11% and co-administered amphetamine decreased clonidine clearance by 44%. Because of the differences in C<sub>max</sub> for the two products, it has been agreed that labeling should discourage interchangeability of the two products on a mg-per-mg basis. All labeling issues have been resolved, including, as noted, the name issue, and the biopharm group has also recommended approval.

### **5.0 CLINICAL DATA**

#### **5.1 Efficacy Data**

Our efficacy review focused on two 5-week, multicenter, randomized, double-blind, parallel group, placebo-controlled trials of clonidine in pediatric patients (ages 6-17) with ADHD (study 301 was a monotherapy and study 302 was adjunctive to stimulant treatment).

-301: This was a fixed dose study (0.2 and 0.4 mg per day). Patients were titrated to their assigned doses over 3 weeks, and maintained for 2 weeks. Both dose groups were statistically significantly superior to placebo on mean change from baseline on the ADHD-RS-IV. Although there was no apparent advantage of the 0.4 mg vs 0.2 mg group on the LOCF analysis, an MMRM analysis suggested a numerical advantage for the higher dose group. Exploratory subgroup analyses suggested that most of the effect was coming from the 6-12 year old group (about 80% of the population), and little from the smaller adolescent group.

-302: This was a flexible dose adjunctive study in which patients who had a partial, but suboptimal, response to either amphetamine or methylphenidate, were optimized on adjunctive clonidine or placebo in a dose range of 0.1 to 0.4 mg per day over 3 weeks, and then maintained for 2 additional weeks. Adjunctive clonidine was statistically significantly superior to adjunctive placebo on mean change from baseline on the ADHD-RS-IV. The only subgroup finding of interest was a suggestion of a larger placebo response in black and Hispanic subgroups.

DSI found the data generated for this program to be acceptable.

-Efficacy Conclusions: I agree with Drs. Mathews, Zhang, and Ishida that the sponsor has demonstrated efficacy for clonidine in the treatment of pediatric ADHD, both as monotherapy and as adjunctive therapy.

## **5.2 Safety Data**

Clonidine was adequately tolerated in this population and there were no new or unexpected safety findings. Somnolence and fatigue were the most common adverse reactions. Hypotension was not a common problem. Of note, there was no indication of any important safety problems with the use of clonidine as an adjunct to stimulant use. Current methylphenidate labeling has language suggesting the possibility of serious adverse events in association with this combination. As part of the review of this application, Drs. Diak and Mathis reviewed the AERS data pertinent to this alleged interaction, and found no support for any problematic interactions. Thus, we will not add this language to the clonidine label, and we will seek deletion of this language from methylphenidate labels.

## **6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We did not take these supplements to the PDAC.

## **7.0 LABELING AND COMPLETE RESPONSE LETTER**

### **7.1 Labeling**

We made a number of modifications to the sponsor's proposed labeling. We have now reached agreement with the sponsor on most of these changes.

### **7.2 CR Letter**

The CR letter includes our draft final labeling.

## **8.0 CONCLUSIONS AND RECOMMENDATIONS**

I believe that the sponsor has submitted sufficient data to support the conclusion that clonidine is effective and acceptably safe in the treatment of pediatric ADHD, both as monotherapy and as adjunctive therapy. We need to reach agreement on final labeling. In addition, the sponsor needs to submit a PA supplement to make parallel changes in the Jenloga label. I will issue the attached CR letter along with our draft final labeling.

cc:

Orig NDA 22-331/S-001/S-002

HFD-130

HFD-130/TLaughren/MMathis/JZhang/MMathews/HPatel

DOC: Clonidine\_ADHD\_NDA22331\_S-001\_S-002\_Laughren\_CR Memo.doc

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

/s/

THOMAS P LAUGHREN  
07/28/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**OFFICER/EMPLOYEE LIST**

**Officer/Employee List**  
**Application: NDA 022331 S-001 & S-002**

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Cantin, Lori  
Fuller, Barbara  
Ishida, Eiji  
Laughren, Thomas  
Mathis, Mitchell  
Patel, Hasmukh  
Wang, Yaning  
Yang, Peiling  
Zhang, Jing



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review Memo

<b>Date</b>	July 20, 2010
<b>From</b>	Jing Zhang, M.D., Ph.D.
<b>Subject</b>	Cross Discipline Team Leader Review
<b>NDA/Supp #</b>	22331/S-001, -002
<b>Proprietary / Established</b>	Kapvay/Clonidine Hydrochloride
<b>Dosage forms / strength</b>	Oral, modified release tablets 0.1 mg, and 0.2 mg
<b>Proposed Indications</b>	Attention deficit/hyperactivity disorder in children and adolescents aged 6 to 17 years old
<b>Recommended:</b>	Approval

### 1. Introduction and Background

Clonidine hydrochloride (Catapres, Boehringer Ingelheim) was first approved by FDA in 1973 under NDA 17-407 for the indication of hypertension. Kapvay (clonidine hydrochloride, Shinoga) is a modified-release formulation of clonidine hydrochloride (HCl) USP developed by Addrenex Pharmaceuticals for the indications of hypertension and attention deficit/hyperactivity disorder (ADHD) with expectation to reduce sedation and other adverse events compared to immediate-release product. (b) (4). On September 29, 2009 the Division of Cardiovascular and Renal Products (DCRP) approved its indication for hypertension in adults with a trade name of Jenloga under NDA 22331. Jenloga has not been marketed since the approval.

This modified-release formulation is achieved by (b) (4). However, with this formulary modification the dosing frequency of Kapvay (clonidine) remains same as original immediate-release clonidine HCl, twice per day.

Clonidine is a centrally acting alpha 2 adrenergic agonist that has been used effectively since the early 70s to treat mild to moderate hypertension. Clonidine has been used off label in the treatment of ADHD for decades in clinical practice. The mechanism of action of clonidine in ADHD is believed to be related to a reduction of norepinephrine turnover in the central nervous system. A dysfunction of the adrenergic system may lead to a disruption of the inhibitory control functions of the prefrontal cortex which could lead to the deficit in behavioral inhibition characteristic of ADHD.

A pre-IND meeting with Addrenex Pharmaceuticals was held on January 16, 2007 during which the ADHD development program was discussed. It was agreed that a 505 (b) (2) application could be submitted for this application and two positive ADHD clinical studies would be necessary. Following this meeting, the sponsor filed IND 76144 for clonidine in the treatment of ADHD in children and adolescents on September 4, 2007. A pre-NDA meeting

was held on March 9, 2009 during which it was agreed that the studies conducted by the sponsor were adequate to file for an NDA.

Addrenex filed this NDA initially on September 30, 2009. On November 20, 2009 Addrenex Pharmaceuticals, Inc. transferred all its rights to this application to Sciele Pharma, Inc. On January 11, 2010 Sciele Pharma, Inc. changed its name to Shionogi Pharma, Inc. Now Shionogi PHarma, Inc. is the sponsor for this sNDA.

## **2. CMC**

This clonidine formulation has been approved for indication of hypertension by DCRP in September 2009. There are no new or unresolved CMC issues for this application.

## **3. Nonclinical Pharmacology/Toxicology**

Juvenile rat studies were the only pre-clinical studies submitted under this sNDA. It was found that slightly delay in sexual maturation in juvenile rats treated with clonidine in these studies. The pharmacology/toxicology reviewer, Ikram Elayan, PhD, recommends labeling modification to describe the study results in the labeling. Additionally, she also requests the sponsor to conduct a juvenile rat study for combination therapy with a stimulant as a post-marketing commitment which the sponsor has committed to conduct the study in the pre-NDA meeting held on March 9, 2009.

## **4. Clinical Pharmacology/Biopharmaceutics**

Andre Jackson, Ph.D. is the clinical pharmacological reviewer for this submission. He found that based on PK data obtained from study CLON 302 there appeared to be a 44% increase in clonidine exposure with amphetamines and an 11% decrease in exposure for clonidine with methylphenidate in children and adolescents taking clonidine as adjunctive therapy compared to the presence of no interacting drug. The clinical significance for his finding is unclear. Study CLON 302, the adjunctive study, is not powered to detect efficacy differences between psychostimulant classes. The sponsor conducted efficacy subgroup analyses on stimulant class (AMPH or MPH) found no statistically significant difference between the CLON+STM (AMPH or MPH) and PBO+STM groups. The sponsor attributed this finding to the small sample size. Our statistical reviewer agreed with them. Safety subgroup analyses by stimulant class found no clear differences in incidence or pattern of TEAEs among CLON+AMPH, CLON+MPH, PBO+AMPH, and PBO+MPH group. Again, due to the small sample size, the results were inconclusive.

Dr. Jackson also found that children body weight greater than 50 kg (<50 kg n=145, and >50 kg n=143) showed less response to clonidine treatment. At the end of 5 weeks (Day 35), the ADHDRS-IV total scores were 29.2, 29.1 and 40.42 in CLON 0.2, 0.4 mg and PBO treatment in Wt <50 kg subgroup, 26.2, 25.4 and 32.3 in CLON 0.2, 0.4 mg and PBO in Wt >50 kg group respectively. He attributed this finding to a larger placebo effect in this patient subgroup. I agree with his interpretation (see his review dated on 7/14/2010).

## **5. Clinical/Statistical**

### **5.1 Efficacy**

#### **5.1.1 Clinical studies essential to regulatory decision (design, analytic features, and results)**

The efficacy and safety of clonidine as either monotherapy or adjunctive therapy in the treatment of ADHD in children and adolescents (6-17 years old) was demonstrated by two 5-week, double-blind, placebo-controlled studies, CLON 301 and CLON 302, conducted in the United States. Study CLON 303 is a 6-12 month open-label, flexible dose extension study which provided additional longer-term safety information to support the indication claim.

#### ***Study CLON-301***

Study CLON-301 was a 5-week, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of two fixed dosing regimens (0.2 mg and 0.4 mg) of clonidine monotherapy in children and adolescents (6 to 17 years old) who met DSM-IV criteria of ADHD hyperactive and hyperactive/impulsive subtypes.

The study was conducted between 22 October 2007 and 6 August 2008 in 15 centers across the U.S.A.

The study included a 5 week double-blind treatment period and a 3 week tapering period (total 8 weeks). Eligible patients were randomly assigned equally to one of the following three treatment groups: clonidine 0.2 mg/d, 0.4 mg/d, or placebo. Dosing for the clonidine groups started at 0.1 mg/d and was titrated in increments of 0.1 mg/week to their respective dose as divided doses. Patients were maintained at their respective dose for a minimum of 2 weeks before being gradually tapered down to 0.1 mg/d at the last week of treatment.

A total of 292 subjects were screened, and 236 were randomized (n = 78, 80, and 78 in CLON 0.2 mg, 0.4 mg and PLA group respectively). One hundred forty-three (60.6%) subjects completed the study. A larger proportion of clonidine treated subjects completed the study compared to placebo (69.2%, 60% & 52% in CLON 0.2 mg, 0.4 mg and PBO respectively). The demographic characteristics were similar across all treatment groups. The majority was male (72.4%) which is consistent with the epidemiological distribution of ADHD—the male-to female ratio is 3-5:1, and white (59.2%). The mean age was 9.4 years, and most subjects were 6-12 years old (82.5%).

The primary endpoint of this study is the mean change from baseline to the endpoint (the end of 5 weeks) of the investigator-completed ADHD rating scale (ADHDRS-IV) total score based on Last Observation Carried Forward (LOCF) analysis in Intend-to-Treat (ITT) population. No key secondary endpoint was pre-specified.

At the end of 5 weeks, both CLON treatment groups were statistically significantly superior to placebo in decrease of ADHDRS-IV total score. The LS mean difference between CLON treatments and placebo at endpoint were -8.48 in CLON 0.2 mg group and -8.99 in CLON 0.4 mg group, and p values were <0.0001 in both CLON treatment groups (Table 1, Ishida's review). The higher dose (0.4 mg) CLON group did not offer additional efficacy benefit—the difference between 0.2 and 0.4 mg groups was only 0.51. The sponsor also conducted two sensitivity analyses using observed cases model and inclusion of an interaction of study site and treatment. Results from these analyses supported the results obtained from the primary analysis.

**Table 1 Primary Efficacy Analysis by Sponsor in Study CLON 301**

Primary analysis	Treatment Group	N	LS Means Model Estimate for Difference (Clonice1-Placebo) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value**
ANCOVA (LOCF)	Clonice1 0.2 mg	74	-8.49 (-12.05, -4.93)	< .0001
	Clonice1 0.4 mg	78	-8.99 (-12.66, -5.32)	< .0001
	Placebo	76	--	--

\* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA

\*\* p-values were obtained by “two independent ANCOVA’s” (No multiplicity adjustment was performed).

[Source: Table 14.2.2 of CLON 301 CSR (page 117)]

The statistical reviewer, Eiji Ishida, M.S., reviewed and confirmed the sponsor's primary analysis results. Additionally he also conducted a mixed model for repeated measure (MMRM) analysis to look into the robustness of the sponsor's efficacy analysis results. The results from MMRM analysis confirmed the efficacy findings obtained from LOCF analysis. The LS mean differences in ADHDRS-IV total score between clonidine treatment and placebo groups at week 5 were -8.2 (p<0.001) in favor of CLON 0.2 mg group, and -11.1 (p<0.001) in favor of CLON 0.4 mg group. It is noted that by MMRM analysis (we believe it is a better analysis method) the difference of treatment effect between two clonidine treatment groups was larger, 2.9. The higher dose clonidine (0.4 mg) treatment showed a larger effect size.

The sponsor also conducted ADHDRS-IV subscale analyses (inattention subscale and hyperactivity/impulsivity subscale), and found that clonidine was effective in treating both inattentive and hyperactive symptoms. Statistically significant reductions(p<0.0001) of both ADHDRS-IV subscale scores at end of 5 weeks were observed in both clonidine treatment groups (inattention subscale: -7.7, -7.7 & -3.4 in CLON 0.2 mg, CLON 0.4 mg and PBO respectively; hyperactivity/impulsivity subscale: -7.9, -8.8 & -4.1 in CLON 0.2 mg, CLON 0.4 mg and PBO respectively).

Both the sponsor and our statistical reviewer conducted subgroup analyses on treatment effect by gender, race and age, and concluded that there were no significant treatment interactions of gender and race. However, both the sponsor and Eiji Ishida, M.S. found that the interaction of treatment and age was significant. Eiji Ishida, M.S. explored the age impact by stratifying the age into two subgroups: 6-12, and >12 years old and found that 6-12 subgroup contributed the overall efficacy—the placebo adjusted LS mean change from baseline in ADHDRS-IV total score was -10.62 (CLON 0.2), and -10.80 (CLON 0.4 mg) in 6-12 year old group compared to -1.53 (CLON 0.2 mg), and -1.69 (CLON 0.4 mg) in >12 years old group. He also pointed out

that >12 years old subgroup was under-represented (n=40, 17.5%), therefore, we can not draw any definitive conclusion from this finding.

### ***Study CLON-302***

Study CLON-302 was a 5-week, multicenter, flexible dose (CLON 0.2 to 0.4 mg), randomized, double-blind, placebo-controlled efficacy and safety study of clonidine as add-on to a psychostimulant in children and adolescents (6 to 17 years) who met DSM-IV criteria of ADHD hyperactive and hyperactive/impulsive subtypes.

This study was conducted between 10 March 2008 and 3 February 2009 in 22 centers across the U.S.A.

This study included a 5 week double-blind treatment period and a 3 week tapering period (total 8 weeks). Patients had been treated with a psychostimulant (methylphenidate or amphetamine) for 4 weeks with inadequate response defined as ADHDRS-IV  $\geq 26$ . Eligible patients were randomly assigned equally to one of the following two treatment groups: clonidine adjunct to a psychostimulant (CLON+STM) or psychostimulant alone (PBO+STM). Dosing for the clonidine groups started at 0.1 mg/d and was titrated in increments of 0.1 mg/week to their respective dose as divided doses. Patients were maintained at their respective dose for a minimum of 2 weeks before being gradually tapered down to 0.1 mg/d at the last week of treatment. Most patients (75.5%) were escalated to the maximum dose of 0.4 mg/d, and the majority (63/77, 82%) of them remained on the 0.4 mg/d for 2-3 weeks.

A total of 243 subjects were screened, and 198 were randomized (n = 102, and 96 in CLON+STM and PBO+STM group respectively). One hundred sixty-five (83.3%) subjects completed the study (Notes: the overall completion rate is higher in CLON 302 compared to that in CLON 301, 60.6%). A larger proportion of CLON+STM treated subjects completed the study (89.2%) compared to PBO+STM treated group (77.1%). The demographic characteristics were similar across all treatment groups. The majority was male (73.6%) which is consistent with the epidemiological distribution of ADHD—the male-to female ratio is 3-5:1, and white (53.8%). The mean age was 10.5 years, and most subjects were 6-12 years old (77.2%).

Per protocol, the investigators were allowed to change the dose of patient's stimulants based on the profile of safety and efficacy observed during the study, but changing the category of stimulants were not allowed. Overall, most subjects (69.6%) had no change in the average daily dose of psychostimulant taken (66.7% and 72.9% in CLON+STM and PBO+STM respectively). The percentage of patients who increased their average daily dose was similar across treatment groups (18.8% and 17.6%).

The primary endpoint of this study is the mean change from baseline to the endpoint (the end of 5 weeks) of the investigator-completed ADHD rating scale (ADHDRS-IV) total score based on Last Observation Carried Forward (LOCF) analysis in Intend-to-Treat (ITT) population. No key secondary endpoint was pre-specified.

At end of week 5, the CLON+STM treatment group showed statistically significant superiority to PBO+STM group in reducing ADHDRS-IV total score. The difference of LS mean change from baseline at the endpoint between CLON+STM and PBO+STM group was -4.48,  $p < 0.0091$  (Table 2, Ishida's review). The sponsor also conducted two sensitivity analyses using observed cases model and inclusion of an interaction of study site and treatment and confirmed the results obtained from the primary analysis.

**Table 2 Primary Efficacy Analysis by Sponsor in Study CLON 302**

Primary analysis	Treatment Group	N	LS Means Estimate of Difference (CLON+STM – PBO+STM) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value
ANCOVA (LOCF)	Clonigel +STM	102	-4.48 (-7.83, -1.13)	0.0091
	Placebo +STM	95	--	--

\* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA [Source: Table 14.2.2 of CLON 302 CSR (page 129)]

Eiji Ishida, M.S., reviewed and confirmed the sponsor's primary analysis results. Additionally he also conducted a mixed model for repeated measure (MMRM) analysis as a sensitivity analysis. The results from MMRM analysis supported the efficacy findings obtained from LOCF analysis conducted by the sponsor. The differences of LS mean change from baseline in ADHDRS-IV total score between CLON+STM and PBO+STM at week 5 were -3.9 ( $p < 0.0274$ ) favoring CLON+STM treatment.

The sponsor also conducted ADHDRS-IV subscale analyses on inattention subscale and hyperactivity/impulsivity subscale, and found statistically significant reduction in both ADHDRS-IV subscale scores at week 5 favoring CLON+STM treatment group (inattention subscale: -7.8 & -5.8 in CLON+STM and PBO+STM respectively,  $p < 0.0169$ ; hyperactivity/impulsivity subscale: -7.9, & -5.8 in CLON+STM and PBO+STM respectively,  $p < 0.0143$ ).

Both the sponsor and our statistical reviewer conducted subgroup analyses on treatment effect by gender, race and age. There were not significant treatment interactions of gender and age observed in this study. The white accounts for the largest proportion of race (53%) and the observed treatment effect ( $\Delta$  in LS mean is -18.3 and -11.9 in CLON+STM and PBO+STM respectively, Ishida's review). Significant placebo treatment effect was observed in the black and Hispanic subgroups (the black:  $\Delta$  in LS mean is -15.3 and -15.1 in CLON+STM and PBO+STM respectively; Hispanic:  $\Delta$  in LS mean is -13.9 and -14.1 in CLON+STM and PBO+STM respectively, Ishida's review). Hispanic only consists of 11.2% of total subjects. But, there was a reasonable presentation of the black (27.4%) in this study. The reason caused this high placebo effect in the black is unclear.

### 5.1.2 Discussion of primary reviewers' comments and conclusions

Both Maju Mathews, MD., the medical reviewer for this submission, and Eiji Ishida, M.S., the statistical reviewer feel that study CLON 301 and 302 provided adequate efficacy evidence to support the claim that clonidine is superior to placebo in the treatment of ADHD, as

monotherapy or as adjunctive therapy, in children and adolescents aged 6 to 17. I agree with their conclusion.

No clear dose-response relationship was found in study CLON 301, a fixed-dose study. Higher dose clonidine treatment group (0.4 mg) compared to low dose clonidine treatment (0.2 mg) showed almost no additional efficacy by LOCF analysis and showed some efficacy advantage by MMRM analysis.

Subgroup analyses identified significant interaction of treatment and age in study CLON 301 which might be caused by under representation of >12 years old subgroup in total subjects. The significant placebo treatment effect was found in the black/African American and Hispanic subgroups in study CLON 302 for unknown reason.

In both studies, subjects with diagnosis of ADHD inattentive subtype were excluded from the studies. However, based on the subgroup analyses on the ADHDRS-IV subscales conducted by the sponsor, clonidine demonstrated similar efficacy in improving both inattention and hyperactivity/impulsivity symptoms measured by ADHDRS-iv inattention and hyperactivity/impulsivity subscales.

### **5.1.3 Pediatric use/PREA waivers/deferrals**

Study CLON 301 and 302 are pediatric studies included children and adolescents aged 6 to 17. We requested to waiver study on children aged 0 to 5 because clonidine does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. A full pediatric waiver on children aged 0 to 5 has been granted by the Pediatric Review Committee (PeRC).

## **5.2 Safety**

### **5.2.1 General safety considerations**

The safety data obtained from study CLON 301, 302 (two 5-week, double-blind, placebo-controlled studies) and 303 (a 6-12 month, open-label extension study) were sufficient to assess the safety of clonidine in the treatment of ADHD in children and adolescents. A total of 557 subjects had been exposed to clonidine in these three studies, 215 subjects had been exposed to clonidine for  $\geq 24$  weeks and 113 subjects had been exposed to clonidine for  $\geq 48$  weeks. The safety assessments used in the study including adverse event (AE) monitoring, ECG, clinical laboratory, vital signs and suicidality assessment are appropriate. Since every study had their unique study design, the safety data from each study could not be pooled. Therefore, no integrated safety summary was provided in this submission.

The safety profile of this modified release clonidine was similar to regular released clonidine (Catapres), and guanfacine ER (Intuniv), another approved  $\alpha_2$ -adrenergic receptor agonist for the indication of ADHD. The important safety concerns related to this drug were hypotension/bradycardia and somnolence/sedation. The common adverse events observed in



these studies included somnolence, fatigue, irritability and dizziness. No new or unexpected safety findings were identified from this submission.

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

There were no deaths reported in study CLON 301, and 302.

There was no serious adverse event (SAE) in study 301. There were 3 SAEs in study 302. Two of these cases occurred in placebo group and 1 case in CLON+STM group (intentional over dose, took 3 additional doses (0.5 mg) of the study drug).

In study CLON 301, treatment-emergent adverse events (TEAEs) leading to discontinuation occurred in 21 (9%) patients and was more common in clonidine treatment groups than in placebo group (7%, 19% and 1% in CLON 0.2, 0.4 mg and PBO respectively). The most common TEAEs led to discontinuation were somnolence and fatigue. In study CLON 302, 4 (2%) patients were discontinued due to TEAEs. Only 1 of the 4 patients received CLON+STM treatment and this patient was discontinued because of bradyphrenia (slow thinking). The significantly lower incidence of TEAEs leading to discontinuation seen in study 302 compared to that in study 301, is likely explained by the flexible dose regimen and stimulants counteracted some common AEs, such as sedation and fatigue in study 302.

The overall incidences of TEAEs in both studies were only slightly higher in the clonidine treatment groups than in the placebo groups (CLON 301: 83% in CLON 0.2 or 0.4 mg and 72% in PBO respectively; CLON 302: 68% and 64% in CLON+STM and PBO+STM respectively). In study CLON 301, the most frequent TEAEs which also occurred more frequent in the active treatment groups than in the placebo group was somnolence (40%, 31% & 7% in CLON 0.2, 0.4 mg and PBO respectively) and fatigue (16%, 13% & 1% in CLON 0.2, 0.4 mg and PBO respectively). None of them were dose related. In study CLON 302, somnolence occurred in 20% of patients in the CLON+STM group and 8% in the PBO+STM group. Fatigue occurred in 16% of patients in the CLON+STM group and 4% in the PBO+STM group.

TEAEs were reported in higher frequency in both study 301 and 302 in the first 3 week dose titration period. The pattern of decreasing frequency of TEAEs over time was most evident for somnolence and fatigue. In study CLON 301, somnolence was reported in the dose titration period (Week 1-3) by 30% and 24% in the CLON 0.2 mg and 0.4 mg group respectively, compared to 12% and 11% respectively in stable maximum dose period (Week 4-5), and 13% and 3% respectively in the tapering period (Week 6-8). In study CLON 302, somnolence reported in CLON+STM group decreased in the three periods from 12% in the 1<sup>st</sup> period, to 8% in the 2<sup>nd</sup> period, and to 1% in the 3<sup>rd</sup> period.

Dose related decreases in blood pressure and heart rate were observed in patients who completed 5 weeks of treatment in study CLON 301. During the treatment period the maximum placebo-subtracted mean change in systolic blood pressure was -4.0 mmHg in

CLON 0.2 mg group, and -8.8 mmHg in CLON 0.4 mg group. The maximum placebo-subtracted mean change in diastolic blood pressure was -4.0 mmHg in CLON 0.2 mg group, and -7.3 mmHg in CLON 0.4 mg group. The maximum placebo-subtracted mean change in heart rate was -4.0 beats per minute on CLON 0.2 mg group and -7.7 beats per minute on CLON 0.4 mg group (The above data were submitted by the sponsor during the labeling negotiation). Similar pattern, but smaller magnitude in decreasing blood pressure and heart rate were observed in study 302.

No clinically significant Q-T prolongation signal was identified in study 301 or 302. Three patients in Study CLON 301 and 0 patients in CLON 302 had QTc values increase from baseline by  $\geq 60$  msec while on clonidine treatment. No patient had an on-therapy QT-cB or QT-cF result of 500 msec or greater in both studies.

There were no clinically significant clinical laboratory changes to suggest an effect of clonidine on clinical laboratory assessments in either study 301 or 302.

A completed clinical study report of CLON 303 was submitted to this sNDA during late review cycle. Study CLON 303 was a 6-12 month, multi-center, open-label, flexible-dose study to assess the longer-term safety of clonidine in children and adolescents (6-17 years old) with ADHD. This study was an extension of study CLON 301 and 302. A total of 303 subjects were enrolled and 53 (17.6%) completed 6 month study (original protocol) and 108 (35.9%) completed 12 month study (amended protocol). There were no deaths in this study. Two SAEs (1 cellulitis and 1 suicidal behavior) were reported and were judged by the investigators as not study drug related. The common AEs profile was similar to that obtained from two clonidine short-term, placebo-controlled studies. No new or unexpected safety signals were identified.

### **5.2.3 Drug-Drug Interaction Between Clonidine and Methylphenidate**

The current methylphenidate and dexamethylphenidate product labels contain the following language regarding a possible drug interaction with clonidine: *“Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.”*

Due to a lack of support for an association with the combined use of clonidine and methylphenidate and serious adverse events, including death, the Catapres (clonidine hydrochloride) label, approved by DCRP on April 7, 2010, no longer contains above language.

This drug interaction caution first appeared in labeling in 2000 with the approval of Concerta apparently based upon four case reports of seriously life-threatening adverse reactions or death with the combination of stimulants and clonidine. Despite the fact that there was no clear relationship between death and the combination of methylphenidate and clonidine, the cautionary statement about a potential drug-drug interaction appeared in the Concerta label in 2000 and after that appeared in the other methylphenidate labels without an apparent critical review of cases.

To address this drug interaction issue, Dr. Maju Mathews reviewed the pertinent clinical data submitted this NDA. Consultations to the Office of Surveillance and Epidemiology (OSE) regarding this issue were performed. The Adverse Event Reporting System (AERS) database for cases of death associated with the concomitant use of selective alpha<sub>2</sub> adrenergic agonists and stimulants was conducted by Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader, OSE (see the review from Ida-Lina Diak and Dr. Mitch Mathis on 7/6/10). Drug utilization review regarding combination use of stimulants and clonidine or guanfacine) was performed by Hina Mehta, Pharm.D., Durg Use Data Analyst, OSE (see her review on 6/25/10).

AERS search identified only one new case of death in the AERS database, which reported the concomitant use of clonidine and methylphenidate. This case provided very limited details and the cause of death was listed as unknown. No cases of serious and unexpected adverse events from the clinical trials data submitted to this sNDA.

Drug utilization analysis (date from 2006-2009) found substantial amounts of concurrent dispensing for clonidine and stimulants, as well as guanfacine and stimulants among the pediatric population. The largest proportion of concurrent use was among patients aged 0-12 years old. At least 21% of pediatric patients on clonidine or guanfacine were on therapy with a stimulant agent concurrently.

Based on the data reviewed, in the absence of published or other data that points to risk for adverse events, Drs. Ida-Lina Diak, Mitch Mathis and Maju Mathews all recommend updating the current methylphenidate and dextmethylphenidate labels to remove the drug interaction statement regarding methylphenidate and clonidine. I agree with their recommendations.

## **6 Labeling Recommendations**

The division has reviewed the sponsor proposed labeling in detail. We have proposed precise labeling language in a separate labeling document. The final draft of labeling will be attached to the action package. The major labeling revisions requested by the division are the following:

1. We request the sponsor adding AEs of hypotension/bradycardia and sedation/somnolence to the Warnings and Precautions section. Pertinent clinical data and monitoring language were also added.
2. We consider the two pivotal studies to support the ADHD claim 5-week studies (b) (4). We requested that the sponsor re-analyzed the safety data from active treatment phase (Week 1 to 5) separately from that obtained from tapering phase (Week 6-8). The common adverse reaction tables in section 6. Adverse Reactions should only include the data obtained from Week 1 to 5.
3. Added common adverse reactions that were reported in at least 5% of drug-treated patients and  $\geq 2$  time the rate of placebo in the section 6. Adverse Reaction.
4. Standard language regarding the diagnosis and treatment of ADHD in general was added in section 1. Indications and Usage.

5. In section 7. Drug Interaction, added “Do not use Kapvay concomitantly with other products containing clonidine (e.g. Catapres).”
6. In section 17.7 Missed Dose, to avoid double dosing, we suggest revising language to: “If patients miss a dose of Kapvay, they should skip the dose and take the next dose as scheduled.”

## **7 DSI Audits**

The Division of Scientific Inspection (DSI) inspected two study sites for each short-term controlled study, Dr. Rakesh Jain/Site #6 and Dr. Kamallesh Pai/Site #9 for CLON301, and Dr. Andrew Cutler/Site #30 and Dr. Matthew Brams/Site #32 for CLON 302. Anthony Orenca, MD is the medical officer for this submission in DSI.

No deviation from regulations was found in the first 3 study sites. Some relatively minor violations were noted in Dr. Brams’s site (Site #32). As Dr. Orenca indicated in his review, these violations are isolated occurrences, and unlikely impact data reliability. Therefore, he concluded that “inspection findings documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Data appear acceptable for the proposed indication.”

## **8 Conclusions and Recommendations**

### **8.1 Recommended regulatory action**

Based on data submitted to the agency, I consider that the sponsor has provided sufficient evidence to support the claim that clonidine is effective and reasonably safe in the treatment of ADHD in children and adolescents aged 6 to 17 years old as either monotherapy or adjunct to psychostimulants. I, in agreement with Dr. Maju Mathews, recommend that the division take approval action on this supplemental NDA. Final approval is also contingent on mutual agreement on labeling.

### **8.2 Safety concerns to be followed postmarketing**

There are no new safety concerns with clonidine that have become apparent from the ADHD trials that would require to be followed postmarketing.

### **8.3 Risk Minimization Action Plan**

Currently, I do not recommend any specific risk minimization actions.

### **8.4 Postmarketing studies required**

A full waiver for study on children 0-5 years old for studying ADHD has been approved by PeRC.

Dr. Maju Mathews recommended a thorough Q-T study as a post-marketing requirement. When clonidine ER (NDA 22499 and 22500, oral suspension and oral tablet, Tris Pharma Inc.) was approved by DCRP for the indication of hypertension, a thorough Q-T study with either their extended release or immediate-release formulation had been requested (see AP letter on 12/3/2009). Therefore, there is no need to request a though Q-T study from Shinoga.

Regarding post-market commitments (PMC), Dr. Maju Mathews recommended the sponsor conducting a maintenance study to assess the long-term efficacy of clonidine. I agree with Dr. Mathews's recommendation.

#### **8.5 Comments to be conveyed to the applicant in the regulatory action letter**

We would request a controlled maintenance study in children and adolescents for the indication of ADHD as discussed above.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

JING ZHANG  
07/20/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-331
Priority or Standard	S

Submit Date(s)	09-30-2009
Received Date(s)	09-30-2009
PDUFA Goal Date	07-30-2010
Division / Office	Division of Psychiatry Products

Reviewer Name(s)	Maju Mathews, MD
Review Completion Date	07/15/2010

Established Name	Clonidine hydrochloride
(Proposed) Trade Name	Kapvay/Clonice
Therapeutic Class	Alpha-2-adrenergic agonist
Applicant	Shinoga

Formulation(s)	0.1 mg & 0.2 mg
Dosing Regimen	BID
Indication(s)	ADHD
Intended Population(s)	Children and Adolescents



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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

I recommend that the Division of Psychiatry Products take an Approval action for NDA 22-331. In my opinion, the sponsor has demonstrated the efficacy and safety of Clonidine in the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children and adolescents (ages 6-17 years-old). Studies CLON-301 and 302 were adequate and well-controlled trials that demonstrated the efficacy of Clonidine, as measured by the change in mean Attention Deficit-Hyperactivity Disorder Rating Scale- IV (ADHD-RS-IV) scores. There was a statistically and clinically significant difference in the treatment effect of Clonidine compared to placebo in both trials.

In my opinion, treatment with Clonidine was reasonably safe and well tolerated in the trials.

Several labeling recommendations have been made. Please refer to section 9.2 Labeling Recommendations for detailed comments. Final approval is contingent on satisfactory response to the agency's recommendations and mutual agreement on labeling as well as the conclusions of the CMC, pharmacology/toxicology, and clinical pharmacology reviewers.

### **1.2 Risk Benefit Assessment**

### **1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies**

The safety profile of TRADENAME is comparable to clonidine, a marketed oral formulation for hypertension. No new safety concerns were identified during the review. Risk Evaluation and Mitigation Strategies are not required at this time.

The sponsor should conduct a dedicated, thorough QT study of clonidine in healthy adult subjects.

## **1.4 Recommendations for Postmarket Requirements and Commitments**

The sponsor has studied the safety and efficacy of Clonidine in the treatment of ADHD in two short term studies. However, ADHD is a chronic condition and patients are on medications for long periods of time, running into years.

The sponsor should conduct a placebo-controlled maintenance trial to assess the long term efficacy and safety of Clonidine in children and adolescents with ADHD. This should probably be a placebo-controlled randomized withdrawal study.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Clonidine is a centrally acting alpha2 adrenergic agonist and has been used effectively to treat mild to moderate hypertension. Clonidine is currently approved in the US in 3 formulations: immediate release, transdermal patch, and epidural injection. Clonidine was approved for the treatment of hypertension as Jenloga on September 29 2009. Jenloga is a patented oral dose, modified release formulation of clonidine hydrochloride. The modified release formulation is achieved by (b) (4)

(b) (4)

In addition to hypertension, clonidine has been evaluated and used extensively off label for several other indications including attention deficit hyperactivity disorder (ADHD), alcohol withdrawal, atrial fibrillation, tic disorders, menopausal flushing, smoking cessation and ulcerative colitis.

The mechanism of action of clonidine in ADHD is thought to be related to a reduction of norepinephrine turnover in the central nervous system. A dysfunction of the adrenergic system may lead to a disruption of the inhibitory control functions of the prefrontal cortex



which could lead to the deficit in behavioral inhibition characteristic of ADHD. Clonidine may restore inhibitory control by regulating noradrenergic function.

## **2.2 Currently Available Treatments for Proposed Indications**

The mainstays of approved treatment for ADHD have been the stimulants, methylphenidate and amphetamines. Included in this category are dexamethylphenidate, dextroamphetamine, methamphetamine, and amphetamine single and mixed salts. As listed below, there are numerous immediate-release and extended-release formulations of stimulants available for the treatment of ADHD. Atomoxetine (Strattera) is a non-stimulant drug approved for the treatment of ADHD. It is a selective norepinephrine reuptake inhibitor. Guanfacine, like clonidine is is an  $\alpha_{2A}$ -adrenergic receptor agonist.

### **Available Treatments for ADHD**

- Adderall (mixed salts of a single entity amphetamine product) Tablets
- Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules
- Concerta (methylphenidate hydrochloride) Extended-Release Tablets
- Daytrana (methylphenidate) Transdermal System
- Desoxyn (methamphetamine HCl) Tablets
- Focalin (dexamethylphenidate hydrochloride) Tablets
- Focalin XR (dexamethylphenidate hydrochloride) Extended-Release Capsules
- Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules
- Methylin (methylphenidate hydrochloride) Oral Solution
- Methylin (methylphenidate hydrochloride) Chewable Tablets
- Ritalin (methylphenidate hydrochloride) Tablets
- Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
- Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules
- Strattera (atomoxetine HCl) Capsules
- Vyvanase (lisdexamfetamine: a pro-drug of amphetamine)
- Intuniv (guanfacine)

Although not approved for the indication, several other drugs that are thought to be

effective in treating some patients with ADHD. These include bupropion (Wellbutrin), tricyclic antidepressants (e.g., imipramine and desipramine) etc.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Clonidine is an approved drug to treat hypertension. 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 and hypotension. Other safety issues include somnolence, headache, fatigue, and dizziness.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The sponsor had a Pre-IND meeting with the FDA on January 16, 2007. It was agreed that a 505(b)(2) application could be submitted for this application. It was also conveyed to the sponsor that two positive studies in ADHD would be needed. In addition, it was also conveyed that it would be necessary to have some open-label safety experience under conditions of usual use, which may include combination with stimulants.

On March 9, 2009, the sponsor had a Pre-NDA meeting with the Agency. At this meeting, it was agreed that the studies conducted by the sponsor were adequate to file for an NDA.

### **2.6 Other Relevant Background Information**

No other relevant background information is available.

### **3 Ethics and Good Clinical Practice**

#### **3.1 Submission Quality and Integrity**

The quality of submission was adequate.

A clinical inspection summary was provided by Dr Anthony Orenca, MD on April 30, 2009. The conclusions of the inspection are as follows:

*Four U.S. clinical investigator sites, two per study protocol, were inspected in support of this application, for Protocols CLON-301 (monotherapy indication) and CLON-302 (addon therapy indication), respectively, with the proposed indication of symptomatic treatment of adolescents with Attention Deficit/Hyperactivity Disorder. No discrepancies were noted with the data listings provided in the NDA and source documents. Inspection findings documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Data appear acceptable for the proposed indication.*

DSI also sent a note to the review division dated 5/18/10, signed by Branch Chief Tejashri Purohit-Sheth, M.D, which stated that

*Research sub-investigators, not listed on the Form FDA Form 1572 "Statement of Investigator" conducted research investigations. Another inspectional finding was the lack of dose titration (e.g., up titration, or static drug dosing) for the investigational drug by patient's responsible guardian, per protocol dose schedules. This was an isolated occurrence, and noted in only one subject.*

*It was concluded these non-critical regulatory deficiencies were considered unlikely to impact patient welfare and safety, and data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.*

### **3.2 Compliance with Good Clinical Practices**

The sponsor states that the studies were conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines (ICH) and all applicable regulations. Compliance with these regulations and guidelines also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study was also carried out in accordance with local legal requirements. The study protocol, all protocol amendments, and the Informed Consent Form (ICF) were reviewed and approved by the central Institutional Review Board (IRB) prior to study initiation.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

A review done by Clinical Pharmacology concluded that clonidine is associated with a higher incidence of somnolence but there was no dose response relation due to titration design. Decreases in blood pressure were also noted. Combination therapy resulted in a 44% increase in clonidine exposure with amphetamines and 11% decrease with methylphenidate. Children greater than 50 kg showed less response to clonidine because of larger placebo effect.

### **4.1 Chemistry Manufacturing and Controls**

Please see review.

### **4.2 Clinical Microbiology**

None

### **4.3 Preclinical Pharmacology/Toxicology**

The Pharmacology Toxicology review concluded that the submission was considered approvable. However they recommended that the slight delay in sexual maturation in juvenile rats treated with clonidine should be described in labeling. They also recommended that the sponsor will need to conduct a juvenile rat study for combination therapy with a stimulant as a post marketing commitment.

### **4.4 Clinical Pharmacology**

#### **4.4.1 Mechanism of Action**

Clonidine is a centrally acting alpha2 adrenergic agonist that has been used effectively to treat mild to moderate hypertension. Clonidine is not a central nervous system stimulant. It has a different mechanism of action than most other antihypertensive agents.

Clonidine has been evaluated and used extensively off label for several other indications, including attention deficit hyperactivity disorder (ADHD). The mechanism of action of clonidine in ADHD is thought to be related to a reduction of norepinephrine turnover in the central nervous system. A dysfunction of the adrenergic system may lead to a disruption of the inhibitory control functions of the prefrontal cortex which could lead to the deficit in behavioral inhibition characteristic of ADHD. By regulating noradrenergic function, clonidine may restore inhibitory control and possibly improve attention and learning.

#### **4.4.2 Pharmacodynamics**

With immediate-release clonidine, blood pressure declines within 30 to 60 minutes after an oral dose with the maximum decrease occurring within 2 to 4 hours. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes

are intact; therefore, orthostatic symptoms are mild and infrequent. There is also a reduction (15% to 20%) of cardiac output in the supine position with no change in the peripheral resistance. During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal hemodynamic response to exercise.

Studies in patients taking immediate-release clonidine have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines. The exact relationship of these pharmacologic actions to the antihypertensive effect of clonidine has not been fully elucidated.

Clonidine acutely stimulates growth hormone release in both children and adults, but does not produce a chronic elevation of growth hormone with long-term use.

#### 4.4.3 Pharmacokinetics

Following oral administration of TRADENAME, peak clonidine levels are reached in 4 to 7 hours, and the plasma half-life averages 13 hours. The absorption of clonidine from TRADENAME is not affected by food. Following oral administration of the immediate-release formulation, about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours and about 50% of the absorbed dose is metabolized in the liver.

The half-life of clonidine from the immediate-release formulation increases up to 41 hours in patients with severe impairment of renal function. Although studies of the effect of renal impairment and studies of clonidine excretion have not been performed with TRADENAME, results are likely to be similar to those of the immediate-release formulation.

The peak to trough ratio (C<sub>max</sub>/C<sub>min</sub>) of clonidine, following repeat dosing with TRADENAME ranges from 1.4 to 1.5. The plasma concentrations of clonidine increased proportionately with increase in dose over 0.1 mg – 0.6 mg twice daily.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 1: Table of Studies Conducted

CLON-301	A phase III, dose response evaluation of the efficacy and safety of TRADENAME® (clonidine HCl sustained release) vs. placebo in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)
CLON-302	A phase III evaluation of the efficacy and safety of TRADENAME® (clonidine HCl sustained release) as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)
CLON-303	An open-label, chronic exposure evaluation of the safety of TRADENAME® (clonidine HCl sustained release) in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)

### 5.2 Review Strategy

For efficacy, studies CLON-301 and CLON-302 were reviewed. To evaluate safety, CLON-301, 302, and 303 were reviewed. Data from the studies were not pooled as the design of the studies were different and this reviewer did not feel that it was appropriate to pool these studies.

A listing of items examined during the course of this review is provided in the table below.

**Table 2: Listing of Items reviewed**

Submission date	Items Reviewed
09/30/2009	<ul style="list-style-type: none"><li>Clinical Study Reports CLON-301,</li></ul>

	CLON-302, CLON-303 <ul style="list-style-type: none"><li>• Application Summary</li><li>• Proposed Labeling</li><li>• Financial Disclosure Information</li><li>• Case Report Forms</li></ul>
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### 5.3 Discussion of Individual Studies/Clinical Trials

A detailed discussion of each individual study is under the review of efficacy.

## 6 Review of Efficacy

### A. STUDIES PERTINENT TO ADHD CLAIM

#### Rationale for Selection of Studies for Review

The sponsor has submitted results of two studies to support efficacy. Both of them will be reviewed under this section:

#### Study Summaries

**Study 1: CLON-301:** A phase III, dose response evaluation of the efficacy and safety of Clonidine vs. placebo in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD).

The study was conducted from 22<sup>nd</sup> October 2007 to 6<sup>th</sup> August 2008 in 15 centres across the United States. A total of 19 investigators participated in the study.

**Methods/Study Design/Analysis Plan:** This is a 5-week (8-week total, including taper down period), multicenter, parallel-group, randomized, double-blind, placebo controlled



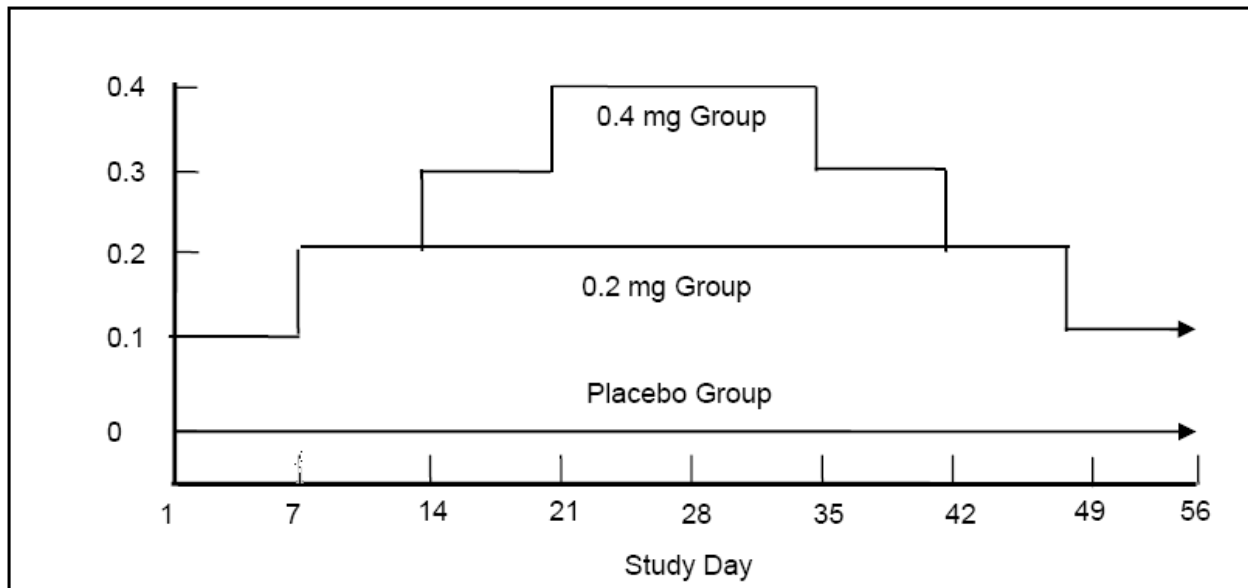
study of the efficacy and safety of two dosing regimens of clonidine in children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD.

A total of 236 male and female subjects were randomly assigned to one of the following three treatment groups: clonidine (CLON) 0.2 mg/day (N=78), CLON 0.4 mg/day (N=80), or placebo (N=78). Dosing for the CLON groups started at 0.1 mg/day and a proper titration schedule was used to escalate subjects to their respective fixed dose. Subjects were maintained at their dose level for a minimum period of 2 weeks before being gradually tapered down to 0.1 mg/day at the last week of treatment. Treatment was discontinued for subjects who could not tolerate their assigned dose.

Prior to initiating the 8-week treatment period, subjects completed a screening period of up to 2 weeks during which all screening assessments were performed and any current ADHD treatments discontinued. During the treatment period, subjects returned to the investigative site weekly to complete efficacy and safety assessments. Subjects discontinued study medication at the Week 8 visit but returned for a closeout safety visit one week later.

Subjects who could benefit from continued treatment with clonidine and desired to do so were offered participation in an open-label follow-on study designed to gather additional efficacy and safety data on clonidine.

### **Figure 1: Study Design of CLON-301**



Important Inclusion Criteria:

- Male or female between 6 and 17 years of age, inclusive
- Diagnosis of ADHD of the hyperactive or combined inattentive/hyperactive subtypes according to DSM-IV criteria
- Minimum score of 26 on the ADHDRS-IV questionnaire at Baseline
- General good health as judged by the Principal Investigator
- Body mass index  $\geq$  5th percentile of the subject's age group according to the CDC growth chart. BMI was calculated using the formula:  $\text{weight (kg)} / [\text{height (m)}]^2$
- Ability to swallow tablets
- General IQ  $\geq$  80 as judged by the Principal Investigator
- Subject as well as parent/guardian able to sign informed assent or consent form.

Important Exclusion Criteria

- Females who were pregnant or lactating or who did not agree to use an acceptable form of birth control.
- Presence of clinically significant illness or abnormality on physical examination or clinical laboratory investigations or ECG's.
- History or presence of concomitant psychiatric disorder, conduct disorder, seizures, syncopal episodes, presence of drug or alcohol abuse or positive drug screen with the exception of ADHD drugs.

### **Efficacy:**

The primary efficacy variable was the comparison between treatment groups on change in scores from Baseline to the Week 5 measure (or discontinuation measure if earlier than Week 5) of the Attention Deficit Hyperactivity Disorder rating Scale (ADHDRS-IV) scale total score using a "Last Observation Carried Forward (LOCF)" analysis.

Secondary efficacy variables included:

- Conners' Parent Rating Scale Revised: Long Form (CPRS-L)
- Sleep Self Report questionnaire – Child's Form (SSR-CF)
- Horacek Adrenergic Dysregulation Scale (HADS)
- Clinical Global Impressions-Severity (CGI-S)
- Clinical Global Impressions-Improvement (CGI-I)
- Parent Global Assessment (PGA)

None of the above endpoints was prespecified as a key secondary endpoint.

### **Results**

#### ***Demographics***

The demographic characteristics were similar across the three treatment groups. No significant differences between the groups were noted. The majority were male (72.4%)

and white (59.2%). Mean subject age was 9 years and most subjects were 6-12 years of age. Mean body weight was 41.1 kg.

**Table 3: Demographic characteristics-ITT subjects**

Summary	Treatment Group			All Subjects	P-Value [1]
	Clonice1 0.2 mg	Clonice1 0.4 mg	Placebo		
ITT Subjects	74	78	76	228	
Gender					
Male	58 (78.4%)	55 (70.5%)	52 (68.4%)	165 (72.4%)	0.3589
Female	16 (21.6%)	23 (29.5%)	24 (31.6%)	63 (27.6%)	
Age (years)					
N	74	78	76	228	0.8988
Mean (Std)	9.6 (2.94)	9.4 (2.89)	9.4 (2.86)	9.4 (2.89)	
Median	9.0	9.0	8.5	9.0	
Min, Max	6.0, 17.0	6.0, 17.0	6.0, 16.0	6.0, 17.0	
Age					
6-12 Years	61 (82.4%)	65 (83.3%)	62 (81.6%)	188 (82.5%)	
>12-17 Years	13 (17.6%)	13 (16.7%)	14 (18.4%)	40 (17.5%)	
Race					
White	45 (60.8%)	46 (59.0%)	44 (57.9%)	135 (59.2%)	0.9889
Black/African American	19 (25.7%)	20 (25.6%)	23 (30.3%)	62 (27.2%)	
Hispanic or Latino	6 (8.1%)	7 (9.0%)	6 (7.9%)	19 (8.3%)	
Other	4 (5.4%)	5 (6.4%)	3 (3.9%)	12 (5.3%)	
Weight (kg)					
N	74	78	76	228	0.5202
Mean (Std)	40.8 (20.59)	40.1 (18.33)	42.3 (17.83)	41.1 (18.87)	
Median	33.7	34.4	36.9	34.8	
Min, Max	20.8, 128.7	17.0, 106.1	20.4, 90.9	17.0, 128.7	

*Reviewer's Comments: As can be seen from the table above, the sex distribution was unequal, with over 2/3<sup>d</sup> of the study subjects being males. The age group was also unequally distributed, with there being over four times the number of subjects in the 6-12 years age group compared to those in the 12-17 year group. This is not surprising as ADHD is more commonly diagnosed in younger boys. This reviewer feels that the sex and age distribution reflects the population distribution of patients who suffer from this condition. I do not believe that this affects the generalizability of the results of the study.*

### **Patient Disposition**

A total of 292 subjects were screened. Of these, 236 were randomly assigned to the study treatments. Six of the 236 randomized were withdrawn from the study shortly after randomization before taking the study medication; therefore, a total of 230 subjects were included in the safety population (76 in 0.2 mg/day, 78 in the 0.4 mg/day and 76 in

the placebo group). Two of the 230 subjects received at least one dose of the study drug but had no post-baseline measurements (One of them withdrew consent and one was lost to follow up).

Overall, the majority of subjects (60.6%) completed the treatment phase. A larger proportion of subjects completed the treatment phase in the CLON 0.2 mg/day group (69.2%) compared with the CLON 0.4 mg/day (60%) and placebo (52.6%).

**Table 4: Patient Disposition in Study CLON-301**

	<b>CLON 0.2 mg</b>	<b>CLON 0.4 mg</b>	<b>Placebo</b>	<b>Total</b>
All Randomized	78	80	78	236
Safety Population	76	78	76	230 <sup>1</sup>
ITT for Efficacy	74	78	76	228 <sup>2</sup>
Completed Treatment Phase	54 (69.2%)	48 (60.0%)	41 (52.6%)	143 (60.6%)
Withdrawn	24 (30.8%)	32 (40.0%)	37 (47.4%)	93 (39.4%)
Withdrew Consent	4 (5.1%)	3 (3.8%)	2 (2.6%)	9 (3.8%)
Adverse Event	5 (6.4%)	15 (18.8%)	1 (1.3%)	21 (8.9%)
Lack of Efficacy	7 (9.0%)	9 (11.3%)	25 (32.1%)	41 (17.4%)
Lost to Follow-Up	6 (7.7%)	2 (2.5%)	4 (5.1%)	12 (5.1%)
Protocol Violation	0	2 (2.5%)	2 (2.6%)	4 (1.7%)
Other	2 (2.6%)	1 (1.3%)	3 (3.8%)	6 (2.5%)
Completed Safety Follow-up	66 (84.6%)	68 (85.0%)	64 (82.1%)	198 (83.9%)

### **Concomitant Medication Use**

During Clon-301, 27 subjects received a concomitant medication that was restricted in the protocol. Of these, 18 received a sedating antihistamine, 8 received bronchodilators, 4 received psychotropics and 2 got oral steroids.

Of the four subjects who received psychotropics, 1 received Lortab, 2 received phenergan and 1 received methylphenidate while tapering off study medication.

Reviewer's Comments: I do not think this affected study results.....

### **Important Protocol Violations**

#### **Entry Criteria Violations**

Three subjects in the placebo group and two subjects in the CLON 0.2 mg/day group did not meet all entry criteria and were granted an exception by the sponsor for study enrollment.

#### **Study Drug Dispensing error**

One subject in the Clon 0.4 mg/day treatment group received an extra week of treatment due to a dispensing error.

#### **Other protocol deviations**

At one site during the study, the ADHDRDS-IV rating scale was mistakenly completed by a parent rather than the PI at the screening, baseline, and week 1 visits for subjects 0701, 0702, 0703 and 0704. This deviation was noted and documented in the CRF comment log.

## Measurement of Treatment Compliance

Treatment compliance for each subject was determined by counting the number of pills taken from the blister packs in conjunction with patient report of dosing compliance; this was conducted at every scheduled visit. Treatment compliance was similar across the three treatment groups. Based on pill counts in conjunction with patient report of dosing, compliance ranged from 93.5% to 94.6% across the three treatment groups and was 94.0% for the overall study population.

Compliance with regard to completion of study visits was similar across the three treatment groups through Week 4. Greater than 83% of subjects in each of the three treatment groups completed study visits through Week 4, and greater than 66% of subjects in each of the three treatment groups completed study visits through Week 5. Approximately 63% of all subjects completed study visits through Week 8. The highest compliance was observed in the CLON 0.2 mg/day treatment group, having 71.6% of subjects complete through Week 8 compared with 62.8% in the CLON 0.4 mg/day and 53.9% in the placebo treatment groups.

## Dosing

The 0.2 and 0.4 mg/day doses chosen for this study were based upon product labels for the immediate release clonidine tablets (Catapres®) and transdermal clonidine patch (Catapres TTS®) supplemented by a review of literature of doses used in clinical trials for ADHD. Upon completion of all baseline assessments, subjects who satisfied all entry criteria at the baseline visit were randomly assigned to one of the three treatment groups.

In the treatment phase, dose escalation began in a double blind fashion using a mix of active and placebo tablets in the dispensed blister pack. Each dose consisted of 2 tablets total. Subjects were instructed to take the morning doses at 8 am ( $\pm 2$  h) and the evening doses at 8 pm ( $\pm 2$  h). The timing of dose ingestion relative to mealtimes was at the parent/guardian or subject's discretion. Each subject started the treatment period with dosing on the morning of Day 1. The subject was dispensed the Week 1 blister pack and instructed to take the morning dose (2 tablets total) at 8 am ( $\pm 2$  h) the next day. At the end of each week, subjects returned to the clinic with the previous week's blister pack(s) and received a new blister pack for the subsequent dosing week until completion of study treatment dosing on Day 56 of the study. The last dose of study medication was scheduled for the evening (8 am  $\pm 2$  h) of Day 56.

## **Efficacy Findings**

The primary efficacy variable was the mean change from Baseline in the Investigator completed ADHDRS-IV scale total score at Week 5, or discontinuation measure if earlier than Week 5 based on an LOCF analysis. At Baseline, the mean total score was similar across the three treatment groups (range 43.8 to 45.0). At Week 5, the mean change from Baseline in ADHDRS-IV in the CLON 0.2 mg/day and CLON 0.4 mg/day treatment groups was -15.6 and -16.6, respectively, and was statistically significantly greater than in the placebo group (-7.5;  $p < 0.0001$ ). The result of the observed case (OC) analysis for completers was similar to the LOCF analysis, although the magnitude of the change was slightly higher in each treatment group (-16.5, -19.4, and -8.0,  $p < 0.0001$ , for the CLON 0.2 mg, 0.4 mg and PBO groups respectively).



**Table 5: Change from baseline to week 5 in the ADHDRS IV total score (ITT Population, LOCF & OC Analyses)**

ADHDRS-IV TOTAL SCORE	TREATMENT GROUP								
	CLON 0.2 mg/day			CLON 0.4 mg/day			PBO		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	43.8	7.47	78	44.6	7.73	76	45.0	8.53
Week 5 (LOCF)	74	28.2	14.06	78	28.1	14.10	76	37.6	11.97
Change from Baseline (LOCF) <sup>1</sup>	74	-15.6	12.96	78	-16.5	13.54	76	-7.5	9.41
p-value (vs. PBO) <sup>2</sup>	<0.0001			<0.0001			--		
Week 5 (OC)	58	26.9	12.77	52	25.1	13.50	59	37.6	12.05
Change from Baseline (OC)	58	-16.5	12.08	52	-19.4	12.75	59	-8.0	9.16
p-value (vs. PBO) <sup>2</sup>	<0.0001			<0.0001			--		

<sup>1</sup> Primary efficacy analysis.

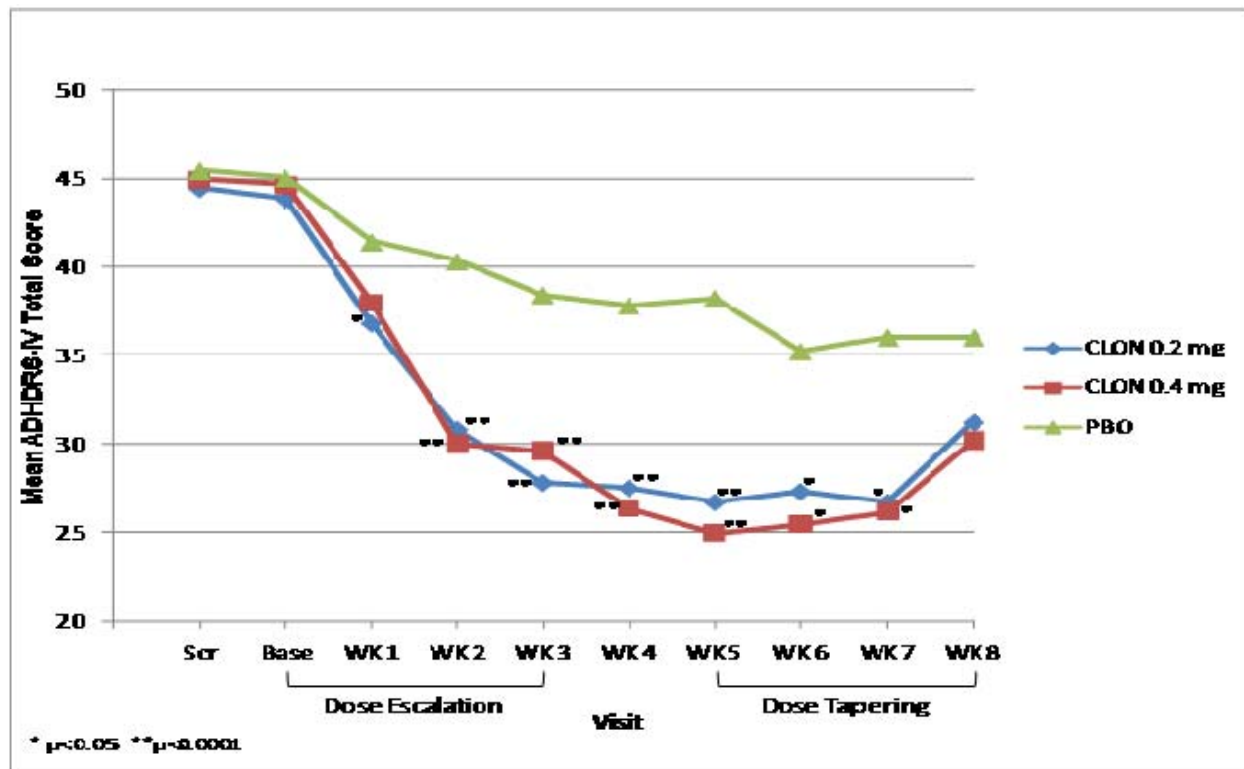
<sup>2</sup> Versus placebo p value; obtained from the treatment parameter in an ANCOVA modeling change from Baseline as a function of Baseline, treatment, and pooled study site.

Abbreviations: LOCF=last observation carried forward; OC=observed cases

## Mean ADHDRS-IV Total Scores over Time

The difference between each active treatment group and placebo was statistically significant ( $p < 0.05$ ) in both the LOCF and OC analyses. Statistical separation from placebo was achieved as early as Week 1 in the CLON 0.2 mg/day treatment group and Week 2 in the CLON 0.4 mg/day treatment group even as the dose was being escalated to target. This treatment difference was maintained throughout the treatment phase, through Week 8 for the LOCF analysis and Week 7 for the OC analysis.

**Figure 2: Mean of the ADHDRS-IV score by treatment and visit (ITT population, Observed Cases)**



## Conclusions

Both dosing regimens of clonidine were efficacious in alleviating symptoms in children and adolescents with ADHD.

At Baseline, for the primary efficacy variable, the investigator-rated ADHDRS-IV total score was similar across the three treatment groups (range 43.8 to 45.0). Treatment with clonidine resulted in a significantly greater mean change from Baseline in the ADHDRS-IV total score at Week 5, based on an LOCF analysis, in both the CLON 0.2 mg/day and CLON 0.4 mg/day treatment groups (-15.6 and -16.6, respectively) than treatment with placebo (-7.5;  $p < 0.0001$ ).

Two additional sensitivity analyses, including the observed case (OC) analysis for

completers, confirmed the results of the primary analysis that the difference between placebo and the CLON 0.2 mg/day or CLON 0.4 mg/day treatment groups was highly significant ( $p < 0.0001$  for each active treatment group in each model). The magnitude of the change was slightly higher in each treatment group (-16.5, -19.6, and -8.1, respectively) for the OC analysis. Moreover, the treatment difference was achieved as early as Week 1 in the CLON 0.2 mg/day treatment group and Week 2 in the CLON 0.4 mg/day treatment group and maintained throughout the treatment phase, through Week 8 for the LOCF analysis and Week 7 for the OC analysis ( $p < 0.05$  each analysis).

**Study 2:** CLON-302: A phase III evaluation of the efficacy and safety of clonidine as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)

**Methods/Study Design/Analysis Plan:**

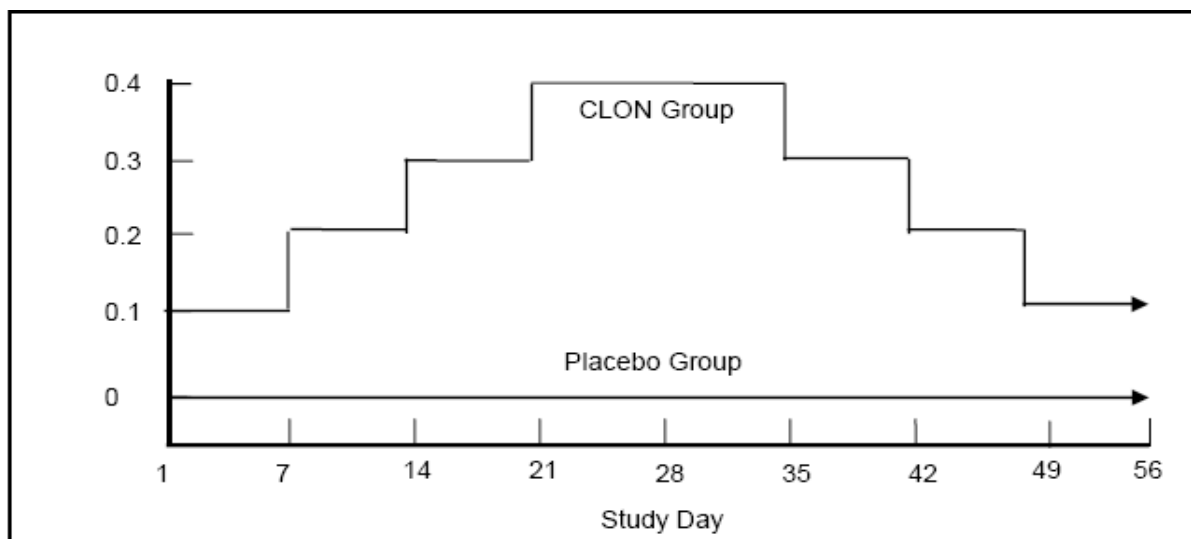
This was an 5-week (8-week including taper down period), multi-center, parallel-group, randomized, double-blind, placebo-controlled study (with clonidine or placebo as add-on therapy in patients who were on stimulants) of the efficacy and safety of a flexible dose of clonidine in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD, hyperactive and combined inattentive hyperactive subtype.

Subjects were randomly assigned to one of two groups: clonidine as add-on to a psychostimulant (CLON+STM) or placebo as add-on to a psychostimulant (PBO+STM). Subjects entering the study should have been on a stable regimen of approved stimulant medication of either methylphenidate or amphetamine (or their derivatives) for a minimum period of 4 weeks and could potentially benefit from the addition of an alpha2 adrenergic agonist as evidenced by a lack of adequate response to this stable regimen of stimulant medication (score on ADHDRS-IV > 26). The CLON dose (or matching placebo) was initiated at 0.1 mg/day and titrated up to a 0.4 mg/day (administered as 0.2 mg q12h) over a 3-week period. The dose was maintained at this

level for a period of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. The investigator could elect to keep a subject on a CLON dose lower than 0.4 mg/day or taper the dose earlier than scheduled in the case of adverse events.

The investigator could also elect to change the dose of stimulant medication based on the profile of safety and efficacy observed, but changing the category of stimulant medication was not allowed. Subjects who could not tolerate a minimum CLON dose of 0.1 mg/day were discontinued. Prior to initiating the 8-week treatment period, subjects completed a screening period (1 to 2 weeks) during which all screening assessments were performed including performance while on the current stimulant treatment regimen. During the treatment period, subjects returned to the investigative site weekly to complete efficacy and safety assessments. Subjects discontinued study treatment at the Week 8 visit and returned for a safety assessment at Week 9. Subjects who might benefit from continued treatment with clonidine and desired to do so were offered participation in an open-label follow-on study designed to gather additional efficacy and safety data on TRADENAME.

**Figure 3: Study Design CLON-302**



#### Inclusion Criteria

- Male or female between 6 and 17 years of age, inclusive

- Diagnosis of ADHD of the hyperactive or combined inattentive/hyperactive subtypes according to DSM-IV criteria
- Stable regimen of approved stimulant medication of either methylphenidate or amphetamine (or derivatives) for a minimum period of 4 weeks prior to Baseline
- Lack of adequate response to the stable regimen of stimulants evidenced by a minimum score of 26 on the ADHDRS-IV questionnaire at Baseline
- Body mass index  $\geq$  5th percentile of the subject's age group according to the CDC growth chart. BMI was calculated using the formula: weight (kg) / [height (m)]<sup>2</sup>

#### Important Exclusion Criteria

- If female of child-bearing potential, pregnant or lactating or did not agree to use a medically acceptable form of birth control
- Females who were pregnant or lactating or who did not agree to use an acceptable form of birth control.
- Presence of clinically significant illness or abnormality on physical examination or clinical laboratory investigations or ECG's.
- History or presence of concomitant psychiatric disorder, conduct disorder, seizures, syncopal episodes, presence of drug or alcohol abuse or positive drug screen with the exception of ADHD drugs.

Efficacy: Primary Efficacy Variable was the comparison between treatment groups on change scores from Baseline to the Week 5 measure (or discontinuation measure if earlier than Week 5) of the Investigator-completed ADHDRS-IV scale total score.

Secondary efficacy variables included the comparison between treatment groups on change scores from Baseline to the Week 5 measure (or discontinuation measure if earlier than Week 5) of:

Investigator-completed ADHDRS-IV subscales (inattention, hyperactivity, and impulsivity) CGI-S, parent-completed CPRS-L and HADS scales child-completed SSR-CF The CGI-I and PGA rating scores at each weekly post-baseline visit were also secondary efficacy variables.

No key secondary endpoint was prespecified

## Results

### Demographics

The demographic characteristics across the two treatment groups, CLON+STM and PBO+STM, were similar without significant differences. For all randomized subjects, the majority were male (73.6%) and White (53.8%). Mean subject age was 10.5 years (median 10.0 years), and most subjects were 6-12 years of age (77.2%). Mean body weight was 39.6 kg (median 35.9 kg).

**Table 6: Demographic characteristics: CLON-302**

Summary	Treatment Group		All Subjects	P-Value [1]
	Clonikel + STM	Placebo + STM		
ITT Subjects	102	95	197	
Gender				
Male	79 (77.5%)	66 (69.5%)	145 (73.6%)	0.2576
Female	23 (22.5%)	29 (30.5%)	52 (26.4%)	
Age (years)				
N	102	95	197	0.9038
Mean (Std)	10.4 (2.50)	10.5 (2.53)	10.5 (2.50)	
Median	10.0	10.0	10.0	
Min, Max	6.0, 17.0	6.0, 16.0	6.0, 17.0	
Age				
6-12 Years	77 (75.5%)	75 (78.9%)	152 (77.2%)	
>12-17 Years	25 (24.5%)	20 (21.1%)	45 (22.8%)	
Race				
White	49 (48.0%)	57 (60.0%)	106 (53.8%)	0.1547
Black/African American	35 (34.3%)	19 (20.0%)	54 (27.4%)	
Hispanic or Latino	11 (10.8%)	11 (11.6%)	22 (11.2%)	
Other	7 (6.9%)	8 (8.4%)	15 (7.6%)	
Weight (kg)				
N	100	93	193	0.7945
Mean (Std)	40.2 (18.57)	38.9 (13.57)	39.6 (16.33)	
Median	36.4	35.7	35.9	
Min, Max	18.8, 112.6	20.0, 76.8	18.8, 112.6	

### Baseline Characteristics

### Patient Disposition

A total of 243 unique subjects were screened. Of those screened, 198 subjects were

randomly assigned to the study treatments (All Randomized population). All 198 subjects were included in the Safety population (102 subjects in the CLON+STM and 96 in the PBO+STM treatment groups).

One of the 198 subjects in the Safety population (Subject 3302, assigned to the placebo group) received at least one dose of study drug but had no post-baseline measurements. The remaining 197 subjects provided evaluable efficacy data and were included in the ITT population.

Overall, the majority of subjects (83.3%) completed the treatment phase. Most subjects (86.9%) completed the follow-up visit. One subject did not complete the follow-up visit due to an AE, and the remaining subjects did not return for the follow-up visit for other reasons shown in the table below.

**Table 7: Subject disposition in Study CLON-302**

	CLON+STM N (%)	Placebo + STM N (%)	Total N (%)
All Randomized	102	96	198
Safety Population	102	96	198
ITT for Efficacy	102	95 <sup>1</sup>	197
Completed Treatment Phase	91 (89.2)	74 (77.1)	165 (83.3)
Withdrawn	11 (10.8)	22 (22.9)	33 (16.7)
Adverse Event	1 (1.0)	3 (3.1)	4 (2.0)
Withdrew Consent	0	8 (8.3)	8 (4.0)
Lack of Efficacy	4 (3.9)	6 (6.3)	10 (5.1)
Lost to Follow-Up	1 (1.0)	0	1 (0.5)
Protocol Violation	5 (4.9)	5 (5.2)	10 (5.1)
Completed Safety Follow-up	95 (93.1)	77 (80.2)	172 (86.9)
Did not complete Safety Follow-up	7 (6.9)	19 (19.8)	26 (13.1)
Adverse Event	0	1 (1.0)	1 (0.5)
Withdrew Consent	2 (2.0)	16 (16.7)	18 (9.1)
Lost to Follow-Up	5 (4.9)	0	5 (2.5)
Protocol Violation	0	1 (1.0)	1 (0.5)
Other	0	1 (1.0)	1 (0.5)

### Concomitant Medication Use

During CLON 302, 20 subjects received one or more of 23 concomitant medications that were restricted in the protocol. This included 15 subjects who received one or more sedating antihistamines (non sedating antihistamines were allowed), 5 subjects who received a bronchodilator (the protocol restricted chronic use greater than 3 times per week), 1 subject who received an oral steroid and 1 subject who received a

psychotropic (Medical Monitor agreed to PI request to add risperidone during the study follow-up period).

## **Important Protocol Violations**

### **Entry Criteria Violations**

Two subjects in the placebo group and four subjects in the CLON+STM group did not meet all entry criteria and except one, was discovered post-randomization. Three of the subjects marginally failed to meet inclusion criteria of BMI and were granted an exception by the sponsor to enroll in the study. One subject failed to meet inclusion criteria of minimum score of 26 on ADHD rating scale. This child was granted an exception and completed the study. One subject (2804, PBO+STM) met exclusion criteria of participating in a clinical trial using a topical gel for the treatment of acne. Investigator granted an exception for the subject to enroll 23 days after the last topical use of medication.

Subject 2502 (PBO+STM) was noted after beginning study drug that she had failed inclusion criteria of diagnosis of ADHD of hyperactive or combined inattentive/hyperactive subtypes, as the subject's diagnosis was ADHD of the inattentive subtype only. She was allowed to continue as she was doing well and tolerating study medication.

### **Subjects who received the wrong treatment or dose of study medication**

Subjects 2205 and 2206 were siblings and it was suspected that they were taking medications from each other's study medication bottles. They were discontinued for noncompliance with study medication instructions.

Subject 2910 (PBO+STM) was inadvertently randomized to the wrong kit number. This deviation was reported and reassignment made.



Subject 2601 was mistakenly not instructed to taper the study medication dose from 0.4 mg/day to 0.3 mg/day following the week 5 visit, and the subject continued on 0.4 mg/day for six additional days. The sponsor was contacted and during the final 2 weeks, the dose was tapered down.

### **Other protocol deviations**

Two subjects changed the class of psychostimulant medication they were taking during the treatment phase of the study. Both entered the study taking an amphetamine (Vyvanse). Subject 2607 switched to Concerta during the second week due to perceived side effect of emotional lability, which resolved one day after taking Concerta. The subject was discontinued after 7 days due to lack of efficacy. Subject 3704 was switched from Vyvanse to Daytrana during the fourth week due to restlessness, which resolved on the same day that the psychostimulant was changed. The subject went on to complete the study as planned.

### **Treatment Compliance**

Compliance with study drug dosing was similar across the two treatment groups, 97.2% and 94.5% for the CLON+STM and PBO+STM groups, respectively. Compliance with regard to completion of study visits was similar across the two treatment groups through Week 4. Greater than 94% and 88% of subjects in the CLON+STM and PBO+STM treatment groups, respectively, completed study visits through Week 4; and greater than 90 and 82% of subjects, respectively, completed study visits through Week 5. Approximately 87% of all subjects completed study visits through Week 8. Higher compliance was observed in the CLON+STM treatment group, having 90.2% of subjects complete through Week 8 compared with 84.4% in the PBO+STM treatment group.

### **Dosing**

## **Efficacy Findings**

The primary efficacy variable was the mean change from Baseline in the Investigator-completed ADHDRS-IV scale total score at Week 5, or discontinuation measure if earlier than Week 5 based on an LOCF analysis. The primary analysis was a comparison of mean scores for the CLON+STM treatment group versus PBO+STM.

At Baseline, the mean total scores were similar, 38.9 and 39.0 in the CLON+STM and PBO+STM treatment groups, respectively. At Week 5, the mean change from Baseline in ADHDRS-IV in the CLON+STM treatment group was -15.7, and was statistically significantly greater than in the PBO+STM group (-11.5;  $p=0.0091$  for treatment difference vs. placebo using an ANCOVA modeling the change from Baseline as a function of Baseline scores, treatment, and pooled study site).

Two additional sensitivity analyses, the primary efficacy model (LOCF) with the treatment by site interaction included and another model based on subjects who completed the study up to Week 5 confirmed the results of the primary analysis that the difference between PBO+STM and the CLON+STM treatment group was statistically significant ( $p=0.0045$  for the model that includes treatment by site interaction;  $p=0.0273$  for the observed case [OC] analysis). The result of the OC analysis for completers was similar to the LOCF analysis, although the magnitude of the change was slightly higher in each treatment group (-16.9 and -13.3, respectively). Placebo-subtracted least square mean differences between the two treatment groups ranged from 4 to 5 points, favoring the CLON+STM group.

**Table 8: Change from Baseline to Week 5 in the ADHDRS-IV Total Score (LOCF & OC Analyses)**

ADHDRS-IV TOTAL SCORE	TREATMENT GROUP					
	CLON+STM			PBO+STM		
	N	Mean	SD	N	Mean	SD
Baseline	102	38.9	6.95	95	39.0	7.68
Week 5 (LOCF)	102	23.1	12.53	95	27.5	13.39
Change from Baseline (LOCF) <sup>1</sup>	102	-15.7	12.30	95	-11.5	12.22
p-value (vs. PBO) <sup>2</sup>	p=0.0091			--		
Week 5 (OC)	92	22.1	12.47	75	25.6	12.83
Change from Baseline (OC)	92	-16.9	12.22	75	-13.3	11.86
p-value (vs. PBO) <sup>2</sup>	p=0.0273			--		

<sup>1</sup> Primary efficacy analysis.

<sup>2</sup> Versus placebo p-value; obtained from the treatment parameter in an ANCOVA modeling change from Baseline as a function of Baseline, treatment, and pooled study site.

## Conclusions

Overall, clonidine, as add-on therapy to ADHD psychostimulants, was efficacious in alleviating symptoms in children and adolescents with ADHD who lacked adequate response on a stable regimen of stimulant medication alone.

Treatment with clonidine for up to 8 weeks as add-on to stimulants in this patient population resulted in a significantly greater mean change from Baseline in the ADHDRS-IV total score at Week 5, based on the LOCF analysis, in the CLON+STM treatment group compared with PBO+STM (-15.7 and -11.5, respectively; p=0.0091). Results from most of the secondary efficacy analyses, supported the results of the primary efficacy analysis and achieved statistical significance (p-value at least <0.05).

## Crosscutting Issues

### Key Secondary Endpoints

There were no prespecified key secondary endpoints.

Overall, results of the secondary efficacy analyses, supported the results of the primary efficacy analysis and achieved statistical significance (p-value at least <0.05). Statistical

significance for a treatment difference between the active and placebo treatment groups was achieved for the investigator-rated scales, CGI-I, CGI-S and subscales of the ADHDRS-IV, and parent-rated scales, HADS, CPRS, derived subscales, and PGA, but not for the child rated sleep scale (SSR-CF) total score or derived subscales.

Patients were on average considered to be moderately to markedly ill at the beginning of the study and by Week 5 of treatment with clonidine, subjects were considered on average to be mildly to moderately ill and much improved with regard to symptoms of ADHD, compared to placebo subjects who showed little change in severity of disease and minimal improvement of symptoms. Parents on average considered subjects minimally improved following treatment with clonidine compared with placebo subjects who were considered to have no change in symptoms.

**Table 9: Secondary Efficacy results for Study CLON-301**

SECONDARY EFFICACY VARIABLE	TREATMENT GROUP								
	CLON 0.2 mg/day			CLON 0.4 mg/day			PBO		
Inattention Subscale of the ADHDRS-IV	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	22.9	3.87	78	23.1	3.81	76	23.4	4.32
Change from Baseline to Week 5 (LOCF)	74	-7.7	6.88	78	-7.7	7.10	76	-3.4	5.13
p-value (vs. PBO) <sup>1</sup>	<0.0001			<0.0001			--		
Hyperactivity/Impulsivity Subscale of the ADHDRS-IV	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	20.9	5.31	78	21.5	5.04	76	21.6	5.59
Change from Baseline to Week 5 (LOCF)	74	-7.9	6.96	78	-8.8	7.26	76	-4.1	5.04
p-value (vs. PBO) <sup>1</sup>	<0.0001			<0.0001			--		
CPRS Total Score	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	128.6	35.82	78	137.2	37.20	76	142.5	35.19
Change from Baseline to Week 5 (LOCF)	74	-40.7	39.01	78	-46.2	48.66	76	-23.3	31.33
p-value (vs. PBO) <sup>1</sup>	0.0002			0.0003			--		
CPRS Oppositional Subscale	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	16.8	7.56	78	18.1	7.91	76	18.4	7.08
Change from Baseline to Week 5 (LOCF)	74	-4.9	6.94	78	-5.5	8.29	76	-2.4	5.22
p-value (vs. PBO) <sup>1</sup>	0.0017			0.0027			--		
CPRS Hyperactivity Subscale	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	17.6	6.93	78	18.3	6.15	76	19.5	6.32
Change from Baseline to Week 5 (LOCF)	74	-6.4	6.95	78	-7.5	7.27	76	-3.8	5.18
p-value (vs. PBO) <sup>1</sup>	0.0004			<0.0001			--		
HADS	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	47.3	21.49	78	50.9	22.11	76	52.7	20.36
Change from Baseline to Week 5 (LOCF)	74	-15.3	18.22	78	-17.3	23.57	76	-8.8	16.72
p-value (vs. PBO) <sup>1</sup>	0.0032			0.0042			--		
Hyper-adrenergia Subscale	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	40.8	14.01	78	43.3	14.40	76	44.8	12.87
Change from Baseline to Week 5 (LOCF)	74	-12.6	13.75	78	-15.3	17.53	76	-7.9	12.26
p-value (vs. PBO) <sup>1</sup>	0.0065			0.0013			--		
SSR-CF Total Score	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	16.0	6.27	77	16.8	6.04	75	17.8	6.48
Change from Baseline to Week 5 (LOCF)	74	-1.9	5.20	77	-1.5	6.67	75	-3.4	5.83
p-value (vs. PBO) <sup>1</sup>	0.2946 (NS)			0.1838 (NS)			--		
SSR-CF Bedtime Subscale	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	8.1	3.91	77	9.1	3.80	75	9.5	4.25
Change from Baseline to Week 5 (LOCF)	74	-1.1	3.59	77	-1.1	3.62	75	-1.9	3.29
p-value (vs. PBO) <sup>1</sup>	0.6164 (NS)			0.2558 (NS)			--		
SSR-CF Sleep Behavior Subscale	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	4.5	2.47	77	4.2	2.24	75	4.3	2.40
Change from Baseline to Week 5 (LOCF)	74	-0.7	2.38	77	-0.1	3.29	75	-0.6	2.55
p-value (vs. PBO) <sup>1</sup>	0.9771 (NS)			0.4205 (NS)			--		
SSR-CF Daytime Sleepiness Subscale	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	3.4	1.82	77	3.5	1.85	75	4.1	1.83
Change from Baseline to Week 5 (LOCF)	74	-0.1	1.98	77	-0.2	2.10	75	-0.9	2.11
p-value (vs. PBO) <sup>1</sup>	0.2523 (NS)			0.5426 (NS)			--		
CGI-S	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	4.7	0.65	78	4.8	0.65	76	4.9	0.65
Change from Baseline to Week 5 (LOCF)	74	-1.2	1.02	78	-1.3	1.14	76	-0.5	0.82
p-value (vs. PBO) <sup>1</sup>	<0.0001			<0.0001			--		
CGI-I	N	Mean	SD	N	Mean	SD	N	Mean	SD
Week 5 (LOCF)	74	2.6	0.96	78	2.8	1.12	76	3.4	0.88
p-value (vs. PBO) <sup>2</sup>	<0.0001			0.0003			--		
PGA	N	Mean	SD	N	Mean	SD	N	Mean	SD
Week 5 (LOCF)	74	3.0	1.32	78	3.2	1.51	76	3.8	1.16
p-value (vs. PBO) <sup>2</sup>	0.0002			0.0043			--		

## **Secondary Efficacy Results for Study CLON-302**

Results from most of the secondary efficacy analyses, supported the results of the primary efficacy analysis and achieved statistical significance (p-value at least  $<0.05$ ). Statistically significant differences favoring the clonidine group were observed for the following secondary endpoints: Investigator-rated scales CGI-I and CGI-S; parent-rated scales, CPRS-L total score and the hyperactivity subscale, Hyper-adrenergia subscale, and PGA (p-value at least  $<0.05$  for each analysis). Often the magnitude of the change was higher in the OC versus the LOCF analysis. The difference between the active treatment group and placebo was usually achieved early in the treatment phase and maintained through Week 7. No statistically significant differences were observed for the HADS, CPRS-L oppositional subscale, and SSR-CF scale total score and subscales.

Thus, clonidine as add-on to psychostimulant therapy was effective in alleviating symptoms of ADHD such as inattention, impulsivity, and hyperactivity. However, it was not effective in alleviating symptoms of sleep disturbance based on the child-rated sleep scale nor aggression based on the CPRS-L oppositional subscale in this population of ADHD patients who lacked adequate response on a stable regimen of stimulant medication alone. Investigators on average considered subjects to be moderately to markedly ill at the beginning of the study and by Week 5 of treatment with clonidine, subjects were considered on average to be mildly to moderately ill and much improved with regard to symptoms of ADHD, compared to placebo subjects who showed minimal improvement of symptoms. Parents on average considered subjects minimally to much improved following treatment with clonidine compared with placebo subjects who were considered to have minimal improvement in symptoms.

**Table 10: Secondary Efficacy Results for Study CLON-302**

SECONDARY EFFICACY VARIABLE	TREATMENT GROUP					
	CLON+STM			PBO+STM		
<b>Inattention Subscale of the ADHDRS-IV</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	20.7	4.22	95	20.8	4.21
Change from Baseline to Week 5 (LOCF)	102	-7.8	6.81	95	-5.8	6.85
p-value (vs. PBO) <sup>1</sup>	0.0169			--		
<b>Hyperactivity/Impulsivity Subscale of the ADHDRS-IV</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	18.2	4.94	95	18.2	5.14
Change from Baseline to Week 5 (LOCF)	102	-7.9	6.70	95	-5.8	6.32
p-value (vs. PBO) <sup>1</sup>	0.0143			--		
<b>CPRS Total Score</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	118.2	37.58	95	120.5	39.57
Change from Baseline to Week 5 (LOCF)	102	-40.2	41.44	95	-27.1	38.25
p-value (vs. PBO) <sup>1</sup>	0.0166			--		
<b>CPRS Oppositional Subscale</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	15.6	7.04	95	16.5	7.53
Change from Baseline to Week 5 (LOCF)	102	-5.1	6.61	95	-3.6	6.31
p-value (vs. PBO) <sup>1</sup>	0.0615 (NS)			--		
<b>CPRS Hyperactivity Subscale</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	14.7	6.27	95	14.6	6.61
Change from Baseline to Week 5 (LOCF)	102	-5.8	6.49	95	-3.8	5.71
p-value (vs. PBO) <sup>1</sup>	0.0166			--		
<b>HADS</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	45.3	20.73	95	47.8	20.79
Change from Baseline to Week 5 (LOCF)	102	-16.0	18.71	95	-13.3	18.84
p-value (vs. PBO) <sup>1</sup>	0.1741 (NS)			--		
<b>Hyper-adrenergia Subscale</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	38.1	13.61	95	39.4	14.36
Change from Baseline to Week 5 (LOCF)	102	-14.1	13.74	95	-10.0	13.70
p-value (vs. PBO) <sup>1</sup>	0.0244			--		
<b>SSR-CF Total Score</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	15.7	6.33	95	16.4	7.44
Change from Baseline to Week 5 (LOCF)	102	-1.9	5.34	95	-1.6	6.12
p-value (vs. PBO) <sup>1</sup>	0.3759 (NS)			--		
<b>SSR-CF Bedtime Subscale</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	8.2	3.75	95	8.6	4.39
Change from Baseline to Week 5 (LOCF)	102	-1.1	3.32	95	-0.8	4.03
p-value (vs. PBO) <sup>1</sup>	0.2154 (NS)			--		
<b>SSR-CF Sleep Behavior Subscale</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	4.0	2.38	95	4.4	2.83
Change from Baseline to Week 5 (LOCF)	102	-0.4	2.39	95	-0.8	2.58
p-value (vs. PBO) <sup>1</sup>	0.5646 (NS)			--		
<b>SSR-CF Daytime Sleepiness Subscale</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	3.4	1.90	95	3.3	1.76
Change from Baseline to Week 5 (LOCF)	102	-0.4	1.82	95	-0.1	1.55
p-value (vs. PBO) <sup>1</sup>	0.2021 (NS)			--		
<b>CGI-S</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Baseline	102	4.7	0.74	95	4.8	0.81
Change from Baseline to Week 5 (LOCF)	102	-1.5	1.23	95	-1.2	1.28
p-value (vs. PBO) <sup>1</sup>	0.0210			--		
<b>CGI-I</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Week 5 (LOCF)	102	2.5	1.16	95	3.0	1.22
p-value (vs. PBO) <sup>2</sup>	0.0065			--		
<b>PGA</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>
Week 5 (LOCF)	102	2.7	1.26	95	3.4	1.38
p-value (vs. PBO) <sup>2</sup>	0.0012			--		

## **Subgroup Analyses**

The statistical reviewer and sponsor conducted an analysis of results by gender, race and age as potential predictors of response using the ITT Population.

In Study 301, an analysis of results by gender showed that the observed treatment effect appeared comparable between genders in both treatment comparisons, except that the female CLON 0.4 mg group had a numerically larger treatment effect.

In the analysis of race (White, Black/African American, Hispanic, Other), the overall treatment effect for clonidine relative to placebo was not affected by race.

The statistical review concluded that the 6-12 year-old subgroup was the contributor of the overall efficacy evidence, while the >12 year-old was not. This may have been due to the small number of subjects of this subgroup, and thus there is no information in the data to draw any conclusion on the efficacy of the >12 year-old subgroup.

In Study 302, the overall treatment effect for clonidine relative to placebo was not affected by gender, age or race.

## **Longterm Efficacy**

There were no long-term efficacy studies done

## **Pediatric Development**

This is a pediatric study

## **Efficacy Conclusions Regarding ADHD**

The phase III studies, Study CLON-301 and Study CLON-302, established statistical evidence of a mean difference in the ADHDRS-IV total score at the study endpoint (Week 5) in favor of TRADENAME treatment against placebo, both as monotherapy and as an add-on to a psychostimulant.



## **7 Review of Safety**

### **Safety Summary**

#### **7.1 Methods**

The evaluation of the safety of clonidine consisted of two general approaches:

- Assessment of the more serious adverse events in the entire study population arising from all datasets; deaths, non-fatal serious adverse events, and adverse events that led to premature discontinuation.
- Examination of the less serious adverse events. This examination encompasses common adverse events, laboratory findings, vital signs data, and ECG findings associated with exposure to CloniceL.

##### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

This review will focus on the safety data from trials CLON-301 and CLON-302.

##### **7.1.2 Categorization of Adverse Events**

Adverse events were categorized under the occurrence of deaths, non-fatal serious adverse events, and premature discontinuations due to adverse events. Additionally common adverse events, vital signs, laboratory test data, and ECG results were also analyzed.

All subjects receiving at least one dose of the study medication were evaluated for safety.

Adverse events were coded using the Coding Symbol for Thesaurus of Adverse Reaction Terms (COSTART) dictionary.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This NDA submission consisted of three trials, one was a placebo controlled study and the other was clonidine as add on therapy to patients currently receiving a stimulant. The third study was an open label long term study. Since they had different designs, this reviewer did not feel that it was appropriate to pool data from the different studies.

## 7.2 Adequacy of Safety Assessments

Safety evaluations were done through adverse event monitoring, which were reported by the subject, as well as those noted by the Investigator. These were recorded in the source documents and on the CRF. AE collection began at the baseline visit prior to start of administration of study drug and continued till study completion.

The sponsor also collected laboratory parameters at screening and day 56 (week 8). If consent could be obtained, blood was collected for pharmacogenomic study. Additional safety assessments included vital signs, physical exams, medical history, ECG's and pregnancy testing.

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

In Study CLON-301, a total of 154 subjects received clonidine, of which 76 received 0.2 mg/day and 78 received 0.4 mg/day. The mean (94.9 AND 87.0) and median (109 AND 107) number of doses taken were similar across the two treatment groups. Treatment compliance was similar across the three treatment groups. The total amount of drug taken for the two clonidine treatment groups were on an average 8.2 mg in the CLON 0.2 mg/day and 10.6 mg in the CLON 0.4 mg/day group.

In Study CLON-302, A total of 102 subjects received clonidine. For the ITT Population, the mean number of doses taken (120.4) and median (132.5) in the CLON+STM group

was similar to the PBO+STM treatment group (mean 113.9, median 132.0). The total amounts of drug taken in milligrams for the CLONICEL treatment group was on average 12.0 mg (median 13.3 mg). Treatment compliance was similar across the two treatment groups (97.2% and 94.5%).

Study CLON-303 was an open-label, chronic exposure evaluation of the safety of clonidine in the treatment of children and adolescents with ADHD. For the 301 subjects included in the Study CLON-303 Safety Population, exposure was calculated by including time on active treatment in the prior double-blind study (CLON-301 or CLON-302). With prior double-blind exposure included, 215 subjects (74.1%) received clonidine for  $\geq 24$  weeks and 113 subjects (37.5%) received clonidine for  $\geq 48$  weeks .

#### 7.2.2 Explorations for Dose Response

Formal explorations for dose response were not done. However, in study CLON-301, it was noticed that the AE's of constipation, nightmares, and tremors were more common in the CLON 0.4 mg group than the 0.2 mg group. The number of subjects who experienced headaches and somnolence were higher in the lower dose groups. No conclusions can be drawn from these numbers regarding causality.

#### 7.2.3 Special Animal and/or In Vitro Testing

There was no special animal and/or in vitro testing done.

#### 7.2.4 Routine Clinical Testing

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

None

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

The other drug in the same class as clonidine is guanfacine (INTUNIV), which was approved by the FDA for the treatment of ADHD in 2009. Guanfacine is also a selective  $\alpha$ -adrenergic receptor agonist. Common adverse events seen with guanfacine include the potential for hypotension, bradycardia, syncope, sedation/somnolence, abdominal pain, dry mouth and constipation.

### 7.3 Major Safety Results

#### Study CLON-301

The overall incidence of AE's, irrespective of relationship to study medication was not higher in the active treatment groups and was not dose-related: approximately 83% of patients in each active group reported at least one AE, compared to 72% in the placebo group. The percentage of TEAEs judged by the investigator to be possibly or probably related to study drug were higher in the active treatment groups (62 to 70%) compared to the placebo treatment group (45%), but were not dose related.

**Table 11: Overview of Adverse Events in CLON-301**

	TREATMENT GROUP					
	CLON 0.2 mg N=76		CLON 0.4 mg N=78		PBO N=76	
AE CATEGORY <sup>1,2</sup>	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)
TEAEs	240	63 (82.9)	230	65 (83.3)	138	55 (72.4)
Related <sup>3</sup> TEAEs (ADRs)	135	53 (69.7)	139	48 (61.5)	60	34 (44.7)
SAEs <sup>4</sup>	0	0 (0.0)	0	0 (0.0)	0	0 (0.0%)
AEs Leading to Discontinuation	5	5 (6.6)	15	15 (19.2)	1	1 (1.3)

1. Subjects may be counted in more than one AE category.
2. This includes all AEs for subjects who were randomized and received at least one dose of study medication.
3. Relationship was determined by the Investigator.
4. There were no SAEs, and therefore, no deaths reported in this study.

#### Study CLON-302

The overall incidence of AEs, irrespective of relationship to study medication, was only slightly higher in the group treated with CLON+STM than in the group treated with PBO+STM (68% and 64%, respectively, reported at least one TEAE). The incidence of TEAE considered by the investigator to be possibly or probably related to study Drug were somewhat higher in the CLON+STM group than in the PBO+STM group: 45% of patients in the CLON+STM group reported at least one of the 100 AE's reported by the group, and 41% of patients in the PBO+STM group reported at least one of the 78 AE's reported by that group.

**Table 12: Overview of Adverse Events in Study 302**

	TREATMENT GROUP			
	CLON+STM N=102		PBO+STM N=96	
AE CATEGORY <sup>1,2</sup>	Events	Subjects n (%)	Events	Subjects n (%)
TEAEs	224	69 (67.6)	174	61 (63.5%)
Related <sup>3</sup> TEAEs (ADRs)	100	46 (45.1%)	78	39 (40.6%)
SAEs <sup>4</sup>	1	1 (1.0)	2	2 (2.1)
AEs Leading to Discontinuation	1	1 (1.0%)	4	4 (4.2%)

### 7.3.1 Deaths

There were no deaths in Study CLON-301 or CLON-302.

### 7.3.2 Nonfatal Serious Adverse Events

In Study CLON-301, there were no serious adverse events.

In Study CLON-302 there were three Serious Adverse Events (SAE's).

#### Patient 2702 (CLON+STM)

13 year old Hispanic male receiving CLON 0.2 mg daily and Concerta 54 mg/day took 3 additional doses (0.5 mg) of the study drug in the second week of study following an argument with sibling and mother. The subject reported this to his mother and was taken to his Primary care Physician (PCP) and was hospitalized. On interview following his discharge, it was determined that this behavior was consistent with previous behaviors and unrelated to study medication.

#### Patient 2907 (PBO+STM)

8 year old female on stable psychostimulant regimen of metadate hit another child with a board during week 4 of the study, while tapering off study medication because of lack of efficacy.

#### Patient 2908 (PBO+STM)

12 year old male on a stable psychostimulant regimen of Concerta 54mg/day and randomized to placebo who threatened his mother with a knife during week 2. The patient was hospitalized and discontinued from the study.

*Reviewer's Comments: None of these events classed as SAE's can be attributed to the effects of study medication.*

### 7.3.3 Dropouts and/or Discontinuations

#### Study CLON-301

In Study CLON-301, the number of patients who discontinued study due to an AE in the low dose (0.2 mg/day), high dose (0.4 mg/day) and placebo groups were 5(7%), 15 (19%), and 1(1%) respectively. In the 0.2 mg group, 3 (3.9%) subjects discontinued because of somnolence and 2(2.6%) discontinued because of fatigue. Among the 15 subjects who discontinued the study drug in the 0.4 mg group, the reasons were somnolence 5 (6.4%), formication 1 (1.3%), fatigue 4 (5.1), GI disorders (1 each of constipation and vomiting), rash 1 (1.3%), Prolonged QT 1 (1.3%) and increased heart rate 1 (1.3%).

**Table 13: Adverse Events Leading to Study Discontinuation CLON-301**

	TREATMENT GROUP		
	CLON 0.2 mg/day N=76	CLON 0.4 mg/day N=78	PBO N=76
PREFERRED TERM	Subjects n (%)	Subjects n (%)	Subjects n (%)
<b>TEAEs leading to discontinuation</b>	<b>5 (6.6)</b>	<b>15 (19.2)</b>	<b>1 (1.3)</b>
Somnolence	3 (3.9)	5 (6.4)	0
Fatigue	2 (2.6)	4 (5.1)	0
Formication	0	1 (1.3)	0
Constipation	0	1 (1.3)	0
Vomiting	0	1 (1.3)	0
Electrocardiogram QT Prolonged	0	1 (1.3)	0
Heart Rate Increased	0	1 (1.3)	0
Rash	0	1 (1.3)	0
Dizziness	0	0	1 (1.3)

#### Study CLON-302

Of the 198 subjects, 4 discontinued because of TEAE's. One subject in the CLON+STM group discontinued because of TEAE's.

**Table 14: Adverse Events leading to Study Discontinuation: Study CLON-302**

	TREATMENT GROUP	
	CLON+STM	PBO+STM
	N=102	N=96
	Subjects n (%)	Subjects n (%)
<b>PREFERRED TERM</b>		
Bradypnea	1 (1.0)	0
Aggression	0	2 (2.1)
Somnolence	0	1 (1.0)
Heart Rate Increased	0	1 (1.0)

Patient 2602 (CLON+STM) was a 16 year old white male on a stable psychostimulant regimen of Vyvanse 30 mg/day and randomized to the CLON+STM group and developed fatigue and slowed thinking during week 2 while on 0.2 mg CLON daily. He



also developed moderate dizziness on the first day of dosing with 0.3 mg daily of CLON during week 4. He reduced his dose and discontinued from further dosing, primarily because of slowed thinking. Symptoms resolved 5 days after discontinuing study drug.

Patient 2202 (PBO+STM) 13 year old white female experienced increase in heart rate while engaged in sports on her fourth day of dosing in the study. The event resolved on the same day, but she was discontinued from the study.

Patient 2908 (PBO+STM) 12 year old on Concerta who threatened his mother with a knife during week 2. Patient was hospitalized and treatment discontinued.

Patient 3203 (PBO+STM) 9-year old white male on stable psychostimulant regimen of Ritalin and Focalin, randomized to placebo who experienced moderate sleepiness, moderate hyperventilation, and moderate weakness in the knees on the third day of dosing. Each event resolved on the same day, but it was decided to discontinue the patient.

*Reviewer's Comments: I reviewed the narratives of all patients who discontinued in both studies. In Study CLON-301, the most common reason for discontinuation were somnolence and fatigue. Both of these are recognized AE's seen in therapy with clonidine. This AE can be adequately managed by education by the clinician and appropriate labeling.*

#### 7.3.4 Significant Adverse Events

##### Study CLON-301

Special event adverse events were classed as 'somnolence' (drowsiness, sleepiness sedation) and fatigue (fatigue and lethargy). Somnolence and fatigue each occurred in 59 patients and 23 patients respectively. 53% of subjects taking 0.2 mg experienced one of these after a mean duration of 9.8 days. 43% of subjects in the 0.4 mg group experienced one of these after a mean duration of 8.3 days whereas only 7.9% of

subjects in the placebo group experienced somnolence or lethargy. The duration (onset of first such TEAE to termination of last such TEAE) of one of these TEAEs was 25 to 30 days for all three treatment groups.

**Table 15: Special Event Adverse Event: Somnolence, sedation, fatigue and lethargy. Safety population: CLON-301**

Summary	Treatment Group		
	Clonice1 0.2 mg	Clonice1 0.4 mg	Placebo
Total Safety Subjects	76	78	76
Total Subjects with at least one Special Interest Adverse Event [1]	40 (52.6%)	33 (42.3%)	6 (7.9%)
Onset of Special Interest Adverse Event (days)			
N	40	33	6
Mean (Std)	9.8 (9.45)	8.3 (6.62)	12.7 (15.62)
Median	8.0	7.0	7.5
Min, Max	0, 56	0, 28	0, 41
Duration of Special Interest Adverse Event (days)			
N	40	33	6
Mean (Std)	29.6 (16.68)	25.2 (19.60)	27.8 (29.16)
Median	26.5	21.0	23.5
Min, Max	5, 64	1, 74	0, 80

## Study CLON-302

Somnolence occurred in 20 patients (20%) in the CLON+STM group and 8 patients (8%) in the PBO+STM group; fatigue occurred in 16% and 4% of these treatment groups, respectively. At least one of these two “Special Interest TEAEs” occurred in 33 patients (32%) in the CLON+STM group and in 11 (11.5 %) in the PBO +STM group. In the active group, the mean onset of either of these events was on Day 14, late in the second week of dose titration (when patients typically had been receiving 0.1mg b.i.d for at least several days). Mean onset of either of these TEAEs was on Day 9 for the placebo patients. The durations (onset of first such TEAE to termination of last such TEAE) of these TEAEs were 16 and 15 days, for the CLON+STM and PBO+STM groups, respectively. The incidence and occurrence of one of these events is not affected by choice of psychostimulant. The duration was longer in the PBO+MPH

subgroup than in the PBO+AMPH subgroup (18 days vs 9 days). However, the duration of the two CLON+STM subgroups are similar.

### 7.3.5 Submission Specific Primary Safety Concerns

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### Study CLON-301

Analyses of TEAEs by System Organ Class (SOC) revealed GI, Psychiatric and Nervous System disorders to be most common. TEAEs from one of these classes were reported by 36%, 33% and 30% of patients respectively. With the exception of constipation and dry mouth, GI disorders were not more common in the active treatment groups than in the placebo groups. Psychiatric disorders and nervous system disorders were more common in active groups than in placebo groups, but, overall, not dose-related. Somnolence occurred in 40%, 31%, and only 7% of patients in the 0.2 mg/day, 0.4 mg/day, and placebo groups respectively. Headache occurred in 30% of the 0.2 mg/day group, but in fewer patients in the 0.4 mg/day and placebo groups.

**Table 16: TEAEs with 2% or greater incidence CLON-301**

	TREATMENT GROUP		
	CLON 0.2 mg/day N=76	CLON 0.4 mg/day N=78	PBO N=76
<i>SYSTEM ORGAN CLASS Preferred Term</i>	<i>Subjects n (%)</i>	<i>Subjects n (%)</i>	<i>Subjects n (%)</i>
<b><i>GASTROINTESTINAL DISORDERS</i></b>			
Abdominal Pain Upper	15 (19.7)	13 (16.7)	14 (18.4)
Nausea	4 (5.3)	7 (9.0)	5 (6.6)
Vomiting	2 (2.6)	2 (2.6)	5 (6.6)
Diarrhoea	3 (3.9)	2 (2.6)	2 (2.6)
Constipation	1 (1.3)	5 (6.4)	0
Dry Mouth	0	4 (5.1)	1 (1.3)
<b><i>NERVOUS SYSTEM DISORDERS</i></b>			
Headache	23 (30.3)	16 (20.5)	15 (19.7)
Insomnia	4 (5.3)	5 (6.4)	1 (1.3)
Tremor	1 (1.3)	3 (3.8)	0
Abnormal Sleep-Related Event	2 (2.6)	1 (1.3)	0
<b><i>PSYCHIATRIC DISORDERS</i></b>			
Somnolence	30 (39.5)	24 (30.8)	5 (6.6)
Nightmare	3 (3.9)	7 (9.0)	0
Emotional Disorder	3 (3.9)	4 (5.1)	1 (1.3)
Aggression	2 (2.6)	1 (1.3)	1 (1.3)
Enuresis	0	3 (3.8)	0
Poor Quality Sleep	0	2 (2.6)	1 (1.3)
Tearfulness	1 (1.3)	2 (2.6)	0
Sleep Terror	2 (2.6)	0	0
<b><i>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</i></b>			
Cough	2 (2.6)	4 (5.1)	11 (14.5)
Pharyngolaryngeal Pain	6 (7.9)	6 (7.7)	3 (3.9)
Nasal Congestion	2 (2.6)	4 (5.1)	2 (2.6)
Rhinorrhoea	2 (2.6)	0	2 (2.6)
Epistaxis	2 (2.6)	1 (1.3)	0
<b><i>INFECTIONS AND INFESTATIONS</i></b>			
Upper Respiratory Tract Infection	10 (13.2)	6 (7.7)	6 (7.9)
Gastroenteritis Viral	5 (6.6)	3 (3.8)	3 (3.9)
Nasopharyngitis	3 (3.9)	2 (2.6)	1 (1.3)
Lower Respiratory Tract Infection	2 (2.6)	1 (1.3)	1 (1.3)
<b><i>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</i></b>			
Fatigue	12 (15.8)	10 (12.8)	1 (1.3)
Irritability	7 (9.2)	6 (7.7)	3 (3.9)
Influenza Like Illness	2 (2.6)	3 (3.8)	1 (1.3)
<b><i>CARDIAC DISORDERS</i></b>			
Dizziness	5 (6.6)	2 (2.6)	5 (6.6)
Bradycardia	0	3 (3.8)	0
<b><i>INVESTIGATIONS</i></b>			
Body Temperature Increased	4 (5.3)	2 (2.6)	2 (2.6)
Heart Rate Increased	0	3 (3.8)	0
<b><i>METABOLISM AND NUTRITION DISORDERS</i></b>			
Decreased Appetite	3 (3.9)	3 (3.8)	3 (3.9)
Thirst	1 (1.3)	2 (2.6)	0
<b><i>EAR AND LABYRINTH DISORDERS</i></b>			
Ear Pain	4 (5.3)	0	1 (1.3)
Otitis Media Acute	3 (3.9)	1 (1.3)	0
<b><i>IMMUNE SYSTEM DISORDERS</i></b>			
Asthma	2 (2.6)	1 (1.3)	1 (1.3)
Multiple Allergies	2 (2.6)	0	1 (1.3)
<b><i>SKIN AND SUBCUTANEOUS TISSUE</i></b>			

TEAEs with greater than 5% incidence or at least twice the incidence in placebo group is presented below in Table 17.

Somnolence (31 to 40% of patients in active groups), fatigue (13 to 16%), irritability (8 to 9%), insomnia (5 to 6%), and emotional disorders (4 to 5%) appeared to occur at greater frequency in the active groups compared with placebo (1 to 7%), but did not appear to be dose-related. Three common, but less frequent TEAEs demonstrated possible dose-related effects: nightmares, constipation, and dry mouth.

**Table 17: TEAEs with 5% or greater incidence in any active treatment group and at least twice the incidence of placebo.**

	TREATMENT GROUP		
	CLON 0.2 mg/day N=76	CLON 0.4 mg/day N=78	PBO N=76
PREFERRED TERM	Subjects n (%)	Subjects n (%)	Subjects n (%)
Somnolence	30 (39.5)	24 (30.8)	5 (6.6)
Fatigue	12 (15.8)	10 (12.8)	1 (1.3)
Irritability	7 (9.2)	6 (7.7)	3 (3.9)
Pharyngolaryngeal pain	6 (7.9)	6 (7.7)	3 (3.9)
Body Temperature Increased	4 (5.3)	2 (2.6)	2 (2.6)
Insomnia	4 (5.3)	5 (6.4)	1 (1.3)
Ear Pain	4 (5.3)	0	1 (1.3)
Emotional Disorder	3 (3.9)	4 (5.1)	1 (1.3)
Nightmare	3 (3.9)	7 (9.0)	0
Constipation	1 (1.3)	5 (6.4)	0
Dry Mouth	0	4 (5.1)	1 (1.3)

#### Study CLON-302

Headache was the most common AE in both treatment groups, occurring in 19 and 20 patients in the CLON+STM and the PBO+STM groups, (19% and 21%), respectively. Only four TEAEs met the criteria of an incidence of at least 5% in the CLON+STM group and at least twice the incidence of the PBO+STM group: somnolence, fatigue, increased body temperature and dizziness.

Somnolence occurred in 20 (20%) patients in the CLON+STM group and only 8 (8%) patients in the PBO+STM group. In this study, somnolence included all reports of sleepiness, drowsiness and similar verbatim terms as well as reports of “sedation”.

Fatigue (which included reports of lethargy, malaise and similar terms), occurred in 16 patients (16%) in the CLON+STM group and in only 4 patients (4%) in the PBO+STM group. The other two TEAEs that met the above criteria were less frequent: increased body temperature and dizziness each occurred in 5 patients (5%) in the CLON+STM group and 2 patients (2%) in the PBO+STM group.

Dry mouth occurred in only 1 patient (1%) in the CLON+STM group and in 2 patients (2%) in the PBO+STM group. Vomiting occurred in 8 patients (8%) in the PBO+STM group but in no patient in the CLON+STM group.

**Table 18: Treatment Emergent Adverse Events with 2% or Greater Incidence in Any Treatment Group by System Organ Class and Preferred Term (CLON 302 Safety Population)**

<i>SYSTEM ORGAN CLASS</i> <i>Preferred Term</i>	<b>Treatment Group</b>	
	<b>CLON+STM</b> <b>N=102</b>	<b>PBO+STM</b> <b>N=96</b>
	<b>Subjects</b> <b>n (%)</b>	<b>Subjects</b> <b>n (%)</b>
<b><i>NERVOUS SYSTEM DISORDERS</i></b>		
Headache	19 (18.6)	20 (20.8)
Insomnia	5 (4.9)	3 (3.1)
Tension Headache	0	2 (2.1)
<b><i>PSYCHIATRIC DISORDERS</i></b>		
Somnolence <sup>1</sup>	20 (19.6)	8 (8.3)
Affect Lability	3 (2.9)	2 (2.1)
Aggression	2 (2.0)	5 (5.2)
Anxiety	2 (2.0)	1 (1.0)
Nightmare	2 (2.0)	1 (1.0)
Emotional Disorder	2 (2.0)	0
Enuresis	2 (2.0)	0
<b><i>GASTROINTESTINAL DISORDERS</i></b>		
Abdominal Pain Upper	12 (11.8)	8 (8.3)
Abdominal Pain	2 (2.0)	1 (1.0)
Diarrhoea	2 (2.0)	4 (4.2)
Nausea	1 (1.0)	3 (3.1)
Dry Mouth	1 (1.0)	2 (2.1)
Vomiting	0	8 (8.3)
Oral Pain	0	3 (3.1)
<b><i>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</i></b>		
Nasal Congestion	9 (8.8)	6 (6.3)
Pharyngolaryngeal Pain	8 (7.8)	4 (4.2)
Cough	6 (5.9)	8 (8.3)
Epistaxis	3 (2.9)	1 (1.0)
Rhinorrhoea	3 (2.9)	0
<b><i>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</i></b>		
Fatigue <sup>1</sup>	16 (15.7)	4 (4.2)
Irritability	5 (4.9)	9 (9.4)
<b><i>INFECTIONS AND INFESTATIONS</i></b>		
Upper Respiratory Tract Infection	4 (3.9)	4 (4.2)
Gastroenteritis Viral	3 (2.9)	0

<b><i>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</i></b>		
Rash	4 (3.9)	2 (2.1)
<b><i>METABOLISM AND NUTRITION DISORDERS</i></b>		
Decreased Appetite	6 (5.9)	4 (4.2)
Increased Appetite	0	2 (2.1)
<b><i>INVESTIGATIONS</i></b>		
Body Temperature Increased <sup>1</sup>	5 (4.9)	2 (2.1)
Heart Rate Increased	0	4 (4.2)
<b><i>CARDIAC DISORDERS</i></b>		
Dizziness <sup>1</sup>	5 (4.9)	2 (2.1)
<b><i>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</i></b>		
Pain in Extremity	2 (2.0)	0
<b><i>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</i></b>		
Joint Sprain	0	2 (2.1)

<sup>1</sup> AEs with a 5% or greater incidence in the CLON+STM treatment group and at least twice the incidence of PBO+STM

### Treatment Emergent Adverse events by Dose

No analyses of TEAE vs dose was done.

### TEAE by severity

Three patients in each study group had TEAEs rated by the investigator as severe: 6 TEAEs in the CLON+STM group and 4 TEAEs in the PBO+STM group.

### TEAE by time

TEAE were classed by according to whether or not the event was present during any of the following three time periods: Day 0 to 21 (period of dose titration), Day 22-35 (stable dose regimen) and after Day 35 (period of down titration of study medication, generally through Day 56). The incidence of TEAEs was highest during the first time period and decreased during the last two periods for both treatment groups. In the CLON+STM group 51 of 102 patients (50%) reported a TEAE during the first time period and 32 of 102 (31%) and 25 of 95 (26%) reported TEAEs in the second and third time periods respectively. Similarly, for the PBO+STM group, 50%, 23% and 22% reported at least one TEAE in the first, second and third periods, respectively. In the CLON+STM group, somnolence decreased in the three time periods from 12% in the first period, to 8% in



the second period to 1% in the third period. The incidence of headache in this group (13%, 8% and 3%), fatigue (14%, 2% and 0%) and upper abdominal pain (8%, 4% and 0%) in these three periods, respectively, showed the same pattern. Similar patterns occurred in the frequency of reporting over time of the most common TEAEs in the PBO+STM group: headache (incidences of 12%, 9%, and 1% in the three time periods, respectively), upper abdominal pain (6%, 1%, and 1%) and somnolence (6%, 1% and 0%).

#### Most Common Treatment Emergent Adverse Events by ADHD Psychostimulant Use

Fifty nine patients received CLON+MPH, 59 patients received PBO+MPH, 43 patients received CLON+AMPH, and 37 patients received PBO+AMPH. The patterns of TEAEs in the CLON subgroups appear unaffected by the choice of stimulant administered.

#### **Table 19: Most Common (5% or Greater Incidence in a CLON+STM group) Treatment-Emergent Adverse Events by Concomitant ADHD Psychostimulant Use**

PREFERRED TERM	AMPHETAMINE		METHYLPHENIDATE	
	CLON+STM	PBO+STM	CLON+STM	PBO+STM
	N=43	N=37	N=59	N=59
	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)
Somnolence <sup>1</sup>	7 (16.3)	2 (5.4)	13 (22.0)	6 (10.2)
Headache	9 (20.9)	8 (21.6)	10 (16.9)	12 (20.3)
Fatigue <sup>1</sup>	9 (20.9)	2 (5.4)	7 (11.9)	2 (3.4)
Abdominal Pain Upper <sup>1</sup>	8 (18.6)	2 (5.4)	4 (6.8)	6 (10.2)
Nasal Congestion <sup>1</sup>	5 (11.6)	0	4 (6.8)	6 (10.2)
Pharyngolaryngeal Pain <sup>1</sup>	4 (9.3)	0	4 (6.8)	4 (6.8)
Cough	4 (9.3)	2 (5.4)	2 (3.4)	6 (10.2)
Decreased Appetite	3 (7.0)	2 (5.4)	3 (5.1)	2 (3.4)
Body Temperature Increased <sup>1</sup>	4 (9.3)	1 (2.7)	1 (1.7)	1 (1.7)
Irritability	4 (9.3)	3 (8.1)	1 (1.7)	6 (10.2)
Dizziness <sup>1</sup>	2 (4.7)	2 (5.4)	3 (5.1)	0
Insomnia	2 (4.7)	1 (2.7)	2 (3.4)	2 (3.4)
Rash	2 (4.7)	2 (5.4)	2 (3.4)	0
Upper Respiratory Tract Infection	1 (2.3)	2 (5.4)	3 (5.1)	2 (3.4)
Epistaxis <sup>1</sup>	2 (4.7)	0	1 (1.7)	1 (1.7)
Rhinorrhoea <sup>1</sup>	2 (4.7)	0	1 (1.7)	0
Gastroenteritis Viral <sup>1</sup>	2 (4.7)	0	1 (1.7)	0
Affect Lability	2 (4.7)	2 (5.4)	1 (1.7)	0
Abdominal Pain <sup>1</sup>	2 (4.7)	0	0	1 (1.7)

### Laboratory Findings

Clinical Laboratory values were obtained at Screening and at Week 8 visit (last day of study drug administration) or discontinuation visit if the patient was discontinued prior to end of study. Laboratory parameters included Chemistry (glucose, urea, creatinine, sodium, potassium, chloride, CO<sub>2</sub>, bilirubin, alkaline phosphatase, uric acid, calcium, albumin, serum HCG, TSH), Hematology (CBC with differential, MCV, MCHC), Urinalysis (pH, blood, protein, glucose, ketones and bilirubin) and Urine drug screen.

## Study CLON-301

Analyses of these results did not reveal significant abnormalities in any patient on active treatment or other evidence of a drug effect on these laboratory parameters. One patient (0717), in the placebo group, had elevated TSH values at Screening which rose during the study at Week 8 (6.46 uIU/mL at Screening and 9.37 uIU/mL at Week 8; upper limit of normal = 4.20 uIU/mL). Following review of the Week 8 laboratory results, the patient was referred to an endocrinologist for further evaluation and was subsequently diagnosed with hypothyroidism for which he began treatment.

One patient on CLON 0.2 mg had an elevation in TSH at Week 8 (3.66 uIU/mL at Screening compared to 6.05 uIU/mL at Week 8; upper limit of normal = 4.20 uIU/mL). The patient went on to enroll in the CLON-303 open-label continuation study and received 6 months of open label treatment. Five months after completing the open-label study, a repeat TSH level was obtained with a result of 4.27 uIU/mL.

## CLON-302

Four patients receiving CLON+STM had possible clinically significant laboratory abnormalities.

Two children (3803 and 4301) had urinalyses results suggestive of urinary tract infections (UTIs). Neither child was symptomatic. Repeat urinalysis for both patients was later performed without UTI therapy and results were normal.

Patient 3604 had a small drop in hematocrit from a low normal value of 38.2% at Screening to a below-normal value of 36.8% at Week 8. Hemoglobin and red cell counts remained just within normal limits. Repeat complete blood count is planned. A TEAE of “anemia” was reported.

Patient 2308 had a Screening white blood cell (WBC) count of  $5.0 \times 10^9/L$  (normal) with a neutrophil count of  $1.35 \times 10^9/L$  (low). At Week 8 the WBC count was  $3.3 \times 10^9/L$  (low) but the differential was not performed; thus the neutrophil count was unknown. The Investigator requested that the subject return for a repeat CBC with differential; however, attempts to contact the subject were unsuccessful.

*Reviewers Comments: These findings were confirmed by this reviewer on a detailed review of data submitted by the sponsor. There were no signals suggestive of a treatment related effect on any of the laboratory parameters. This reviewer is of the opinion that use of clonidine in this population did not show any effect on the laboratory parameters.*

#### 7.4.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate and body temperature) were collected at Screening, Baseline prior to dosing, at weekly on-therapy visits and at closeout visits. Vital signs were measured with the subject in a sitting position and resting for at least two minutes prior to taking the measurement. The dominant arm was used for blood pressure and heart rate measurements.

##### 7.4.3.1 Blood pressure

##### Study CLON-301

Changes from baseline in Systolic Blood pressure (SBP) were dose related. Mean Systolic BP decreased from baseline values by upto 1.5 mm Hg during weeks 2 through 5 in the 0.2 mg/day group and by upto 6 mm Hg during weeks 2 through 5 in the 0.4 mg/day group. The mean change from weeks 2 to 5 was -0.7 mmHg in the 0.2 mg/day group and -4.58 mmHg in the 0.4 mg/day group. The minimum and maximum observed SBP in the 0.2 mg/day group were 80 mm Hg and 139 mm Hg respectively. In the 0.4

mg/day group, the minimum and maximum observed SBP were 72 mm Hg and 143 mm Hg respectively. In the placebo group, the minimum and maximum observed values were 82 mm Hg and 147 mm Hg respectively.

Mean Diastolic Blood pressure (DBP) changed from Baseline values with increases of about 0.5 mm to decreases of about 2 mm during Weeks 2 through 5 in the 0.2 mg/day group. Mean DBP decreased about 4 to 5 mm Hg during Weeks 2 through 5 in the 0.4 mg/day group and increased about 0.5 to 1.5 mm Hg at most time points in the placebo group. The mean change from weeks 2 to 5 was -1 mm Hg for the 0.2 mg/day group and -4.38 mmHg for the 0.4 mg/day group. The minimum and maximum observed DBP in the 0.2 and 0.4 mg/day groups were 41 mm Hg and 84 mm Hg respectively. In the 0.4 mg/day group, the minimum and maximum observed values in the low and high dose groups were 40 and 89 respectively. In the placebo group, the minimum and maximum observed values were 48 mm Hg and 117 mm Hg respectively.

Overall, the placebo-subtracted mean changes in blood pressure ranged from -2.2 mmHg on Tradename 0.2 mg/day to -6 mmHg on Tradename 0.4 mg/day. The placebo subtracted mean change in diastolic pressure was -2 mmHg on Tradename 0.2 mg/day to -5.4 mmHg on Tradename 0.4 mg/day.

#### Study-CLON-302

Mean changes in blood pressure were modest in the active treatment group. Mean SBP decreased about 4 to 5 mm Hg from Baseline values during weeks 2 through 5 in the CLON+STM group and increased about 1 mm Hg during most time points in the PBO+STM group. The minimum and maximum observed values in the low and high dose groups in SBP were 64 and 145 respectively in the CLON+STM group and 59 and 147 in the PBO+STM group.

Mean DBP decreased about 1 to 4 mm Hg during Weeks 2 through 5 in the CLON+STM group compared with no change or 1 mm of Hg increase in the PBO+STM group at most time points. The minimum and maximum observed DBP in the 0.2 and 0.4 mg/day groups were 42 mm Hg and 108 mm Hg respectively. In the PBO+STM group, the minimum and maximum observed values in the low and high dose groups were 44 and 113 respectively.

#### 7.4.3.2 Heart Rate

##### CLON-301

Mean heart rate generally decreased from Screening values by 3 to 4 beats per minute (bpm) during weeks 2 through 5 in the 0.2 mg/day group and decreased by about 5 to 6 bpm in the 0.4 mg/day dose group. The mean change in heart rate from weeks 2 to 5 was -2.5 bpm in the clonidine 0.2 mg/day and -5 bpm in the 0.4 mg/day groups. The change in the placebo group was -0.76 bpm. The placebo-subtracted change in heart rate was -3.25 to -5.75 bpm in the 0.2 mg/day and 0.4 mg/day groups respectively. The minimum observed heart rate was 46 and the maximum rate was 117 bpm on 0.2 mg/day of clonidine. On 0.4 mg/day, the minimum and maximum rates were 47 and 120 respectively. In the placebo group, the minimum and maximum observed heart rates were 55 and 103 respectively.

##### CLON-302

Mean heart rate decreased from Baseline by 4 to 5 beats per minute (bpm) in the CLON+STM group compared with increases of 1 to 3 bpm at most time points in the PBO+STM group. The minimum and maximum heart rates in the CLON+STM treatment group was 50 and 125.

#### 7.4.3.3 Body temperature

#### CLON-301

There were no meaningful changes in body temperatures between any of the three treatment groups.

However, 4 subjects in the CLON 0.2 mg group, 2 subjects in the 0.4 mg/day group and 2 subjects in the placebo group developed increased body temperatures. All the readings returned to normal levels by the next visit and the increased temperatures were thought to be not related to study drug.

#### CLON-302

There were no meaningful changes in Body Temperature in either treatment group. Five patients in the CLON+STM group and 2 patients in the PBO+STM group had TEAEs of increased body temperature. None were considered possibly related to study drug. All but one report of increased temperature (in the PBO+STM group) were associated with a reported infection.

#### 7.4.4 Electrocardiograms (ECGs)

Twelve-lead ECGs were obtained at the Screening visit and repeated 3 times at 10 minute intervals; an average reading was used for screening purposes. A single reading was obtained at the Baseline visit unless otherwise indicated. In addition, ECGs were collected at Days 7, 14, 28, 42, and 56 (Weeks 1, 2, 4, 6, and 8 visits) and at the Week 9 (Safety Follow- Up/Close-out) visit.

#### CLON-301

A total of 745 ECG readings were obtained from subjects in the CLON 0.2mg/day group, 773 from subjects in the CLON 0.4mg/day group, and 749 from subjects in the placebo group. ECGs were obtained three times at Screening and once at Baseline (from which four ECGs, the Screening/Baseline average values were obtained), one

time during each on-therapy visit at Weeks 1, 2, 4, 6 and 8, and one ECG on the week 9 closeout visit. Week 4 visits represent the ECG assessment visit at which maximum doses were given. Investigators were allowed to obtain additional ECGs at their discretion. I have separately analysed these findings under heart rate and QT intervals.

Heart Rate: Bradycardia was defined as a heart rate less than 55 bpm for ages 6 to 11 and less than 50 for ages 12 to 17. Tachycardia was defined as a heart rate more than 134 for children aged 6 to 11 or >119 for children aged 12 to 17.

At baseline/screening, the incidence of sinus bradycardia in the low dose, high dose and placebo groups were 12%, 4%, and 7% respectively; during therapy, these increased to 18%, 25% and 12% respectively.

Subject 0605 in the CLON 0.4 mg group had one reading of HR at 48 at week 4. This returned to normal by the next week.

Subject 0609 had one reading of HR at 53 and two subsequent readings at 52.

Subject 0707 had one reading of 55 at week 1.

None of these patients reported TEAE's of symptoms associated with symptomatic bradycardia. All of these were considered related to study medication.

At baseline/screening, the incidence of tachycardia was made in 4%, 1% and 3% of patients in the low, high and placebo groups respectively. During drug therapy, the incidences of this diagnosis were 4%, 5% and 3% respectively.

Three patients were reported to have sinus tachycardia.

Subject 0609 had a reading on HR at 115 at week 9.



Subject 0614 had three readings at week 1 which were 108, 104 and 109. Patients ECG's were also abnormal and hence study medications were stopped. However, patient received cardiology overread after patient had been off drug for 10 days. The readings were normal, but medical monitor felt that patient had been off drug for too long and was hence felt to be inappropriate to start him back on the study drug.

Subject 0647 in the 0.4 mg group had HR readings >115 with a maximum reading of 126 at week 8. Subject had a 'stomach virus'.

#### ECG changes- QTc Values

No patient had an on-therapy QTcB or QTcF result of 500 msec or greater.

There were no differences in incidence of increase of QTcB or QTcF of 30 msec or less between active and placebo groups. The incidence of increases in QTc of 30 msec to 60 msec were 17%, 20.5%, and 26% for QTcB and 9%, 17% and 9% for QTcF in the low dose, high dose and placebo groups, respectively.

Three patients had QTc values which increased from Screening/Baseline averages by at least 60 msec while on therapy with study medication.

Subject 0715 in the low dose group had average baseline/screening QTcF and QTcB of 399 and 409 msec respectively that rose while patient was on only 0.1 mg/day to 466 msec and 494 msec respectively. On 0.2 mg dose the next week, the values returned to baseline/screening levels. The patient was discontinued. However, the reason for discontinuation was fatigue.

Patient 0618 had average baseline/screening QTcF and QTcB of 398.5 msec and 404 msec, which rose at week 4, while on 0.4 mg/day to 467 msec and 480 msec

respectively. The patient was discontinued. The reason for discontinuation was the AE of prolonged QT.

Patient 0928 had baseline/screen QTcB mean reading of 403.8, which increased at week 6 to 468.0. QTcF at screen was 408.3 and increased at week 6 to 443. Both these had returned to baseline values by week 8.

#### Study CLON-302

A total of 1041 ECG readings were obtained from subjects in the CLON+STM group and 944 from subjects in the PBO+STM group. ECGs were obtained three times at Screening, once at Baseline (from which initial 4 ECGs the Screening/Baseline average values were obtained), one time during on-therapy Weeks 1, 2, 4, 6 and 8, and one ECG at the week 9 closeout visit. Week 4 visits represent the ECG assessment visit at which maximum doses could be given. Investigators were allowed to obtain additional ECGs at their discretion.

Heart rate decreases were consistent with the pharmacologic effect of clonidine. The mean Heart rate decreased by about 7 beats per minute (bpm) in the CLON+STM group compared to decreases of less than 1 bpm in the PBO+STM group.

Corrected QT in the CLON+STM group showed small or no change from Screening/Baseline values when compared with changes in the PBO+STM group.

QTcB *decreased* by 2.5 msec and QTcF *increased* by 3 msec in the CLON+STM group compared with a 2 msec *increase* in QTcB and a 1 msec *increase* in QTcF in the PBO+STM groups. These small changes do not suggest an effect of active treatment on QTc. Changes in QRS and PR intervals were minimal. QRS intervals increased by less than 1 msec in both treatment groups and PR interval increased about 1 msec in both treatment groups.

No patient in the study had a QTcF of 450 msec or more, and no patient had a QTcB of 475 msec or more. For changes in either QTcB or QTcF, there were no suggested differences between the CLON+STM and PBO+STM groups in the incidence of individual increases from average Screening/Baseline to any on-therapy value of QTcB or QTcF of 30 msec or less, of more than 30 msec to 60 msec, or of greater than 60 msec.

One patient in the PBO+STM group had an increase of QTc of >60 msec. Subject 3806 in the PBO+STM group had QTcB screen value of 374.5 and QTcF of 366. At the week 2 ECG, the QTcB value was 445 msec, which is a shift of 70.5 msec. The QTcF value was 407, which was a shift of 41 msec. The shifts at week 4, 6, 8 and closeout on QTcB were 26.5, 35.5, 30.5 and 54.5 and on QTcF were 21, 20, 17 and 34 respectively. The patient completed the study.

*Reviewer's Comments: This reviewer is of the opinion that monitoring done with regards to vital signs were adequate. In both the studies, changes in blood pressure were noted. Changes from baseline in Systolic Blood pressure (SBP) were dose related, with mean Systolic BP decreasing from baseline values by upto 1.8 mm Hg 0.2 mg/day group and by 5 to 6 mm Hg in the 0.4 mg/day group. Mean Diastolic Blood pressure (DBP) decreased about 4 to 5 mm Hg.*

*No subjects had QTc>500. Three subjects in the monotherapy group had an increase in QTc>60 msec while on therapy and one had to be discontinued from the trial. This reviewer discussed the case with the QT team who suggested that no further consult was warranted at this time.*

#### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were done.

#### 7.4.6 Immunogenicity

No data on immunogenicity was submitted.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Overall, the incidence of patients with a TEAE is higher in the active groups than placebo, although there is not a relationship with dose. The numbers and incidences of patients with TEAEs are 63 (83%), 65 (83%) and 55 (72%) in the low dose, high dose and placebo groups respectively. There were 240, 230 and 138 TEAEs in each of these groups, respectively.

#### 7.5.2 Time Dependency for Adverse Events

Time dependency was evaluated by noting if the event was present during any of the following three time periods: Day 0 to 21 (period of upward dose titration, achieved on Day 7 for the low dose group, achieved on Day 21 for the high dose group), Day 22-35 (stable maximum dose) and after Day 35 (period of down titration, generally through Day 56).

Overall, the incidence of TEAEs was slightly higher during the first time period and similar during the last two periods. For all patients in the study, TEAEs occurred in 129 of 230 (56% of patients) during the first time period; in 102 of 223 (46% of patients) in the second time period, and in 98 of 211 (46% of patients) in the third time period. The pattern of relatively higher reporting of TEAEs during the first time period was strongest for the high dose group which reported TEAEs in 62%, 45% and 50% in the first, second and third time periods, respectively, and weakest for the placebo group which reported TEAEs in 42%, 37% and 35% of patients in these three time periods, respectively. In particular, the high dose group reported a much higher rate of

somnolence (24%) during the first period than during the later two periods, (11% and 3%, respectively). Headache also followed a strong pattern of decreasing frequency with time in the high dose group. The low dose group showed similar, but less striking reductions in somnolence and headache with time. The placebo group tended to report fewer headaches and more cough in the third time period than in earlier time periods.

### 7.5.3 Drug-Demographic Interactions

No such analyses was conducted.

### 7.5.4 Drug-Disease Interactions

No analyses conducted.

### 7.5.5 Drug-Drug Interactions

Adverse events related to interactions between clonidine and methylphenidate are of special interest as this is a commonly used regimen and the sponsor is seeking such an indication in this NDA. The label of methylphenidate contains the statement: "Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination has not been systematically evaluated."

The proposed label of clonidine in section 7.5 (b) (4) ) reads:

(b) (4)

There have been concerns raised in the literature about the potential for interaction between clonidine and methylphenidate. These were from four reports of life-

threatening or fatal cases in children. This was published in a paper by Robert Fenichel in 1995. The four cases are described below:

A 6 year old boy was treated with methylphenidate for 2 months. Ten days after the addition of clonidine, he experienced a sudden onset of dizziness and pallor. He was found to have a blood pressure of 40/20 and a heart rate of 30 bpm. Clonidine was discontinued and he recovered uneventfully following overnight treatment with i.v. fluids.

A 7-year old boy, treated with clonidine and methylphenidate for over a year, complained of abdominal pain and then had a cardiac arrest. He had been born prematurely and had required neonatal intensive care. Autopsy revealed extensive fibrotic scarring of the heart involving the mitral papillary muscles and left ventricle, and death was attributed to cardiac complications of severe perinatal hypoxia.

A 8-year old girl, treated with methylphenidate for over 2 years and clonidine for 3 months, experienced protracted vomiting twice after general anesthesia. One week later she awoke in the morning, vomited and collapsed. Blood analysis found no clonidine or methylphenidate. The cause of death was unknown.

A 9-year old boy with multiple neuropsychiatric problems was being treated with methylphenidate, clonidine, fluoxetine and promethazine. He complained of headache and nausea, had a grand mal seizure, and 4 hours later had three more grand mal seizures and 4 hours later had three more grand mal seizures and a cardiac arrest. Autopsy showed that plasma levels of fluoxetine, as well as promethazine were extraordinarily high. The death was attributed to intentional overdose.

In study CLON-302, the overall incidence of AE's was only slightly higher in the group treated with CLON+STM than in the group treated with PBO+STM (68% and 64% respectively).

There were no deaths and one serious or severe TEAE's leading to discontinuation from the study in the CLON+STM group and 4 in the PBO+STM group.

The single serious TEAE in the CLON+STM group involved an intentional overdose of three tablets of study medication and was termed as 'attention-seeking behavior'. Study medication was restarted and the child completed the study without further events.

The severe TEAEs in the CLON+STM group included one child who developed three severe TEAEs during Week 7 of the study: "memory disorder" (a single 5-10 minute episode of "zoning out" with loss of memory), an episode of anger, and "movement disorder" (increased mouth noises for a day). One child in the CLON+STM group developed severe fatigue and severe "bradyphrenia" (slow thinking) associated with moderate dizziness. Another patient in this group reported a severe sore throat.

The one patient in the CLON+STM group who discontinued study drug because of a TEAE, was the patient with severe bradyphrenia and fatigue, noted in the preceding paragraph.

The Division of Psychiatry products also requested that the Division of Pharmacovigilance I (DPV I) search the Adverse Events reporting System (AERS) database for cases of death associated with combination. The review concluded that

*'Based on the data reviewed, in the absence of published or other data that points to risk for adverse events, we recommend updating the current methylphenidate and dexamethylphenidate labels to remove the drug interaction statement regarding methylphenidate and clonidine.'*

*Reviewer's Comments: In all of the three fatalities described in the literature, the presence of multiple contributing factors precludes attributing the deaths to clonidine, methylphenidate, or the combination. The one case of the 6-year old boy, can be explained by the fact that clonidine can lower blood pressure and heart rate, and not necessarily to the combination.*

*Study CLON-302 did not find significant differences between the CLON+STM and PBO+STM groups in AE's except somnolence (18.6% vs 7.3%), fatigue (13.7% vs 4.2%) and dizziness (4.9% vs 1%). Of the subjects who experienced dizziness, the differences were in the group that was treated with clonidine+methylphenidate (3 subjects with dizziness compared to 0 in the PBO+STM group).*

*Treating patients with a combination of TRADENAME and stimulants has been shown to be well tolerated. I would hence recommend that the language regarding the possibility of serious adverse interactions between clonidine and methylphenidate be removed from the label of methylphenidate.*

*At this time, there is no reason to conclude that the combination of clonidine and methylphenidate has any additional safety concerns.*

## **7.6 Additional Safety Evaluations**

### **Study CLON-303**

**An open-label, chronic exposure evaluation of the safety of CLONICEL® (clonidine HCl sustained release) in the treatment of children and adolescents with ADHD.**

This was a 12-month, multi-center, open-label study of the safety of a flexible dosing regimen of clonidine in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD. Candidates for enrollment in this study were subjects who completed Study CLON-301 or Study CLON-302, were good candidates for continued treatment with clonidine in the opinion of the Principal Investigator, and expressed the desire to do so. Approximately 350 subjects were targeted for enrollment in this chronic dosing study, but the actual final number was dependant on the percent of patients in CLON 301 and CLON-302 who elected to continue treatment with clonidine. Dosing started at 0.1 mg/day (given in the evening) and a proper titration schedule was used to escalate



patients to a maximum of 0.4 mg/day, given as 0.2 mg b.i.d. Subjects were maintained at the maximum tolerated dose for up to 12 months when they were gradually tapered off treatment. Treatment was discontinued for subjects who could not tolerate a minimum of 0.1 mg/day. In addition to treatment with clonidine, patients could also receive treatment with other medications for their ADHD symptoms, including stimulants and/or antidepressants.

During the review cycle, the sponsor submitted the complete study report for this study. Results: A sample size for enrollment was not determined; enrollment depended on the number of subjects from CLON-301 and CLON-302 who elected to continue treatment in CLON-303.

A total of 303 subjects were enrolled in CLON-303 and their status is as follows:

**Table 20: Disposition of Study Subjects in CLON-303**

	CLONICEL <sup>1</sup>
Planned, N	350
Enrolled, N	303
Final Dataset, N	301
Efficacy Evaluable, N	290
Safety Population <sup>1</sup> , N	301
Completed Original Protocol (6 months), n (%)	53 (17.6)
Completed Amendment 1 (12 months), n (%)	108 (35.9)
Discontinued Prematurely <sup>2</sup> , n (%)	140 (46.5)
Withdrew Consent	45 (15.0)
Adverse Event	18 (6.0)
Lack of Efficacy	16 (5.3)
Lost to Follow-up	37 (12.3)
Protocol Violation	15 (5.0)
Other <sup>2</sup>	9 (3.0)

#### Exposure:

For the 301 subjects included in the Study CLON-303 Safety Population, exposure was calculated by including time on active treatment in the prior double-blind study (CLON-301 or CLON-302). With prior double-blind exposure included, 215 subjects (74.1%) received clonidine for  $\geq 24$  weeks and 113 subjects (37.5%) received clonidine for  $\geq 48$  weeks .

**Table 21: Overview of Treatment-Emergent Adverse Events in Study CLON-303 (Safety Population)**

Summary	All Subjects
Total Safety Population, n	301
Subjects with one or more TEAEs, n (%)	246 (81.7)
Total Number of TEAEs, n	954
Subjects with one or more Related <sup>1</sup> TEAEs (Adverse Drug Reactions), n (%)	178 (59.1)
Total Number of Related <sup>1</sup> TEAEs (Adverse Drug Reactions), n	438
Subjects with one or more Serious Adverse Events, n (%)	2 (0.7)
Total Number of Serious Adverse Events, n	2
Subjects with one or more Adverse Events Leading to Discontinuation <sup>2</sup> , n (%)	17 (5.6) <sup>2</sup>

Deaths: There were no deaths in the program.

Serious Adverse Events: There were 2 serious adverse events in the 215 patients in the safety program. One was an episode of cellulitis associated with second-degree burns incurred in a motor bike accident that was unlikely due to a relationship with the study drug. The other was an event of suicidal behavior, which was not associated with clinical signs or symptoms of a large overdose.

Discontinuations: Eighteen patients (5.6%) discontinued because of a TEAE. These included three patients with somnolence, two with headache and one each with anger, depressed mood, auditory hallucinations, self mutilation, fatigue, irritability, dizziness QT prolongation, sleep terror, abdominal pain, stomach discomfort and suicidal behavior (also an SAE).

Treatment Emergent Adverse Events: The most common TEAEs were expected adverse events of clonidine or common adverse events expected of the population.

**Table 22: Common Treatment Emergent Adverse Events –Study CLON 303**

Preferred Term, n (%)	All Subjects (N=301)
Somnolence	96 (31.9)
Headache	49 (16.3)
Upper Respiratory Tract Infection	39 (13.0)
Abdominal Pain Upper	37 (12.3)
Fatigue	37 (12.3)
Irritability	28 (9.3)
Insomnia	28 (9.3)
Cough	25 (8.3)
Decreased Appetite	25 (8.3)
Body Temperature Increased	22 (7.3)
Gastroenteritis Viral	20 (6.6)
Nasal Congestion	18 (6.0)
Vomiting	17 (5.6)
Pharyngolaryngeal Pain	16 (5.3)

There were no changes in chemistry or hematology values over time to suggest a drug effect. Vital sign assessments revealed that changes in blood pressure and heart rate appeared to be drug related and consistent with the known pharmacology of the drug.

During the course of the study, 4 subjects reported TEAEs consistent with hypotension, 4 reported TEAEs related to increases in heart rate, and 1 subject reported a TEAE related to dyspnea. None of these events were serious, severe, or resulted in discontinuation, and each event resolved.

ECG-recorded decreases in heart rate were consistent with the known pharmacology of clonidine. Heart rate decreased by a mean of 8-10 bpm at most time points. Mean weight increased during the study, probably reflecting the expected growth of children during the long-term study.

Mean body weights increased by 0.9 kg at the Month 2 visit, 2.1 kg at the Month 6 visit and 4.5 kg at the Month 12 visit.

There were 4 TEAEs that appeared to be related to ECG findings. All four patients, 0418, 0703, 0714 and 0721, were reported to have TEAEs of QT prolongation. All four TEAEs were considered mild and possibly related to study drug. One of these patients, 0418 was discontinued because of the TEAE. The other patients continued on therapy without dose adjustment.

**Patient 0418** was a 7 year-old white female whose pre-dosing ECGs in both CLON-301 and CLON-303 demonstrated higher-than-normal QTcB/QTcF values (average of four assessments in CLON-301 = 462/458 msec and a single assessment in CLON-303 = 472/448 msec, compared with upper limits of 449/449 msec). The values remained little changed throughout CLON-301 and 4 months into CLON-303. Three weeks later, the values rose on repeated ECGs: QTcB values varied between

499 and 532 msec; QTcF values varied between 496-520 msec. There were no large changes in heart rate to explain these latest changes in QTc.

The PI contacted the Sponsor's Medical Monitor at that time, leading to the patient's discontinuation from the study. Five days later, the QTc values were similar to those throughout the study (but remained higher than normal age-related values).

The patient was referred to a cardiologist who confirmed post-study elevated QTc values of 460-480 msec (correction factor not provided), which he considered "borderline elevations". Exam and family history were not revealing, and the patient is being followed by the cardiologist without restrictions. The Investigator considered the event mild and possibly related to study drug.

**Patient 0703** was a 10 year-old white male who experienced a one-time QTcB/QTcF elevation on the last day of dosing (Month 6).

The patient had completed CLON-301 study after randomization to the 0.4 mg daily dose group. In that study the average QTcB/QTcF on four pre-dosing ECGs were 424/412 msec (highest QTcB/QTcF were 443/427 msec). Heart rates were 65 to 74 bpm. The single Baseline QTcB/QTcF values in CLON-303 were considerably lower, 403/399 msec. The child was titrated up to 0.3 mg daily in CLON-303, and took this dose on most days of the trial.

There was little change in QTcB/QTcF values during the study until the patient's final Month 6 visit when he had been tapered down to 0.1 mg daily. ECG on that day demonstrated QTcB/QTcF values of 462/433. Heart rate, which had ranged between 53 to 79 bpm at prior visits, was higher (88 bpm) at Month 6, which may have contributed to the one-time increase in QTc.

A week after the last dose, ECG values (QTcB/QTcF and heart rate) were similar to those at Baseline.

The Investigator considered the event to be mild and possibly related to study drug.

**Patient 0714** was a 9 year-old white female whose Month 6 ECG (the patient's scheduled final visit) showed an abnormal elevated QTcB/QTcF of 452/401 msec (normal range up to 449/449 msec). The patient had received 0.3 mg for the last 2 ½ months of treatment; she received 0.1 mg on the day of the 6 month visit. A TEAE of "Prolonged QT" was reported. The Investigator considered the event to be mild and possibly related to study drug. However, this value was similar to (even slightly less than) the abnormal CLON-303 Baseline values of 453/409 msec. QTcB/QTcF values a month after final dosing were normal. All other QTcB/QTcF values during the study were normal, as were all Baseline and on-therapy values obtained during the CLON-301 study (0.2 mg dosing group). Thus the event did not represent a true change from Baseline.

**Patient 0721** was an 11 year-old white female who had an abnormal QTcB at Week 2 while receiving 0.2 mg per day of study drug. QTcB/QTcF values were 456/405 msec. Baseline values were similar: 443/412 msec. A TEAE of mild QT prolongation, possibly related to study drug, was reported. Week 3 and 4 QTcB/QTcF values (on 0.3 mg study drug daily) were 458/426 msec and 447/412 msec, respectively. The TEAE was considered resolved at Week 4.

The patient was discontinued for lack of efficacy a month later. A final ECG, obtained 2 weeks after final dosing demonstrated QTcB/QTcF values of 392/371 msec.

In the CLON-301 study, the patient had been randomized to the 0.2 mg/day dosing group. All QTcB/QTcF values in that study were normal, without evidence of drug related effects.

*Comments: The exposure to clonidine in this study satisfies the ICH recommendations. The results from CLON-303 are consistent with the known pharmacology of the drug and its mechanism of action. The safety profile is similar to results obtained from the controlled trials. There are no new safety signals identified.*

#### 7.6.1 Human Carcinogenicity

No data on carcinogenicity was submitted

#### 7.6.2 Human Reproduction and Pregnancy Data

No reproduction or pregnancy data was submitted

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment of effects on growth was conducted.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were two cases of overdose in the clinical program. One of them was in study CLON-302 and the other was in study CLON-303.

##### Overdose in Study CLON-302

**Patient 2702:** A 13 year old Hispanic male receiving 0.2 mg CLON daily (0.1 mg b.i.d) and Concerta (methylphenidate) 54 mg/day took 3 additional doses of the study drug during the second week (receiving a total of 0.5 mg), after an argument with sibling and mother. He reported this event to his mother the following morning and was taken to his primary care physician, complaining of a stomach ache and feeling anxious since taking the extra medication. He was admitted to the hospital for a suspected suicide attempt. Study medication was temporarily held, although he was continued on Concerta 54

mg/day and received clonidine immediate release 0.2 mg daily on two of his three days in the hospital.

The Investigator met with the child and mother on the day of hospital discharge, and after the interview and review of hospital and prior records, was convinced that the event “did not appear premeditated, related to depression, or sincere desire to do himself harm.” The Investigator noted that the child had a documented history of impulsive behavior and he strongly believed that the event was “attention-seeking behavior”, consistent with previous behaviors and unrelated to study medication. Study medication was restarted that day at 0.1 mg daily and was eventually titrated to 0.4 mg daily. The child completed the study without further adverse events.

#### Overdose in Study CLON-303

**Patient 1105:** A 14-year old white male who was diagnosed with ADHD, combined type, had completed study CLON-301 (0.2 mg daily dose group) and was enrolled in CLON-303 a week later. He was titrated up to 0.2 mg twice daily with good response to treatment with much improved ADHD symptoms.

At the Month 3 visit, 140 tablets (0.1 mg tabs) of study medication were dispensed. That same evening, the patient reported that he had ingested all 140 tablets (a potential 14 mg dose in this 65 kg child). Empty study drug containers were found at home. The event apparently occurred following a disagreement with the patient’s girlfriend. He was evaluated that evening in the emergency room and admitted to the hospital intensive care unit (ICU) for psychiatric observation.

The child was given charcoal in the ambulance but it was not known whether pill fragments were recovered. On subsequent stomach lavage, no pill fragments were found. The child experienced no clinical sequelae and vital signs were stable and no intervention was required for blood pressure or heart rate. There was some skepticism



by hospital personnel regarding the reported amount of drug ingested, given the lack of signs or symptoms of a large overdose. According to the child's father the child had remained awake following the overdose until 1:15am and then fell asleep, and experienced drowsiness during the two days following the overdose but was oriented to date and time.

The child was transferred to a psychiatric facility, and was reported to have been started on Prozac, and was initially very hyperactive, but calmed down. The child was physically stable and was doing well six weeks after the event.

Thus, important details regarding whether an actual overdose occurred, the state of mind of the subject at the time of the event, diagnoses and follow up care remain unknown. The event was considered by the Investigator to be moderate in severity and probably not related to study medication.

Abuse potential wasn't studied.

## **7.7 Additional Submissions / Safety Issues**

None

## **8 Postmarketing Experience**

JENLOGA has not been marketed since approval.

## **9 Appendices**

### **9.1 Literature Review/References**

The sponsor has submitted a review of the literature in support of the efficacy of clonidine in treating symptoms of ADHD. An review of the literature from 1980 to 1999 (Connor et al., 1999) revealed 39 publications that reported on clonidine's efficacy and side effects for symptoms of ADHD and coexisting conditions in children. Of these, 11 studies provided sufficient information to be included in a meta-analysis.

A total of 150 patients received clonidine in these 11 studies. The mean ages in the studies ranged from 8 to 16 years. The dose of clonidine averaged 0.18 mg/day with a range of 0.10 to 0.24 mg/day. The average duration of treatment was 11 weeks with a range of 3 to 51 weeks. Using the most conservative approach of determining effect sizes, the authors found that clonidine demonstrated positive treatment effects on symptoms of ADHD in all 11 studies, with parents reporting more benefits than teachers or clinicians, probably due to clonidine's main effects on behavior, more so than on attention or cognition. The most frequent side effects of clonidine included sedation, irritability, dry mouth, hypotension, dizziness, and sleep disturbance (generally awakening in the middle of the night). Skin irritation and erythema were a common problem reported by patients using the clonidine transdermal patch.

Connor et al. (2000) randomly assigned 24 children with ADHD to receive, in blinded fashion, clonidine alone, methylphenidate (MPH) alone or the combination of both agents for 3 months. Only the clonidine monotherapy group showed significantly decreased fine motor speed. Total adverse events were similar in the three groups with a 'trend for the combination clonidine and MPH group to have lower mean severity of side effects.' The only specific adverse event noted in the report was of drowsiness and sleepiness which were rated on a check list and found to be of similar severity in all three groups.

Two important clinical studies were funded by the National Institutes of Health (NIH). The first was a randomized double-blind placebo-controlled parallel-group study of 16 weeks treatment with clonidine, methylphenidate (MPH) or the combination of both treatments in 136 children with Tourette's Syndrome and comorbid ADHD (TACT Study, Tourette Syndrome Study Group 2002). Although underpowered to show differences between any two of the four groups, the two groups receiving clonidine (clonidine alone and clonidine plus MPH) showed statistically better improvement in the primary endpoint, the Conners' Abbreviated Symptom Questionnaire for Teachers (CASQ-Teacher) than the two groups not receiving clonidine (MPH alone and placebo). Similarly, the groups receiving MPH (MPH alone and MPH plus clonidine) showed statistically significantly better improvement in the ASQ-Teacher score than the two groups not receiving MPH (clonidine alone and placebo). While improvements of each of the single drug groups for this primary endpoint were virtually identical and only marginally significant, the combination of clonidine and MPH showed larger treatment effects which were statistically significant vs. placebo ( $p < 0.0001$ ).

The second study funded by NIH, the Clonidine in ADHD Trial (CAT Study, Palumbo et al., 2008), which was performed by a subset of investigators of the first study, evaluated 122 patients with ADHD without chronic tic disorder using a study design very similar to that of the TACT study. This study evaluated the efficacy, safety, and tolerability of clonidine used alone or with methylphenidate in children with any subtype of ADHD, randomly assigned to clonidine, methylphenidate, clonidine in combination with methylphenidate, or placebo according to a 2 x 2 factorial design. Treatment duration was 16 weeks with doses flexibly titrated up to 0.6 mg/day for clonidine and 60 mg/day for methylphenidate. Clonidine was not found to improve ADHD symptoms, whereas subjects treated with methylphenidate showed significant improvement compared to those not treated with methylphenidate on the primary outcome measure, ASQ Teacher Questionnaire. One explanation might be a relatively small sample size; another

explanation might be that the analysis collapsed both clonidine groups (clonidine, clonidine + methylphenidate) and both non-clonidine groups.

However, subjects treated with clonidine had greater improvements on the Conner's Abbreviated Symptom Questionnaire for Parents and Children's Global Assessment.

*Comments: The literature review provides additional evidence for the safety and efficacy of clonidine for the treatment of ADHD.*

## 9.2 Labeling Recommendations

The major labeling recommendations have been summarized as following.

### 1. Indications and Usage

I recommend that the duration of the studies be stated as 5-week studies.

### 2. Warnings and Precautions

It is recommended that the risk of hypotension and sedation/somnolence be added to this section

I also recommend that the section on Abrupt Discontinuations be shortened to reflect events actually observed.

### 3. Adverse Reactions

I recommend that the term emotional disorder be removed from this section. The sponsor should also specify the rule they have used in including events in this section.

### 4. Indications and Usage

In section 1, on Indications and usage, it is recommended that the language be revised to include the fact that long term studies have not been done.

Standard language regarding the diagnosis and treatment of ADHD also be added.

### 5. General Dosing Information

In section 2.1, on General Dosing Information, the sponsor states

(b) (4)

However, this contradicts the information in the Warnings section re Abrupt Discontinuation, as patients are likely to

be exposed to a much lower dose on discontinuation. We request that the sponsor clarify this discrepancy.

6. [REDACTED] (b) (4)

In section 2.2, the sponsor states that [REDACTED] (b) (4). We would ask that the sponsor clarify and define this more precisely.

## 7. Warnings and Precautions

We ask that the sponsor provide additional details about the potential for hypotension and bradycardia. We also ask that the sponsor add language about somnolence.

## 8. Adverse Reactions

In section 6.1 on Adverse reactions, the sponsor has combined the common adverse reactions noted in both dose groups. However, we would ask that the adverse events be listed under the two different dose groups as the rates of adverse events differ between the two doses. It is important for clinicians to know at what doses are different AE's seen. In a revised label, [REDACTED] (b) (4). We ask that the sponsor submit tables with actual events seen. We also ask that the sponsor break up the adverse reactions to those seen in the treatment period and those in the taper down phase.

We ask that the sponsor add a section on 'Adverse events leading to discontinuation'.

## 9. Clinical Studies

In section 14, under clinical studies, the whole section has been revised to include only pertinent information. It is recommended that the tables and graphs be removed, as these can be difficult to interpret.

## 10. Missed Dose

This section on 'missed dose' has been revised to change the recommendation to 'If patients miss a dose of Tradename, they should skip the dose and take the next dose as scheduled'. This was done as there is the risk of patients taking double the dose, if the time they remembered was too close to the time of the next dose.

[REDACTED] (b) (4)

Clinical Review  
{Maju Mathews, MD}  
{NDA 22-331}  
{CLONICEL, Clonidine}

---

### **9.3 Advisory Committee Meeting**

Not applicable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

MAJU MATHEWS  
07/16/2010

JING ZHANG  
07/16/2010

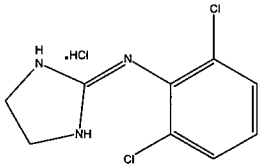
**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**CHEMISTRY REVIEW(S)**



<b>CHEMIST'S REVIEW #2</b>		1. ORGANIZATION ONDQA/DPA1		2. NDA NUMBER 22-331	
3. NAME AND ADDRESS OF APPLICANT ( <i>City and State</i> ) Shinogi Pharma, Inc. Five Concourse Parkway, Suite 1800 Atlanta, GA 30328.				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG KAPAVAY		7. NONPROPRIETARY NAME Clonidine Hydrochloride Extended-Release Tablets		SE1-001 SE1-002	09-29-2009
8. SUPPLEMENT PROVIDES FOR: a new indication, Attention Deficit Hyperactivity Disorder				9. AMENDMENTS DATES 03-12-2010 08-05-2010	
10. PHARMACOLOGICAL CATEGORY Alpha 2-adrenergic agonist		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Tablets		14. POTENCY 0.1, 0.2 mg			
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride				16. RECORDS AND REPORTS  CURRENT YES__ NO REVIEWED YES__ NO	
 <p style="text-align: center;">C<sub>9</sub>H<sub>6</sub>Cl<sub>2</sub>N<sub>3</sub>·HCl      Mol. Wt. 266.56</p>					
17. COMMENTS Please refer to my review notes.					
18. CONCLUSIONS AND RECOMMENDATIONS This supplement is recommended for approval from the stand point of Chemistry, manufacturing and controls					
19. CHEMIST					
NAME Nallaperumal Chidambaram, Ph.D.		SIGNATURE			DATE COMPLETED 09-16-2010
<u>DISTRIBUTION</u>	ORIGINAL NDA	DIVISION FILE	Chemist: N. Chidambaram Ph.D.	CSO: HirenPatel HFD-130	Branch Chief: Hasmukh Patel Ph.D.

**REVIEW NOTES**

This drug product is approved for the treatment of hypertension in September 2009. The current application is submitted to seek approval for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). I recommended approval of this supplement pending satisfactory resolution of the trade name (refer to my Review #1 dated 07/16/2010). Since then, DMEPA has determined KAPVAY as an acceptable trade name.

The applicant wanted to describe this product as a modified-release formulation as the drug product is deliberately modified to protract the release rate but the dosing interval is the same as immediate release dosage form (twice daily). Modified-release is not one of the dosage modifiers listed in CDER Data Standards Manual to describe protracted release of the drug. This issue was discussed with Dr. Rik Lostritto, Director, Division I, ONDQA and Ms. Yana Mile, CDER Expert on Nomenclature and Compendial issues. Ms. Yana Mile took this issue to USP expert committee on nomenclature and they supported the use of the term extended-release for this product though there is no change to the dosing frequency (refer to Mr. Hiren Patel's Memo to file dated 07/27/2010).

Based on the above, the Division of Psychiatry Drug Products notified the applicant that it is appropriate to use extended-release dosage modifier to this application (refer to action letter dated 07/28/2010). In addition, the above action letter advised the applicant to submit a Prior Approval Labeling Supplement to the referenced NDA (NDA 022331 with the trade name of Jenloga is approved to treat hypertension) and include revised labeling that supports Jenloga (clonidine hydrochloride) extended-release tablets.

The current submission contains revised container labels incorporating above recommended changes for KAPVAY.



**EVALUATION:** The provided container labels are found to be acceptable.

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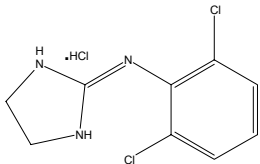
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NALLAPERUM CHIDAMBARAM

09/17/2010

HASMUKEH B PATEL

09/17/2010

<b>CHEMIST'S REVIEW #1</b>		1. ORGANIZATION ONDQA/DPA1		2. NDA NUMBER 22-331	
3. NAME AND ADDRESS OF APPLICANT ( <i>City and State</i> ) Shinogi Pharma, Inc. Five Concourse Parkway, Suite 1800 Atlanta, GA 30328.				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG		7. NONPROPRIETARY NAME Clonidine Hydrochloride		SE1-001 SE1-002	09-29-2009
8. SUPPLEMENT PROVIDES FOR: a new indication, Attention Deficit Hyperactivity Disorder				9. AMENDMENTS DATES 03-12-2010	
10. PHARMACOLOGICAL CATEGORY Alpha 2-adrenergic agonist		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Tablets		14. POTENCY 0.1, 0.2 mg			
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride				16. RECORDS AND REPORTS	
 <p style="text-align: center;">C<sub>12</sub>H<sub>9</sub>Cl<sub>2</sub>N<sub>3</sub>·HCl      Mol. Wt. 266.56</p>				CURRENT    YES__ NO	
				REVIEWED   YES__ NO	
17. COMMENTS This drug product is approved in September 2009 for the treatment of hypertension. The current application is submitted to seek approval for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The applicant has not provided any new CMC information but has provided a claim for categorical exclusion based on revised calculation of expected introduction concentration (EIC) of the active moiety that will likely enter into the aquatic environment. The amount that is expected is found to be 0.003 ppb.  The applicant provided draft carton and container labels for the trade name <b>KAPVAY</b> that is currently under review in DMEPA and their input is expected by 07/26/2010. The trade name (b) (4) that was proposed earlier was found to be not acceptable. The carton label was not reviewed because the trade name is still under review.  Provided information is found to be acceptable.					
18. CONCLUSIONS AND RECOMMENDATIONS This supplement is recommended for approval from the stand point of Chemistry, manufacturing and controls pending satisfactory resolution of the trade name.					
19. CHEMIST					
NAME Nallaperumal Chidambaram, Ph.D.		SIGNATURE			DATE COMPLETED 07-13-2010
<b><u>DISTRIBUTION</u></b>	ORIGINAL NDA	DIVISION FILE	Chemist: N. Chidambaram Ph.D.	CSO: HirenPatel HFD-130	Branch Chief: Hasmukh Patel Ph.D.

### REVIEW NOTES

Please note that following changes were recommended to the **DESCRIPTION** section of the label to be consistent with the label approved in the Division of Cardio-Renal Drug Products on 05/25/2010, and the same has been communicated to the applicant on 07/13/2010.

#### Applicant proposed revision:

[REDACTED] (b) (4)  
0.1  
mg and 0.2 mg tablet is equivalent to 0.087 mg and 0.174 mg, respectively, of the free base.

The inactive ingredients are sodium lauryl sulfate, lactose monohydrate, hypromellose type 2208, partially pregelatinized starch, colloidal silicon dioxide, and magnesium stearate. The formulation is designed to delay the absorption of active drug in order to decrease peak to trough plasma concentration differences. Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride.

#### FDA proposed revision (consistent with the version approved on 05/25/2010):

[REDACTED] (b) (4)  
- Each (b) (4) 0.1 mg and 0.2 mg tablet is equivalent to 0.087 mg and 0.174 mg, respectively, of the free base.

The inactive ingredients are sodium lauryl sulfate, lactose monohydrate, hypromellose type 2208, partially pregelatinized starch, colloidal silicon dioxide, and magnesium stearate. The formulation is designed to delay the absorption of active drug in order to decrease peak to trough plasma concentration differences. Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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NALLAPERUM CHIDAMBARAM

07/15/2010

Note that the incoming date for the amendment (document #40) is different in EDR (3/12/2010) and in DARRTS (3/16/2010)

HASMUKH B PATEL

07/16/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**PHARMACOLOGY REVIEW(S)**

## **SUPERVISORY PHARMACOLOGY/TOXICOLOGY MEMO**

NDA 22-331.

Submissions: Supplements 001 (monotherapy) and 002 (adjunctive therapy with stimulants), letter-dated 9/29/2009, received 10/1/2009.

Drug: clonidine hydrochloride, as modified-release 0.1- and 0.2-mg and oral tablets  
[proposed trade name is Kapvay, which is pending approval].

Sponsor: Shionogi Pharma, Inc.

Indication: mono- and adjunctive (with stimulants) therapy for ADHD in pediatric patients (6-17 years of age).

Reviewer: Linda H. Fossom, Ph.D., Pharmacologist, Team Leader.  
Division of Psychiatry Products, HFD-130.

**Background:** The Sponsor has submitted the current efficacy supplements to NDA 22-331 for the modified-release formulation of clonidine HCl, which was recently approved as Jenloga for treatment of hypertension (9/29/2009). Other (immediate-release) formulations of clonidine HCl have marketed for treatment of hypertension, since it was originally approved in 1973 (under NDA 17-407, as Catapres Tablets, sponsored by Boehringer Ingelheim).

The non-clinical studies that supported the approval of NDA 22-331, for hypertension, are considered generally adequate to support the current NDA supplements for ADHD; however, a juvenile rat study was required to support the proposed use of clonidine in pediatric patients (as communicated at our 3/9/2009 meeting with the Sponsor).

**Summary of the Reviewer's issues with the juvenile rat study:** The final report for the juvenile rat study was submitted under these supplements and has been reviewed in detail by Ikram Elayan, Ph.D., Pharmacologist (review finalized 7/2/2009). In her review, Dr. Elayan has thoroughly and critically evaluated the results of the juvenile rat study, as well as the dose-range finding study that supported dose selection for the pivotal study. The description of the results of this study, including a slight delay in sexual maturation in males, has been included in labeling, section 8.4 Pediatric Use, and reflects Dr. Elayan's assessment.

However, Dr. Elayan had some concerns regarding the adequacy of the doses of clonidine that were tested in female rats in the reproductive arm of the pivotal juvenile rat study. Doses up to 0.3 mg/kg were used in the pivotal study (with 10 weeks of dosing), based on severe ( $\geq 18\%$ ) decreases in body weights at  $\geq 1$  mg/kg in the 14-day dose-range finding study. It should be noted that the pivotal study was conducted in two parts: 1) toxicology and assessment of neurobehavioral development; and 2) assessment of



reproductive potential. For the toxicology/neurobehavioral part, the drug content of dosing solutions was confirmed, systemic exposure was verified, and clinical signs and body weights were assessed. None of these parameters were assessed in the reproductive part of the study; however, the same doses were used. As Dr. Elayan pointed out, in the toxicology/neurobehavioral part of the study, the ~10% decrease in body weights observed at the end of the 10-week administration at the high dose of 0.3 mg/kg in male rats indicated that dosing was adequate. However, no decrease in body weight (or any other significant toxicity) was observed in female rats, either early in dosing (as seen in the dose-range finding study) or at the end of dosing. Dr. Elayan also noted that in the reproductive part of the study, body weights were not assessed; and there was no independent verification of the dosing solutions: drug solutions were not assayed (though the Sponsor indicated that they were prepared similarly to those used in the toxicology/neurobehavioral part of the study) and systemic exposures were not determined.

Based on these concerns, Dr. Elayan recommended that effects of clonidine on reproductive potential in female juvenile rats be assessed at a dose higher than 0.3 mg/kg. She suggested that this higher dose be selected based on the results of the currently available juvenile rat studies (dose-range finding and pivotal) and proposed 0.5 mg/kg as a reasonable choice. She suggested that this could be added as an extra monotherapy arm in the combination study of clonidine with a stimulant in juvenile rats, which the Sponsor will be conducting as a PMR.

**Team Leader's comments on those issues:** While I appreciate Dr. Elayan's position, I do not agree that additional testing of a higher dose of clonidine for effects on reproductive potential in female juvenile rats is warranted. Although there was no (confirming) evidence of effects of clonidine up to 0.3 mg/kg in female rats in the pivotal studies, this high dose was appropriately chosen for both males and females, based on severely decreased body weights at  $\geq 1$  mg/kg administered for 14 days, with premature sacrifice of pups administered 3 mg/kg, in the dose range-finding study. Additionally, decreased body weights were seen in males at 0.3 mg/kg in the pivotal study, confirming that this dose was appropriately chosen. I share Dr. Elayan's concern that there appears to have been no independent confirmation of the dosing solutions used in the reproductive part of the pivotal study; however, the drug solutions were apparently prepared as for the neurobehavioral part of the study, where drug exposure was confirmed. Additionally, the reproductive findings of a delay of preputial separation in male rats at 0.3 mg/kg (included in labeling) and a delay of vaginal opening in all treated females that was not significantly different from controls (and will not be included in labeling) provide some evidence of toxicity in this part of the study, in the absence of body weight data. Finally, choosing an appropriate higher dose to be tested in females is problematic. Dr. Elayan and I agree that a dose of 1 mg/kg (or higher) would not be justified based on the dose-range finding study. However, the dose of 0.5 mg/kg suggested by Dr. Elayan, though probably the highest reasonable dose, does not seem enough different from the dose of 0.3 mg/kg to be likely to provide additional useful information.

**Labeling summary:** This product will have separate trade names and labeling for the two indications (hypertension and ADHD). The description of the non-clinical studies in the labeling for the current product will be described similarly to the labeling for Jenloga. However, certain sections of Jenloga labeling will be revised, as below:

- 1) the Mechanism of Action and Pharmacodynamic sections (under 12 Clinical Pharmacology) will be revised to reflect the current indication of ADHD;
- 2) in sections 8.1 Pregnancy (under 8 Use in Specific Populations) and 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility (under 13 Nonclinical Toxicology), clinical safety margins for doses in animals will be provided, based on mg/m<sup>2</sup> doses, rather than providing HEDs as used in Jenloga labeling; and
- 3) the results of the juvenile rat study will be included in section 8.4 Pediatric Use (under 8 Use in Specific Populations).

**Conclusions/Recommendations:** From a Pharmacology/Toxicology perspective, there are no issues that would prevent the approval of this NDA, with a PMR for a juvenile rat study for the combination of clonidine with a stimulant, so support the safe use of clonidine with stimulants in pediatric patients and to provide additional safety information for labeling.

Linda H. Fossom, Ph.D., Pharmacologist, Team Leader *{see appended electronic signature page}*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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LINDA H FOSSOM  
07/28/2010

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 22-331

Supporting document/s: SDN-15 (Supplement 001);  
SDN-16 (Supplement 002)

Applicant's letter date: 9/29/09

CDER stamp date: 10/1/09

Product: Modified-release clonidine hydrochloride

Indication: Monotherapy and adjunctive therapy to  
stimulant medications for treatment of Attention  
Deficit Hyperactivity Disorder

Applicant: Shionogi Pharmaceuticals Inc.

Review Division: Division of Psychiatry Products (DPP)

Reviewer: Ikram Elayan, Ph.D.

Supervisor/Team Leader: Linda Fossom, Ph.D.

Division Director: Thomas Laughren, M.D.

Project Manager: Hiren Patel, Pharm.D.

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# **1 Executive Summary**

## **1.1 Recommendations**

The only recommendation, based on the results of the juvenile rat studies submitted, is that the slight delay in sexual maturation in juvenile rats treated with clonidine should be described in the labeling (see below).

### **1.1.1 Approvability**

The submission is considered approvable from a preclinical point of view, pending negotiation of labeling.

### **1.1.2 Additional Non Clinical Recommendations**

The sponsor will need to conduct a juvenile rat study for combination therapy with a stimulant as a post-marketing commitment, as was agreed upon previously. Below is suggested wording:

In order to support safe use of clonidine in combination with stimulants in pediatric patients and to provide additional safety information for labeling, you must conduct a juvenile animal study of clonidine in combination with a stimulant as a post-marketing commitment (as communicated in the minutes of our 3/9/09 meeting).

Additionally, because of concern about the adequacy of dosing, especially in females, in the juvenile rat studies, this reviewer recommends that a higher dose of clonidine be used as an added monotherapy arm in females in the combination study of clonidine with stimulants which will be conducted as a Phase IV commitment (see above). This higher dose should be based on the findings seen so far with the doses used in the submitted studies (a dose of 0.5 mg/kg might be reasonable based on the findings). However, it should be noted that unacceptable ( $\geq 18\%$ , compared with controls) decreases in body weights were seen at doses of 1 mg/kg and greater in the 14-day dose range finding study. Assessment of toxicity (i.e. body weight effect) in the study should be investigated since this was lacking in the current reproductive part of the study conducted under this submission (see more details in the Discussion of Limitations of the Reproductive Study, below).

### **1.1.3 Labeling**

Because this drug product was recently approved by the Division of Cardioresenal Products (September 29, 2009), as Jenloga for the treatment of hypertension, the



preclinical sections of the labeling for Jenloga were used as a basis for the preclinical sections for the labeling of this product for the ADHD indication. The product will have a different tradename (not yet finalized) for the ADHD indication and the sponsor has provided a separate labeling for the ADHD indication.

The sponsor has proposed some changes in the non-clinical sections of the approved Jenloga labeling.

In descriptions of animal study findings, they propose using human safety factors provided by the animal doses instead of specifying the human equivalent dose compared to the animal dose as was presented in the Jenloga labeling. We agree with this approach, but using safety factors as multiples of the animal dose, based on a  $\text{mg/m}^2$ , which resulted in safety factors that are different from those proposed by the sponsor.

The language that pertains to the mechanism of action proposed by the sponsor will need to be modified since the proposed mechanism of action for this product for ADHD proposed by the sponsor is hypothetical and there is not adequate data to support it.

Finally, the results from the juvenile animal studies that were submitted for this indication, specifically the effects observed on sexual maturation in male rats, need to be described in the labeling under section 8.4, because these findings might relate to sexual maturation in children treated with this compound. It was noted that there was no apparent effect on fertility at doses used in this study, as compared to the effect seen in adult female rats treated with higher doses as described in the labeling of Jenloga (see the changes suggested to the labeling as proposed by the reviewer below).

Proposed changes to the Sponsor's labeling by the Pharmacology/Toxicology reviewer:

**TRADENAME (clonidine hydrochloride modified release) tablets, oral**  
**Initial U.S. Approval: 2010**

-----INDICATIONS AND USAGE-----

Monotherapy: TRADENAME® (modified release clonidine hydrochloride) is indicated in the treatment of attention deficit/hyperactivity disorder (ADHD). (1)

Add-on Therapy: TRADENAME® (modified release clonidine hydrochloride) is also indicated as add-on therapy to stimulant medication in the treatment of ADHD. (1)

TRADENAME® is a centrally acting alpha-2 adrenoceptor agonist. (1)

## **8. USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C

(b) (4)

No adequate and well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless clearly needed.

Note: the labeling approved for Jenloga will be used here except that the human safety margins will be changed to reflect the MRHD used for the ADHD indication. The following is extracted from the Jenloga labeling. However, a decision is to be made on which style to use, i.e. safety margins or HED:

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

Oral administration of clonidine HCl to pregnant rabbits during embryo/fetal organogenesis, at doses up to 80 mcg/kg/day (human equivalent dose 26 mcg/kg/day), produced no evidence of teratogenic or embryotoxic potential. In pregnant rats, however, doses as low as 15 mcg/kg/day (HED 2.4 mcg/kg/day) were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating and throughout gestation. Increased resorptions were not associated with treatment at the same or higher dose levels (up to 150 mcg/kg/day (HED 24 mcg/kg/day)) when treatment of the dams was restricted to gestation days 6-15. Increases in resorptions were observed in both mice and rats at 500 or more mcg/kg/day (HED 80 mcg/kg/day for rats and 40 mcg/kg/day for mice) when the animals were treated on gestation days 1-14.

### 8.4 (b) (4) Pediatric Use

(b) (4)

A study was conducted in which young rats were treated (b) (4) from day 21 of age to adulthood.

(b) (4)

approximately 3 times the (b) (4) maximum recommended human dose (MRHD) of 0.4 mg/day on a mg/m<sup>2</sup> basis. (b) (4)

(b) (4) There (b) (4) no drug effect on fertility (b) (4)

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

(b) (4). Clonidine is not a central nervous system stimulant. The mechanism of action of clonidine in ADHD is not known. (b) (4)

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

(b) (4)  
There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Fertility of male or female rats was unaffected by (b) (4) doses as high as 150 (b) (4) (approximately 3 times (b) (4)). In a separate experiment, fertility of female rats appeared to be affected at dose levels of 500 to 2000 mcg/kg (10 (b) (4) 40 times the (b) (4) MRDHD on a (b) (4) basis; (b) (4)

### 13.2 (b) (4)

In several studies with oral clonidine hydrochloride, a dose-dependent increase in the incidence and severity of spontaneous retinal degeneration was seen in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys showed a concentration of clonidine in the choroid.

In view of the retinal degeneration seen in rats, eye examinations were performed during clinical trials in 908 patients before, and periodically after, the

start of clonidine therapy. In 353 of these 908 patients, the eye examinations were carried out over periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmological findings were recorded and, according to specialized tests such as electroretinography and macular dazzle, retinal function was unchanged.

In combination with amitriptyline, clonidine hydrochloride administration led to the development of corneal lesions in rats within 5 days.

Note: no changes to the language proposed to section 13.2 (b) (4) by the reviewer and the Sponsor's proposed language above is considered acceptable except that the section to be entitled "Ocular Toxicity" as seen in the Jenloga labeling.

## 1.2 Brief Discussion of Nonclinical Findings

Juvenile rat studies were the only preclinical studies submitted under these NDA Supplements. These included a dose range finding study, which was used to select doses for the definitive studies. In the definitive studies, the general toxicological effect of drug, the effect of treatment on bone length and density, and the effect of treatment on neurobehavioral and reproductive development were evaluated in juvenile rats.

The doses used for the definitive studies, although not clearly optimal, were considered appropriately chosen, based on the findings from the dose range finding study (see the Integrated Summary Section for more details). The results from these studies at the doses used did not indicate any toxicity that was of a concern in any of the parameters evaluated, except a slight delay in sexual maturation (preputial separation) in males at the high dose of 0.3 mg/kg. The slight delay in vaginal opening seen in all treated female groups did not reach statistical significance. The reviewer believes it could be due to less than optimal dosing in this group (see the Integrated Summary Section for more details). There appeared to be no effect on fertility in juvenile animals treated with these doses in the definitive study, although fertility was adversely affected in adult female rats treated with higher doses (as described in Section 13.1 of labeling).

## 2 Drug Information

**2.1 Drug:** clonidine hydrochloride

**2.1.1 CAS Registry Number:** 4205-91-8

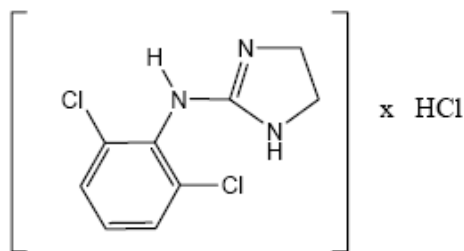
**2.1.2 Generic Name:** clonidine hydrochloride

**2.1.3 Code Name:** none

**2.1.4 Chemical Name:** 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride

**2.1.5 Molecular Formula/Molecular Weight:** C<sub>9</sub>H<sub>9</sub>Cl<sub>2</sub>N<sub>3</sub>.HCl/MW 266.6

**2.1.6 Structure**



**2.1.7 Pharmacologic class:** centrally acting alpha<sub>2</sub> adrenergic agonist

**2.2 Relevant IND/s, NDA/s, and DMF/s:** IND 76,144

**2.3 Clinical Formulation:** tablets (0.1 mg)

**2.3.1 Drug Formulation:**

(b) (4)

**2.3.2 Comments on Novel Excipients**

None.

**2.3.3 Comments on Impurities/Degradants of Concern**

None.

**2.4 Proposed Clinical Population and Dosing Regimen:**

Monotherapy and adjunctive therapy for ADHD in children and adolescents ages 6-17 years.

**2.5 Regulatory Background:**

The active ingredient clonidine was approved in 1973 under NDA 17-407 (Catapres tablets, Boehringer Ingelheim) for the treatment of hypertension. Recently, a modified-release formulation (Jenloga) was the subject of NDA 22-331 for the treatment of hypertension and was approved by the Division of Cardiovascular and Renal Products (9-29-09). Clonidine (HCl), in the same formulation used for Jenloga, is proposed for the treatment of ADHD under the current NDA; however, a different trade name will be proposed for this indication, a matter that is still under discussion. Thus, different trade names will be used for the same product under different indications and separate labeling has been submitted for the ADHD indication to be distinguished from that approved for the hypertension indication (Jenloga).

**3 Studies Submitted:**

- Fourteen-Day Oral Range Finding Study of Clonidine HCl in Rats,
- Ten-Week Oral GLP Toxicity Study of Clonidine HCl in Juvenile Rats with a Ten-Week Recovery Period, and

- Fertility and Early Embryonic Development Study in Rats Given Clonidine HCl From 3 to 13 Weeks of Age.

**3.1 Studies Reviewed:** all submitted studies are reviewed here.

**3.2 Studies Not Reviewed:** none

**3.3 Previous Reviews Referenced:** The original review of clonidine in Catapres (NDA 17-047) and NDA 22-331 modified-release for the treatment of hypertension (Jenloga) approved 9/29/09.

## 9 Special Toxicology Studies: Juvenile Animal Studies

### 9.1 DOSE RANGE-FINDING JUVENILE RAT STUDY:

Study title: Fourteen-Day Oral Range-Finding Study of Clonidine HCl in Rats

Study no.: 0978-08279

Study report location: Not specified

Conducting laboratory and location:



Date of study initiation: 11 July, 2008

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: XE 1080 and purity 99.5% (BP-EP) or 99.7% (USP)

#### Key Study Findings:

Doses used in this range finding study were 0, 0.1, 0.3, 1, and 3 mg/kg/day for 14 days administered orally by gavage to rat pups from PND 21. Rat pups treated with 3 mg/kg/day were terminated on Day 8 due to severe ocular effects (corneal opacities) and a large decrease in mean body weight (~23%, compared to controls). Rat pups treated with 1 mg/kg/day had a decrease in mean body weight of ~19% compared to controls and the group treated with 0.3 mg/kg/day had a decrease in mean body weight of ~9%. A decrease in activity was observed in all treated groups. Based on these findings the Sponsor considered the result of this study sufficient for the selection of the doses to be used in the definitive study.

#### Methods

Doses: 0 (group 1), 0.1 (group 2), 0.3 (group 3), 1.0 (group 4), and 3.0 (group 5) mg/kg/day  
Frequency of dosing: Once daily for 7 days (group 5) or 14 days (groups 1-4)  
Route of administration: Oral by gavage  
Dose volume: 5 ml/kg



Formulation/Vehicle: water  
Species/Strain: Sprague Dawley rats  
Number/Sex/Group: 8/sex/group  
Age: 21 days  
Weight: 36.4-50 gm  
Satellite groups: none  
Unique study design:  
Deviation from study protocol: Group 5 was sacrificed on Day 8 due to what the sponsor described as severe toxicity

## Observations and Results

### Mortality

Methods: Rats were observed twice daily.

Results: There were no unscheduled deaths. Group 5 was terminated on Day 8 of the study due to severe ocular effects and substantial decrease in growth rate (see body weight data below for details).

### Clinical Signs

Methods: Clinical observations were conducted once daily for all groups

Results: Decreased activity was observed at all doses, abdominal distention and piloerection at doses of 0.3 mg/kg/day or higher. Ocular changes, such as cloudy corneas, and/or corneal opacities with exophthalmus were observed in all HDM and HDF generally throughout the treatment period in group 5 and were observed in 3M treated with 1 mg/kg/day. The observation of these findings was as follows: in males treated with 1 mg/kg two animals had bilateral corneal cloudiness (#25, #28), another one had corneal cloudiness in one eye (#32), one had bilateral corneal opacities (#25), and one animal was observed with exophthalmus and corneal opacity in one eye (#28). These changes were not observed in F treated with this dose. In M treated with the HD of 3 mg/kg, five animals had bilateral corneal opacities (#35, #36, #38, #39, and #40) and one had a unilateral opacity (#34), while five had bilateral corneal cloudiness (#33, #37, #38, #39, and #40) and one had a unilateral cloudiness in the cornea (#36). In animals that had corneal opacity and cloudiness, the cloudiness was described on an earlier day than the opacity was described. It is possible that those animals with cloudiness developed the opacities after they have developed the cloudiness. In F treated with this dose, three had bilateral corneal opacities (#73, #75, #77) and three had unilateral opacities (#76, #78, #79), while 4 had bilateral corneal cloudiness (#73, #74, #77, #80) and three had unilateral corneal cloudiness (#76, #78, #79). These observations can be compared to the confirmed observation of ocular changes at the

time of necropsy. The following table extracted from the sponsor's submission summarizes these findings and incidences:

### Incidence of Clonidine-Related Clinical Signs

Dose (mg/kg/day) =	Males					Females				
	0	0.1	0.3	1	3	0	0.1	0.3	1	3
Decreased activity	---	50%	All	All	All	---	All	All	All	All
Piloerection	---	---	All	All	All	---	---	All	All	All
Distended abdomen	---	---	13%	38%	All	---	---	25%	13%	All
Cornea cloudy or opaque	---	---	---	38%	All	---	---	---	---	All
Exophthalmus	---	---	---	13%	13%	---	---	---	---	13%
Peri-orbital staining	---	---	---	---	25%	---	---	---	---	63%

--- = clinical sign not observed

The ocular findings were considered severe enough by the sponsor to sacrifice group 5 after seven days of administration (in addition to the body wt effect, see below).

One M from the group treated with 0.3 mg/kg/day was observed to have a seizure after the third dose, but this was not considered related to treatment since this was not observed in subsequent treatments in this animal and was not observed at higher doses.

## Body Weights

Methods: body wts were recorded twice weekly

Results: there was a decrease in body wt gain at dosages 0.3 mg/kg/day or greater. As a result, a decrease in absolute body wt was observed in those groups also by the end of the study. The following table summarizes the effect on body wt gain (growth) and body wt as submitted by the sponsor. The % decrease calculated for the body wt compared to the control was done by the reviewer (as seen penciled on the table) and it reflects a decrease of 9% in M and 8% in F compared to the control by the end of the study in group 3 (0.3 mg/kg). A decrease of ~18% in M and 19% in F compared to control was seen in group 4 (1 mg/kg) by the end of the study. A decrease of ~23% compared to control was seen in group 5 (3 mg/kg) on Day 7 of treatment which resulted in the termination of this group (in addition to the ocular findings that were observed).

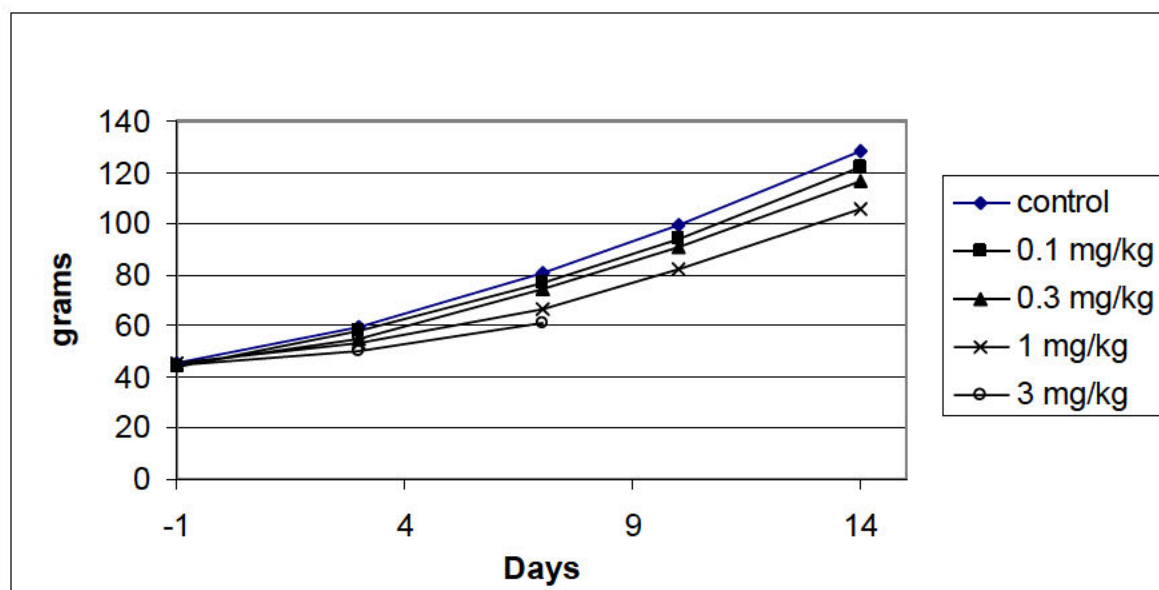
Summary of Growth and Body Weight Data

Dose (mg/kg/day) =	Males					Females				
	0	0.1	0.3	1	3	0	0.1	0.3	1	3
Body weight (g)										
Pretest (Day -1)	45.4	43.9	44.9	45.1	44.5	43.8	42.0	42.8	42.8	42.5
Day 7	80.3	76.9	74.2	66.8	61.1	74.0	71.6	67.0	62.0	58.6
Day 14	128.6	121.7	116.7	105.6	91.7	111.0	106.5	101.6	89.7	81.1
Growth										
Day -1 to Day 7										
(grams)	35.0	33.0	29.2	21.7	16.6	30.2	29.6	24.2	19.3	16.1
(%)	77%	75%	65%	48%	37%	69%	70%	57%	45%	38%
Day -1 to Day 14										
(grams)	83.2	77.8	71.8	60.6	---	67.2	64.5	58.8	46.9	---
(%)	183%	177%	160%	134%	---	153%	154%	137%	110%	---
Versus control										
Day -1 to 7	NA	-3%	-16%	-38%	-52%	NA	+1%	-17%	-35%	-45%
Day -1 to 14	NA	-3%	-13%	-27%	---	NA	+1%	-10%	-28%	---

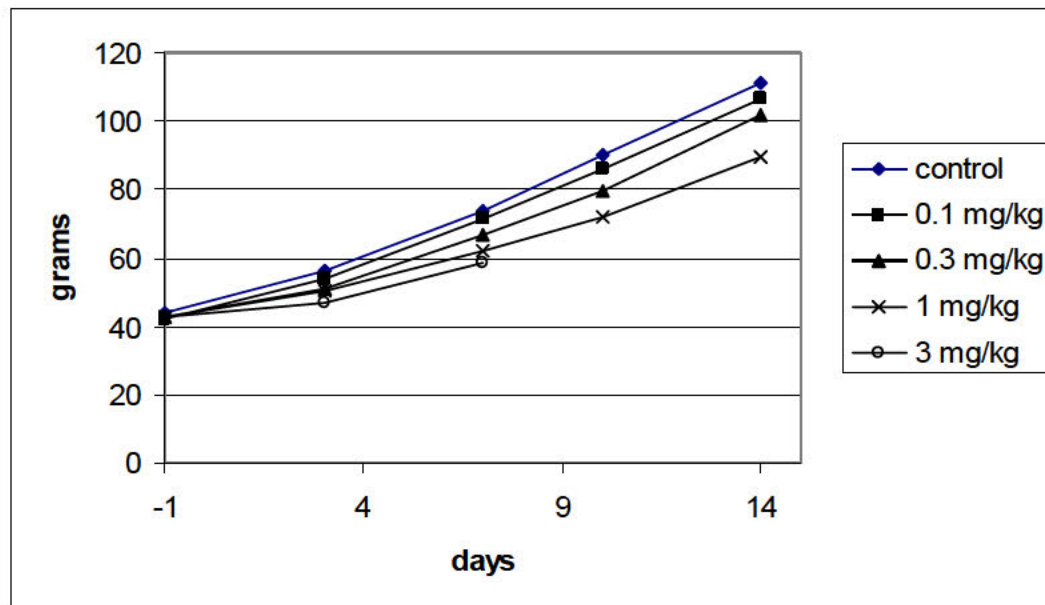
--- = group terminated on Day 8, so no data available.

The following figures were plotted by the reviewer using the data provided by the sponsor for mean body weights.

**Figure 1 Mean body weight in males treated with clonidine for two weeks (HD rats at 3 mg/kg were terminated after day 8 of dosing.)**



**Figure 2 Mean body weights in females treated with clonidine for two weeks (HD rats at 3 mg/kg were terminated after day 8 of dosing.)**



## Clinical Chemistry

**Methods:** at scheduled terminations (Day 8 for group 5 and Day 15 for groups 1-4), blood was collected from each rat and the following parameters were evaluated:

Sodium	Total cholesterol
Potassium	Triglycerides
Chloride	Total protein
Alkaline phosphatase	Albumin
Alanine aminotransferase	Globulin (calculated)
Aspartate aminotransferase	Albumin/globulin ratio (calculated)
Glucose	Calcium
Blood urea nitrogen	Inorganic phosphorus
Total bilirubin	

**Results:** there were some changes observed that might be related to treatment. The sponsor considered the changes as clinically insignificant. These changes included slightly higher mean cholesterol concentration at all dose levels. Slightly lower mean albumin, calcium and phosphorus concentrations at all dose levels. Slightly higher mean glucose and triglyceride concentrations and alkaline phosphatase activity at 3 mg/kg/day. The sponsor suggested that the changes in glucose and triglyceride

concentrations probably reflect metabolic shifts secondary to the large effect on body wt or reduced growth rate especially at the HD. As for the higher levels of alkaline phosphatase activity, the sponsor stated that this could be due to the young age of these animals since alkaline phosphatase activity usually declines with maturation in these animals. The following table was extracted from the Sponsor's submission summarizing mean values for these parameters:

**Table 1 Mean clinical chemistry values in rats treated from PND 21 for 14 days**

<b>Selected Mean Clinical Chemistry Data</b>										
<b>Dose (mg/kg/day)</b>	<b>Males</b>					<b>Females</b>				
	<b>0</b>	<b>0.1</b>	<b>0.3</b>	<b>1</b>	<b>3*</b>	<b>0</b>	<b>0.1</b>	<b>0.3</b>	<b>1</b>	<b>3*</b>
Alk phosphatase (U/L)	259	220	253	278	313	205	238	256	267	319
Glucose (mg/dL)	105	73	81	97	120	98	85	93	87	114
Cholesterol (mg/dL)	99	119	119	120	122	114	128	120	126	120
Triglyceride (mg/dL)	55	99	74	53	100	80	95	71	51	122
Albumin (g/dL)	3.9	3.6	3.7	3.6	3.7	4.1	3.7	3.7	3.8	3.8
Calcium (mg/dL)	11.6	11.3	11.2	11.3	11.0	11.8	11.6	11.4	11.3	11.2
Phosphorus (mg/dL)	16.1	14.7	14.3	14.5	14.1	15.4	14.1	14.3	14.2	14.6

\*Group terminated on Day 8 at 29 days old; remaining groups terminated on Day 15 at 36 days old.

## Gross Pathology

**Methods:** at necropsy rats were examined visually for external abnormalities including palpable masses. The abdominal, thoracic, and cranial cavities and their contents were also examined.

**Results:** macroscopic observations at necropsy were limited to the ocular changes consistent to the ocular changes described under clinical observations. These ocular changes were considered severe enough to be dose-limiting. In males treated with 1 mg/kg two animals had bilateral corneal opacities (#25, #28), another one had corneal cloudiness in one eye (#32), and one animal was observed with exophthalmus in one eye (#28). These changes were not observed in F treated with this dose. In M treated with 3 mg/kg, five animals had bilateral corneal opacities (#35, #36, #38, #39, and #40) and one had a unilateral opacity (#34), while two had bilateral corneal cloudiness (#33, #37). In F treated with this dose, two had bilateral corneal opacities (#73, #75) and two had unilateral opacities (#77, #78), while 2 had bilateral corneal cloudiness (#74, #80) and 4 had unilateral corneal cloudiness (#76, #77, #78, #79). The following summary table of the necropsy observations as provided by the sponsor is included here:

**Table 2 Summary of ocular findings at necropsy in juvenile rats treated with clonidine for 14 days****Summary of Necropsy Observations**

	<b>Group 4 1 mg/kg</b>		<b>Group 5 3 mg/kg</b>	
<b>Necropsy Observation</b>	Males	Females	Males	Females
Cornea Cloudy	1	0	2	6
Corneal Opacity	2	0	6	4
Exophthalmus	1	0	0	0

**Organ Weights and Histopathology: not conducted.**

**Toxicokinetics: not conducted.**

There was no evaluation for plasma concentrations in this study.

**Stability and Homogeneity:**

It was not clear if any testing was conducted for the stability and homogeneity of the prepared solutions; no data were provided. However, the sponsor referenced an article from the literature suggesting the stability of clonidine in solution (0.1 mg/ml) for ~28 days at 4 °C (Am. J. Hospt. Pharmac, vol. 49, issue 1, 122-125, 1992). The data submitted indicated that the concentrations of the dosing solutions ranged between 91.5 to 97.6% of the intended concentrations for all the dose groups used in the study. A validation for the method used for the detection was provided (test was referred to as "Assay", and method # was provided as AC-AM-148-R3 on the HPLC/GC test form).

## 9.2 PIVOTAL JUVENILE RAT STUDY: including neurobehavioral assessment

Study title: Ten-week oral GLP toxicity study of clonidine HCl in juvenile rats with a four-week recovery period

Study no.: 0978-09008

Study report location:

Conducting laboratory and location:

(b) (4)

Date of study initiation: 02 March 2009

GLP compliance: Yes (few measurements were not conducted under GLP, see later in the review). No significant effects on the studied parameters.

QA statement: Yes

Drug, lot #, and % purity: Clonidine HCl, lot# XK0551, Purity 99.4%

### Key Study Findings

The sponsor used the following doses for this definitive study: 0, 30, 100, and 300 micro gr/kg/day. The doses used here were based on the results of the 14-day dose range findings study in which a dose 0.3 mg/kg was associated with ~9% decrease in body wt compared to control (at the next higher dose of 1 mg/kg a decrease of ~19% in body weight compared to control was observed). There were no drug related deaths in this study. A decrease in activity was observed within hours of dosing at MD and HD in all animals on numerous occasions in the study. A decrease in body weight of ~9% was observed in M treated with the HD throughout the study while a decrease that ranged between 4-8% in body weight was observed in F treated with the same dose only through the first 23 days of the study (the decrease in body wt tended to be less dramatic by the end of the study with only a 2% decrease observed at the end of dosing). The doses used in this study did not result in corneal opacities that were seen at the higher doses used in the dose range findings study. A slight increase in glucose levels (20% in M and 28% in F at the HD compared to control) was observed, but was attributed to the pharmacology of the drug and thus was not considered as biologically significant by the sponsor. There was a slight increase in glucose levels in the urine. A slight decrease in kidney weight was observed at all doses, but no histopathological findings were observed in the kidney (or in any other organ). There was no effect of treatment on bone length or density. There was no effect for treatment on locomotor activity or on learning and memory tests. Plasma concentrations increased with dosing and females had slightly higher levels than males, but this was not considered a significant difference.

## Methods

Doses: 0, 30, 100, and 300 µg/kg/day  
Frequency of dosing: Once daily  
Route of administration: Oral by gavage  
Dose volume: 5 ml/kg  
Formulation/Vehicle: water  
Species/Strain: Sprague Dawley rats  
Number/Sex/Group: 15/sex/group  
Age: 21 days  
Weight: 29.5-51.5 g  
Satellite groups: TK group and a toxicity recovery group  
(15/sex/group)  
Unique study design: none  
Deviation from study protocol:

## Observations and Results

### Mortality:

Methods: animals were observed twice a day for mortality.

Results: no drug related deaths were observed. One female (CYB3F207) from the MD group was euthanized in extremis on Day 86 due to injury during the weighing procedure that was associated with an abdominal wound and thus resulting in the deterioration of the condition of this animal. Gross and microscopic pathologic findings indicated an intestinal perforation and peritonitis and the cause of the moribund condition.

### Clinical Signs

Methods: examination for general signs of toxicity were conducted once daily

Results: decreased activity was observed within hours of dosing in most animals treated with the LD on one or two days and all animals treated with MD and HD on numerous days. Piloerection was also observed within few hours of dosing in most animals treated with LD on one day only (M) or few days (F) and in all animals treated with MD and HD on numerous days. The decreased activity in animals was attributed to the sedative effect of clonidine while the piloerection was considered as an adaptive response to the lower body temperature, which was presented by the sponsor as one of the pharmacological effects of clonidine in rats (Livengston, Br. J. Pharmac 81:189-193,1984).



## Body Weights

Methods: body weights were recorded for all animals twice weekly

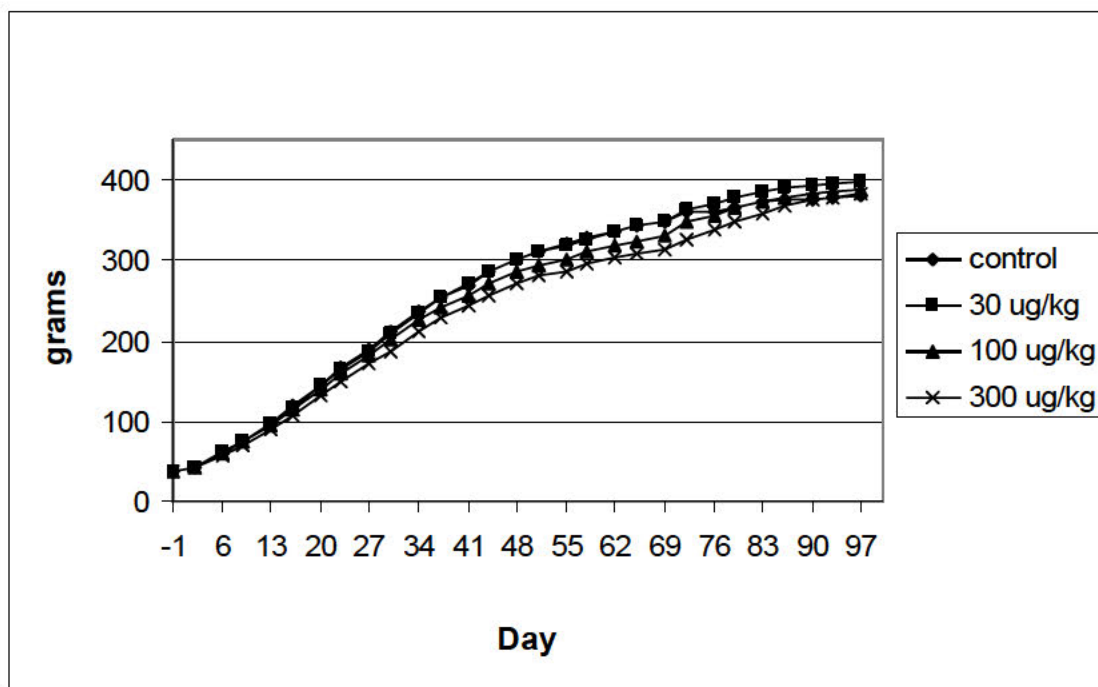
Results: There was no effect on absolute body wt in animals treated with 30 µg/kg. A slight decrease (~5% compared to control) was seen in M treated with 100 µg/kg while no effect was seen in F from this group. A 10% decrease compared to the control group in absolute body wt was observed in M treated with 300 µg/kg almost throughout the dosing period; however, decreases in body wt in F from this group were observed early in the study (ranged from 4% to ~8% compared to the control up to day 23 of treatment) but the decrease was only 2% compared to the control group by the end of the dosing period. There was no effect on body wt at the end of the recovery period in any of the treated groups compared to the control group. The following table provided by the sponsor summarizes the effect on body wt:

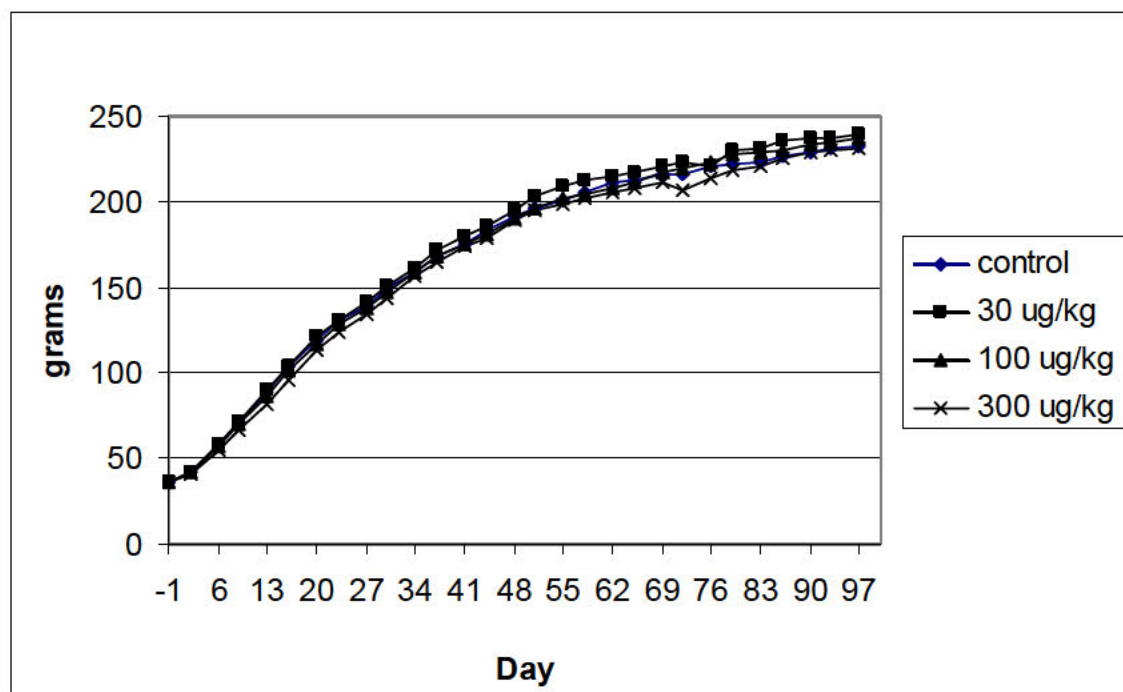
**Table 3 Effects on by weight as a result of treatment with clonidine in juvenile rats**

Test material = Dose (µg/kg/day) =	Males				Females			
	H <sub>2</sub> O 0	Clonidine HCl			H <sub>2</sub> O 0	Clonidine HCl		
	0	30	100	300	0	30	100	300
Body weight gain (g)								
1 <sup>st</sup> month (Days -1 to 30)	175	172	164	151	114	115	111	108
2 <sup>nd</sup> month (Days 34 to 69)	112	115	103	102	57	60	58	55
Recovery period	27	37	46	62	16	17	14	23
Body weight (g)								
Day 30	212	209	201	188	150	151	148	144
Day 69 (end of dosing)	349	348	330 <sup>5/10</sup>	313 <sup>5/10</sup>	216	221	217	212 <sup>2/10</sup>
Day 97 (end of recovery)	382	398	388	383	232	239	237	231

The following figures were created by the reviewer and reflect the effect of treatment on body weight throughout the study.

**Figure 3 Mean body weights in males treated with clonidine for 10 weeks**



**Figure 4 Mean body weights in females treated with clonidine for 10 weeks**

## Feed Consumption

Methods: food consumption was recorded weekly

Results: there was an increase in food consumption observed sporadically in M treated with MD and HD (~10% compared to control) and in all treated F groups (~10% or slightly greater). The sponsor considered this increase as not significant and not drug related (according to Sponsor possibly due to adaptive response to increase body temperature).

## Ophthalmoscopy

Methods: an ophthalmic examination by direct ophthalmoscopy was conducted by a veterinarian on all rats prior to assignment to the study, on toxicity rats on days 12, 33, and 68, and on toxicity rats near the end of the recovery period.

Results: at the doses used in this study, there appears to be no drug effect on ophthalmic parameters. However, there were a couple of males with corneal opacity, one from the LD group (CYB2M059) that had a transient unilateral corneal opacity of the right eye on Day 33 only, while another male from the HD group (CYB4M103) had a

unilateral corneal opacity of the right eye on Days 33 and 68. This animal was sacrificed at the end of the treatment period. There were no ophthalmic findings in animals of the recovery group. The sponsor stated that neither of the corneal findings observed in this study resembled the “distinct, severe bilateral corneal opacities seen in higher dosages of the range-finding study” (see Study (b) (4) 0978-08279). The sponsor considered these findings unrelated to clonidine, and “most likely a consequence of traumatic insult, because they occurred only in one eye of each animal, one opacity disappeared despite continued dosing, and opacities did not occur in any female”. The reviewer believes that the high dose was not high enough to trigger the observation of these opacities that were found at higher doses in the range finding studies.

## Hematology

Methods: whole blood was collected at scheduled euthanasia. The following parameters were evaluated:

White blood cell count	Mean cell volume
Absolute differential leukocyte count	Mean cell hemoglobin
Red blood cell count	Mean cell hemoglobin concentration
Hemoglobin	Platelet count
Hematocrit	Reticulocyte count

In addition, coagulation parameters such as prothrombin time and activated partial thrombin time were evaluated.

Results: some changes were observed in treated animals. Some of these changes included a slight increase in red blood cells, hemoglobin, and hematocrit (in F only at the LD), a statistically significant decrease in reticulocytes in M treated with MD (not seen in the recovery group) and the effect was not seen in F. In M treated with HD, a slight but statistically significant increase in neutrophils, hemoglobin, and hematocrit, as well as a decrease in lymphocytes and reticulocytes were observed. Similar findings were seen in F treated with the same dose (increases in red blood cells and platelets were also observed). There was no effect seen in F at the end of the recovery period, while in M a statistically significant increases in mean corpuscular volume and mean corpuscular hemoglobin was observed and an increase in reticulocytes was observed compared to the decrease that was observed at the end of the treatment period. According to the sponsor, there were no microscopic changes in bone marrow (no data provided). According to the sponsor, the differences between treated groups and the control described above are considered slight and within normal reference ranges and thus did not indicate an adverse drug effect. The reviewer tends to agree with the sponsor's conclusion. There was no treatment relate effect on coagulation parameters.

**Clinical Chemistry**

Methods: whole blood was collected at scheduled euthanasia. The following parameters were evaluated:

Sodium	Total cholesterol
Potassium	Triglycerides
Chloride	Total protein
Alkaline phosphatase	Albumin
Alanine aminotransferase	Globulin (calculated)
Aspartate aminotransferase	Albumin/globulin ratio (calculated)
Glucose	Calcium
Blood urea nitrogen	Inorganic phosphorus
Creatinine	Total bilirubin

Results: the following changes in some parameters were summarized by the sponsor in the following table:

**Table 4 Summary of the effects on clinical chemistry parameters in clonidine treated juvenile rats:**

Test material = Dose (µg/kg/day) =	Males				Females			
	H <sub>2</sub> O	Clonidine HCl			H <sub>2</sub> O	Clonidine HCl		
	0	30	100	300	0	30	100	300
Alkaline phosphatase (U/L)								
End of dosing	101	116	117	130	84	96	107	106
End of recovery	99	92	96	102	88	87	88	89
Phosphorus (mg/dL)								
End of dosing	9.9	10.5	10.5	11.1	9.4	10.2	10.8	10.8
End of recovery	9.8	9.9	9.8	9.9	9.8	9.6	9.3	9.7
Alanine aminotransferase (U/L)								
End of dosing	46	51	50	50	38	45	44	43
End of recovery	55	52	49	47	40	42	39	41
Aspartate aminotransferase (U/L)								
End of dosing	91	93	100	97	88	98	94	100
End of recovery	92	89	86	85	89	94	90	94
Creatinine (mg/dL)								
End of dosing	.68	.69	.69	.75	.71	.72	.73	.79
End of recovery	.71	.72	.74	.72	.79	.79	.80	.78
Albumin (g/dL)								
End of dosing	4.0	4.1	4.1	4.2	4.0	4.1	4.2	4.3
End of recovery	4.1	4.1	4.2	4.1	4.3	4.3	4.3	4.3
Calcium (mg/dL)								
End of dosing	11.1	11.3	11.2	11.5	10.8	11.0	11.3	11.4
End of recovery	11.2	11.4	11.5	11.5	11.4	11.5	11.1	11.3
BUN (mg/dL)								
End of dosing	19	20	23	27	22	22	24	27
End of recovery	20	20	19	19	24	24	24	23
Glucose (mg/dL)								
End of dosing	181	161	169	219	114	92	106	146
End of recovery	164	175	175	169	96	101	96	98
Chloride (mM)								
End of dosing	101	103	101	98	104	103	102	99
End of recovery	100	100	100	100	102	102	102	102

All these changes were reversible as they were not observed at the end of the recovery period.

The increase in glucose levels observed in animals treated with HD compared to control (~20% in M and 28% in F) was attributed by the sponsor to the effect of clonidine as an alpha2-adrenergic agonist in suppressing insulin release (Ruffolo RR, The alpha-2-adrenergic receptors, Clifton, NJ: Humana Press, 1988, p. 187-280) and/or in centrally mediated gluconeogenesis enhancement (DiTullio, J Pharmcol Exper Ther 228(1):168-173, 1984). Accordingly, the sponsor considered these effects not to be adverse. The other observed changes were also considered not adverse since they were slight in magnitude or within or slightly higher than the normal range (ALP and P). In addition,

since no histopathological changes were observed indicating organ pathology that can correlate with changes in these parameters, the sponsor considered them “not clinically meaningful”. The reviewer agrees with the sponsor’s evaluation of these changes as not clinically significant; however, the increase in glucose levels can be considered as a drug related effect. The increase in ALP and P could be attributed to a drug effect even though there were no histopathological findings that might relate to these changes.

## Urinalysis

**Methods:** urine was collected from five toxicology animals per sex per group near the end of the dosing period, and the same five animals near the end of the recovery period. The following parameters were evaluated:

Specific gravity	Urobilinogen
pH	Bilirubin
Nitrite	Occult blood
Protein	Color and appearance
Glucose	Microscopy of sediment (if protein
Ketones	equals or exceeds 100 mg/dL or occult
	blood equals or exceeds 50 ery/ $\mu$ L)

**Results:** the following changes were the findings reported for the effect of clonidine treatment on urine parameters:

**Table 5 Effect of clonidine treatment on urine parameters in juvenile rats:**

Test material = Dose ( $\mu$ g/kg/day) =	Males				Females			
	H <sub>2</sub> O 0	Clonidine HCl 30	Clonidine HCl 100	Clonidine HCl 300	H <sub>2</sub> O 0	Clonidine HCl 30	Clonidine HCl 100	Clonidine HCl 300
Specific gravity								
End of dosing	1.03 6	1.03 9	1.02 4	1.01 8	1.03 7	1.02 6	1.01 5	1.01 4
End of recovery	1.03 6	1.03 2	1.03 3	1.03 3	1.03 8	1.04 1	1.04 1	1.04 0
Protein (mg/dL)								
End of dosing	246	138	113	3	19	7	1	0
End of recovery	406	166	114	39	20	29	15	103
Ketones (mg/dL)								
End of dosing	12	12	9	0	9	3	0	0
End of recovery	12	9	6	15	9	12	12	12

There was also an increase in glucose levels in urine. This effect was attributable to the pharmacodynamic effect of clonidine on glucose serum levels (see Clinical Chemistry section). The effects on urine specific gravity, urine ketone and glucose concentration were reversible at the end of the recovery period. However, the effect on protein levels was reversible in F only but not in M. The significance and the reason for this decrease in protein levels is not clear and the sponsor promoted this effect as “beneficial” rather than adverse.

## **Gross Pathology**

Methods: at necropsy, animals were examined for external abnormalities. The abdominal, thoracic, and cranial cavities and their contents were examined for abnormalities. Bone marrow slides were prepared from each animal but were not evaluated.

Results: no treatment related findings.

## **Organ Weights**

Methods: organs specified in the histopathology table below, were removed, examined, and weighed. Pre-necropsy fasted body wts were used for calculation of organ weight to body wt ratios. Organ wts were expressed as absolute values and as organ weight:body weight and organ weight:brain weight ratios.

Results: some changes in some organ wts were observed such as a slightly lower kidney wt at all dose levels with the effect also seen when the kidney wt was expressed relative to body or brain wt. This effect was reversed at the end of the recovery period and there were no histopathological findings associated with this decrease. Liver wt was slightly higher in F at all doses with no obvious dose effect and there was no effect in M. This effect was reversed at the end of the recovery period and there were no histopathological findings with this increase. Slightly lower spleen and thymus wt at the HD in both sexes. The effect was mostly reversed by the end of the recovery period and there was no histopathological findings seen with this decrease.

## **Bone length and density:**

Methods: the femur not used for bone marrow slide preparation was used for the evaluation of bone length, width, and density. Bones from 5 rats/sex/group were used for the assessment of bone density using underwater bone density (Archimedes Principle) and Micro Computed Tomography (CT) scan measurements of trabecular and cortical density. The bone evaluation component was not conducted in complete compliance with GLP regulations since the analysis laboratory test site does not have GLP capability.



Results: mean femur length, width, underwater density, trabecular density by CT scan, and cortical density by CT scan were similar in all groups and there was no difference between control and treated groups at the end of the dosing and recovery periods.

## **Histopathology**

Adequate Battery: at necropsy, tissue samples specified in the table below were placed in 10% neutral buffered formalin. The fixed tissues from control and HD group and tissues from the rat that was euthanized early in MD group were then processed and stained with hematoxylin and eosin and examined by light microscopy by the study pathologist who then issued the pathology report.

**Table 6 List of tissues collected and examined**

<b>Tissue</b>	<b>Organ Weight Taken</b>	<b>Collected and Preserved in 10% NBF</b>	<b>Microscopic Examination</b>
Adrenal glands*	X	X	X
Aorta (thoracic)		X	X
Brain	X	X	X
Cecum		X	X
Cervix		X	X
Colon		X	X
Duodenum		X	X
Epididymides*	X	X	X
Esophagus		X	X
Eyes		X	X
Femur, proximal		X	
Heart	X	X	X
Identification (tail)		X	
Ileum		X	X
Jejunum		X	X
Kidneys*	X	X	X
Lacrimal gland		X	X
Lesion(s)		X	X
Liver	X	X	X
Lungs		X	X
Lymph node - cervical		X	X

Tissue	Organ Weight Taken	Collected and Preserved in 10% NBF	Microscopic Examination
Lymph node - mesenteric		X	X
Mammary gland (region)		X	X
Muscle (biceps femoris)		X	X
Optic nerves		X	X
Ovaries*	X	X	X
Pancreas		X	X
Peyer's Patch with jejunum and/or ileum		X	X
Pituitary		X	X
Prostate		X	X
Rectum		X	X
Salivary gland, mandibular		X	X
Sciatic nerve		X	X
Seminal vesicles		X	X
Skin		X	X
Spinal cord – cervical, thoracic		X	X
Spleen	X	X	X
Sternum with marrow		X	X
Stomach		X	X
Testes*	X	X	X
Thymus (region)	X	X	X
Thyroids/Parathyroids*	X	X	X (1 parathyroid)
Tongue		X	
Trachea		X	X
Urinary bladder		X	X
Uterus		X	X
Vagina		X	X

Peer Review: no peer review was conducted for this study. Histopathology evaluation was conducted by (b) (4) with (b) (4) as the veterinary pathologist. A pathology report was provided by (b) (4) and co signed by the principal Investigator from (b) (4) (b) (4)

Histological Findings: there were no treatment related findings.

The one animal that was moribund (CYB3F207, treated with the mid-dose of 100 ug/kg) was reported to have gross and microscopic findings reflective of intestinal perforation and peritonitis and that was considered the cause of death.

## Special Evaluation

**Locomotor activity evaluation:** rats were evaluated near the end of the 10-week treatment period and near the end of the recovery period (15/sex/group, the animals used during the treatment period were different from those used during the recovery period), by measuring the distance traveled during test periods in a BASi Force Place Actimeter (FAP). Rats were placed for 5-min test period during which their activity was recorded. Measurement of distance traveled by each animal during the five 1-min intervals, and during the total 5-min recording period were evaluated. All testing was performed during the morning period prior to daily dosing to “avoid the known acute post-dosing effect of decreased activity caused by clonidine”. The locomotor activity component was conducted in complete compliance with GLP regulations as the actimeter device, however, according to the sponsor although the device “having completed a validation process according to (b) (4) SOPs, does not completely comply with GLPs”.

**Results:** there was no effect on the distance traveled by the treated animals compared to the control. It is not clear if the vertical motor activity of animals can be captured by this instrument. However, the clinical signs did not include any description of an increase in motor activity, to the contrary a decrease in motor activity was observed immediately after treatment. Since the evaluation of motor activity using this instrument was done in the morning and before drug treatment, then the decrease in motor activity encountered immediately after drug treatment was reversed before the next dosing.

**Learning and memory evaluation:** spatial learning and memory were evaluated in rats scheduled for termination near the end of the 10-week dosing period and near the end of the recovery period (15/sex/group, the animals used during treatment were different from those used during recovery), by using the Morris water maze (MWM). Learning was evaluated by measuring the change in swim time used to escape the water over nine training trials. Memory was evaluated by a single probe trial in each rat four days following the learning trials. For each training or probe trial, a rat was placed in the MWM at a specific location in the tank and allowed to swim for a maximum of 120 seconds or until it found the escape pedestal and climbed out of the water. If an animal failed to find the escape pedestal within the 120-seconds time limit, then it was guided

to the escape pedestal and allowed to climb out of the water and visualize its location before returning to its cage.

**Results:** There appeared to be no treatment effect of clonidine on learning the Morris water maze in rats, either during treatment or after the recovery period. All rats including the control took progressively less time finding the target during several (9) daily training trials, as indicated by the decrease in escape time, during both the treatment period and the recovery period. The following table provided by the sponsor summarizes these findings:

**Table 7 Effect on clonidine treatment on learning**

Test material = Dose (µg/kg/day) =	Males				Females			
	H <sub>2</sub> O	Clonidine HCl			H <sub>2</sub> O	Clonidine HCl		
	0	30	100	300	0	30	100	300
Mean escape time (sec)								
End of dosing								
1 <sup>st</sup> trial	105	97	102	94	90	95	106	100
9 <sup>th</sup> trial	57	43	54	52	48	40	42	64
End of recovery								
1 <sup>st</sup> trial	81	115	83	100	111	111	107	95
9 <sup>th</sup> trial	50	30	38	41	53	61	54	51
Decrease in escape time (sec)								
End of dosing								
End of dosing	48	54	48	42	42	55	64	36
End of recovery								
End of recovery	31	85	45	59	58	50	53	44

In trials conducted to investigate the effect on memory by conducting probe trials four days after the learning trials, all rats tended to have longer time to escape during the memory probe trial compared to their last learning trial (which indicates that they did not completely retain the learning experience). However; all groups performed better than in their first learning trial and there was no difference between the control and treated groups, which suggests that the drug had no effect on memory for this task. The results of this test are summarized in this table as provided by the sponsor:

**Table 8 Effect of clonidine treatment on memory**

Test material = Dose ( $\mu\text{g/kg/day}$ ) =	Males				Females			
	H <sub>2</sub> O 0	Clonidine HCl			H <sub>2</sub> O 0	Clonidine HCl		
		30	100	300		30	100	300
Mean escape time (sec)								
End of dosing								
1 <sup>st</sup> learning trial	105	97	102	94	90	95	106	100
9 <sup>th</sup> learning trial	57	43	54	52	48	40	42	64
Probe (memory) trial	68	70	81	80	55	66	75	64
End of recovery								
1 <sup>st</sup> learning trial	81	115	83	100	111	111	107	95
9 <sup>th</sup> learning trial	50	30	38	41	53	61	54	51
Probe (memory) trial	66	92	67	71	85	92	85	75

## Toxicokinetics

**Methods:** whole blood samples were collected after the first dose (via a terminal cardiac puncture) and near the end of dosing period (via a peripheral vein). Samples were collected at 1-h post dose (group 5) and prior to dosing (at the end of the study) and at 0.5, 1, 2, 4, 8, and 24h after dosing from groups 6-8. Three animals per sex in each dose group were sampled at each time point. Samples were shipped and to (b) (4) for analysis.

**Results:** clonidine was rapidly absorbed with a  $t_{\text{max}}$  of 0.5-1 h. Systemic exposure tended to increase linearly with dosing. There was no sex difference in plasma levels. Systemic exposure was lower at the end of the study compared to the beginning of the study. The sponsor attributed this difference to the increase in the rate of clonidine clearance from plasma as rats matured. In addition, CL/F values were lower on Day 1 compared to Day 69, which was also contributed to the reflection of the maturation of the excretory systems as the rats matured. CL/F values were higher in M than in F, on both days, and there was a slight decrease in CL/F with increase in dose. The following table provided by the sponsor summarizes these values:

**Table 9 Plasma clonidine concentration in juvenile rats****Table 6. Noncompartmental Clonidine Toxicokinetic Parameters in Juvenile Rats**

Dose (µg/kg)	Day	Sex	C <sub>MAX</sub> (pg/mL)	T <sub>MAX</sub> (h)	λ <sub>z</sub> (1/h)	t <sub>½</sub> (h)	AUC <sub>LAST</sub> (h*pg/mL)	AUC <sub>INF</sub> (h*pg/mL)	CL/F (mL/h/kg)
30	1	Female	3320	1.00	0.105	6.57	11596	20247	1482
		Male	3510	1.00	0.224	3.10	12876	15376	1951
		Overall	3410	1.00	0.165	4.84	12236	17811	1716
100	1	Female	10700	2.00	0.187	3.70	65764	66456	1505
		Male	16300	0.50	0.158	4.40	52560	53569	1867
		Overall	13500	1.25	0.172	4.05	59162	60012	1686
300	1	Female	26700	0.50	0.143	4.84	207716	213602	1404
		Male	35000	0.50	0.158	4.40	184916	188471	1592
		Overall	30900	0.50	0.150	4.62	196316	201037	1498

Dose (µg/kg)	Day	Sex	C <sub>MAX</sub> (pg/mL)	T <sub>MAX</sub> (h)	C <sub>MIN</sub> (pg/mL)	λ <sub>z</sub> (1/h)	t <sub>½</sub> (h)	AUC <sub>τ</sub> (h*pg/mL)	CL <sub>ss</sub> /F (mL/h/kg)
30	69	Female	2970	1.00	0.00	0.225	3.08	14091	2129
		Male	3120	1.00	0.00	0.410	1.69	9951	3015
		Overall	3050	1.00	0.00	0.317	2.39	12021	2572
100	69	Female	6250	2.00	0.00	0.123	5.64	55126	1814
		Male	5460	0.50	0.00	0.258	2.69	31549	3170
		Overall	5860	1.25	0.00	0.190	4.16	43338	2492
300	69	Female	20800	4.00	195	0.229	3.03	165627	1811
		Male	12500	2.00	92.5	0.251	2.76	147555	2033
		Overall	16600	3.00	144	0.240	2.89	156591	1922

**Stability and Homogeneity:**

Methods: the sponsor indicated that dosing solutions were prepared

(b) (4)

(b) (4)

(b) (4) (the sponsor stated it was ~Day 15, but the reviewer believes it would have been day 8 of testing, since the study started on March 11 and the exit sample was collected on March 18, 2009). One set of the duplicate was stored at 2-8 °C until analyzed while the other was stored at - 20 °C. The samples were analyzed using a validated method (the sponsor included the method in the dose finding study results but not here, see the review of that study earlier). The method used in this study was referred to as SAP-1408, however, it was labeled as AC-AM-148-R3 in the dose finding study. It is not known if they are the same. In addition, the Sponsor referred to the formulation validation report number and the formulation stability report number as 1002-091408-001, however, this report was not included in this submission.

Results: the Sponsor indicated that the method of detection for the method used here ("validate (b) (4) was in the range of (b) (4) Analysis of dosing formulations indicated that the doses prepared were in the (b) (4) of the nominal concentration. The sponsor stated that the formulations were stable during the period of use (8-weeks), however, the presented data documented the stability for samples collected in the first week (i.e. 1 week stability) and no samples were collected to prove the stability for more than one week. The samples were collected (other than those collected in the first week) and stored refrigerated and analyzed after 8 weeks and since they were similar to the values obtained from the first week samples, the sponsor considered that the stability was confirmed for those samples as well (i.e. after 8 weeks). The sponsor provided data from the literature that clonidine solutions when stored at 2-8 C are stable for 28 days (see review of previous study for reference). Therefore, the stability of the prepared solutions in this study even though not confirmed for the whole period, could be considered as adequate since the samples were prepared either weekly or biweekly.



**9.3 PIVOTAL JUVENILE RAT STUDY: reproductive assessment:**

Study title: Fertility and early embryonic development study in rats given clonidine HCl from 3 to 13 weeks of age

Study no.: 0978-09009

Study report location: Retained in the conducting laboratory for five years

Conducting laboratory and location:



Date of study initiation: 02 March 2009

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Clonidine HCl, Lot #XK0551, 99.4%

**Key Study Findings**

In the reproductive study to assess the effect of the treatment on sexual maturation and reproduction in treated juvenile animals, the study utilized the same doses that were used in the toxicology and neurobehavioral assessment part of the definitive study. However, there was no evaluation of clinical signs or recording of body weight in these animals. Therefore, one has to assume that the findings in these parameters that were observed in the toxicology and neurobehavioral assessment part of the study hold for the reproductive part of the study. At these doses, there was a slight delay in sexual maturation in M treated with HD as reflected by a delay in preputial separation compared to control animals (a delay of 3 days). A delay in vaginal opening was observed in F at all doses compared to the control group (a delay of 3-5 days), but was not statistically significant. There was no effect on sperm number or motility in treated males and there were no effects on any of the reproductive parameters evaluated in this study.

**Methods**

Doses: 0, 30, 100, and 300 µg/kg/day  
Frequency of dosing: Daily  
Route of administration: Orally by gavage  
Dose volume: 5 ml/kg  
Formulation/Vehicle: Solution/water  
Species/Strain: Sprague Dawley rats  
Number/Sex/Group: 25/sex/group  
Age: 21 days  
Weight: 27.2-52.2 g  
Satellite groups: none

Unique study design: Animal from each sex were treated for 70 days and after a 4-week recovery period they were cohabitated with untreated animal from the opposite sex for up to 21 days at the time the males were sacrificed and sperm analysis including sperm motility and count was conducted for treated males only. The females were maintained and were euthanized on an estimated GD 14 for postmortem evaluation (examination of the reproductive tract, record the number of ovarian corpora lutea, number of females pregnant, the number and location of uterine implantation sites, the number of early and late resorptions, live fetuses, and dead fetuses).

Deviation from study protocol:

## **Observations and Results**

### **Mortality:**

Methods: animals were observed twice a day for morbidity, mortality, injury, and availability of food.

Results: one M (CYC2M46) treated with the low dose of 30 µg/kg of clonidine HCl was found dead on Day 12. The death was reported by the sponsor as “accidental due to trauma”. One male from the untreated group was sacrificed on Day 6 due to overgrowth and fracture of the incisors.

**Clinical Signs:** not evaluated.

**Body Weights:** recorded for the purpose of dose adjustment only; not reported.

**Feed Consumption:** not evaluated.

**Ophthalmoscopy:** not conducted.

**ECG:** not conducted.

**Hematology, Clinical Chemistry, Urinalysis:** not conducted.

**Gross Pathology and Organ weights:** not conducted.

**Histopathology:** not conducted; however, treated females were examined to evaluate the effect on reproductive parameters (see below).

Methods: this study was designed to investigate the effect of clonidine treatment on sexual maturation and reproductive parameters. Animals were treated for 70 days commencing on PND 21. During the treatment period animals were evaluated for sexual maturation (vaginal opening in F and preputial separation in M, starting from PND 21 until achieved). At the end of the treatment period, a 4-week recovery period was implemented and at the end of this period treated animals were cohabitated with untreated animals from the opposite sex for up to 21 days (animals were cohabited in pairs). After the confirmation of mating, treated females were maintained for 14 days and then euthanized for postmortem evaluation of reproductive parameters (examination of the reproductive tract, record the number of ovarian corpora lutea, number of females pregnant, the number and location of uterine implantation sites, the number of early and late resorptions, live fetuses, and dead fetuses). Sperm analysis that consisted of analysis of sperm motility and count was conducted for treated males (15 animals). For the measurement of sperm motility, the right vas deferens was excised and immediately placed in a petri dish and a 2-minute period was used for the sperms to disperse and then images were taken for the sperms for motility analysis. A sperm sample was collected and loaded into a prewarmed (b) (4) (b) (4). Some samples contained less than 25 sperms and they were not used for calculations. Sperm number was evaluated using the right epididymis. The number of sperms/g of tissue was measured using a staining method that is used for this purpose and using an analyzer.

Results:

Sexual maturation: a delay in sexual maturation reflected by a delay in preputial separation in M treated with HD compared to the control group. The mean age at sexual maturation in M was 45, 45, 45, and 48 days at 0, 30, 100 and 300 µg/kg/day; respectively. The difference between the control and HD groups was statistically significant. An effect was also observed in F where the mean age at sexual maturation was 44, 49, 48, and 47 days at 0, 30, 100, and 300 µg/kg/day; respectively (for individual values please see Appendix at the end of the review). However, the

difference between treated and the control animals was not statistically significant at any dose. The sponsor concluded that the mean sexual maturation age for all groups, male and female, were considered normal and the "slight differences when compared to the control group mean could not definitely be attributed to clonidine HCl".

Reproductive parameters: there were no differences between treated F mated with untreated M or untreated F mated with treated M and the control animals in any of the reproductive parameters evaluated (see the list in the description of methods above).

Sperm analysis: there was no effect of treatment on the number and motility of sperm in treated M compared to the control group.

**Toxicokinetics:** no evaluation of plasma levels was conducted.

### **Stability and Homogeneity**

According to the Sponsor, all formulations were with 3% of the nominal (i.e. ranged from 97%-103%), none of samples identified as vehicle control contained clonidine HCl, and the results from the entrance and exit samples confirm that clonidine HCl was stable in dose formulations during the period of use. There were no data submitted in this study to support the sponsor's statement; however, in the previously reviewed part of the study the sponsor indicated that the formulation used in that study were used in this study also and discussion pertaining to this issue was presented in the review of that study (see above for review of study # 0978-09008).

**Discussion of the Limitations of the Reproductive Study:**

The only treatment-related effect that was seen in this study was a delay in preputial separation in males treated with the high dose of 0.3 mg/kg. The slight delay in vaginal opening seen in all treated female groups did not reach statistical significance.

The doses used in this reproductive study are the same as those used in the study of toxicology and the neurobehavioral development; however, there was no TK assessment or evaluation of the effect of the treatment on clinical signs or on body weight of animals in the study for assessment of effects on reproductive potential. Although it is assumed that adequate dosing and similar exposures were achieved in the reproductive study, there is no direct evidence to support this. However, the sponsor stated that the dosing solutions were prepared similarly to those used in the toxicology/neurobehavioral study and that the measured levels were within the acceptable range of nominal doses.

Nonetheless, this reviewer is concerned that adequate doses/exposures may not have been tested for reproductive effects in female rats, because there was no toxicity observed up to the high dose of 0.3 mg/kg. The lack of any effect of treatment could reflect suboptimal concentrations of the drug in plasma; clonidine levels were not measured in these animals and have to be inferred from the levels seen in animals used for the toxicology/neurobehavioral study. It should also be noted that the high dose of 0.3 mg/kg was not associated with dose-limiting findings in females in the toxicology/neurobehavioral study, where there was only a transient and modest decrease in body weight gain and body weights at the end of dosing were only 2% lower than controls. Body weights were not assessed in the reproductive study. However, it should also be noted that unacceptable ( $\geq 18\%$ , compared with controls) decreases in body weights were seen at doses of 1 mg/kg and greater in the 14-day dose range finding study.

Therefore, this reviewer suggests that a higher dose of clonidine be used as an added monotherapy arm in female rats in the combination study of clonidine with stimulants which will be conducted as a Phase IV commitment. Such a dose should be decided based on the findings seen so far with the doses used in the submitted studies (a dose of 0.5 mg/kg might be a dose of choice based on the findings we have so far).

## 11 Integrated Summary and Safety Evaluation

Because the current oral formulation of clonidine has recently been approved as Jenloga for treatment of hypertension, only a juvenile animal (rat) study (or studies) to assess 1) general toxicology, 2) neurobehavioral development and 3) reproductive potential of clonidine was required to support the use of clonidine in children under the supplements for the current indication of ADHD. For their juvenile rat studies (separate studies were conducted to assess toxicology/neurobehavioral and reproductive potential), the sponsor selected doses of 0, 0.03, 0.1, and 0.3 mg/kg. These doses were based on a 14-day dose range finding study, where unacceptable decreases in body weights ( $\geq 18\%$  compared with controls) were seen at doses  $\geq 1$  mg/kg and decreased body weight and ocular toxicity at the high dose of 3 mg/kg resulted in premature termination of the group at day 8. In the definitive studies, the only significant finding was a slight delay in preputial separation in male rats at the high dose of 0.3 mg/kg.

The doses used in the definitive studies can be considered adequate in males based on the effect of the high dose on body weight ( $\sim 9\%$  decrease compared to control), as measured in the toxicology/neurobehavioral study. However, neither the expected decrease in body weight nor any other limiting toxicity was seen in females in the definitive studies. At the end of dosing in the toxicology/neurobehavioral study, there was only a 2% decrease in body weight observed in females treated with the high dose of 0.3 mg/kg, even though that dose had produced an  $\sim 8\%$  decrease in females in the 14-day range finding study and the next higher dose of 1 mg/kg produced much larger decrease in body weight ( $\sim 18\%$  decrease compared to control). In the reproductive study, body weights were not assessed and no other clear indications of toxicity were seen.

Although the dose selection was reasonable based on the findings in the dose range finding study, this reviewer is particularly concerned that adequate doses/exposures may not have been tested for reproductive effects in female rats, because there was no toxicity observed up to the high dose of 0.3 mg/kg in that study. The lack of any significant effect of treatment could reflect suboptimal concentrations of the drug in plasma; clonidine levels were not measured in these animals and have to be inferred from the levels seen in animals used for the toxicology/neurobehavioral study. It should also be noted that the high dose of 0.3 mg/kg was not associated with dose-limiting findings in females in the toxicology/neurobehavioral study either, where there was only a transient and modest decrease in body weight; and body weights were not assessed in the reproductive study (as discussed above).

Therefore, this reviewer recommends that a higher dose of clonidine be used as an added monotherapy arm in female rats in the combination study of clonidine with stimulants which will be conducted as a Phase IV commitment (see below). This higher dose should be based on the findings seen so far with the doses used in the submitted studies (a dose of 0.5 mg/kg might be reasonable based on the findings). However, it

should be noted that unacceptable ( $\geq 18\%$ , compared with controls) decreases in body weights were seen at doses of 1 mg/kg and greater in the 14-day dose range finding study.

Nonetheless, it seems safe to conclude that at the doses used in the definitive studies, clonidine was not associated with adverse effects in juvenile rats treated to maturity. The only notable finding was a slight delay in sexual maturation that was observed in males at the high dose of 0.3 mg/kg. The lack of effect in females could have been affected by the less than optimal dosing in females and thus might have been evident if a higher dose had been used in these animals. It should be pointed out that fertility was affected in adult female rats treated at slightly higher doses of  $\geq 0.5$  mg/kg (as described in the labeling).

It should be noted that the human average AUC value as calculated from the  $C_{ss} \cdot \tau$  ( $C_{ss} \cdot 24$ ) was  $\sim 17,814$  pg.h/ml in patients (6-17 years of age) treated with 0.4 mg (this is the average value, however, some subjects had levels of up to  $\sim 60,480$  pg.h/ml, see data provided by Biopharm reviewer Dr. Andre Jackson). Therefore, based on the AUC values from the rats treated at the highest dose of 0.3 mg/kg in this study, the human safety factors will be  $\sim 5$  (based on the average human AUC) and as low as 2 (based on the individuals with higher plasma concentrations).

Regarding the labeling of this product, the preclinical information in the labeling for Jenloga, which was recently approved by the Division of Cardioresenal Products, will be used as a basis for the labeling of the ADHD indication. In contrast to Jenloga labeling, where the animal doses were described as human equivalent doses (HEDs), the sponsor proposed using safety factors as multiples of the maximum recommended human dose. While we agree with this change, we have calculated slightly different safety factors, based on  $\text{mg}/\text{m}^2$  doses. In addition, the language in the Jenloga labeling that pertains to the mechanism of action needs to be changed to reflect the indication of ADHD (rather than hypertension). Finally, the results from the juvenile animal studies that were submitted and reviewed here, specifically the effects observed on sexual maturation in treated male rats, should be described in the labeling under section 8.4, because this finding might relate to sexual maturation in children treated with this compound. It could also be noted that there appeared to be of no effect on fertility contrary to what was observed in adult female that were treated with higher doses as described in the labeling.

The ocular toxicity seen with clonidine in adult animals (spontaneous retinal degeneration in albino rats, corneal lesions in rats treated with a combination of clonidine and amitriptyline and clonidine concentration in the choroid in dogs and monkeys treated with clonidine) was described in the Jeloga labeling (section 13.2) and will be retained in the current labeling for ADHD. In the juvenile studies submitted and reviewed here, the findings of ocular opacities were mainly evident in the dose ranging study at the high dose of 3 mg/kg (all animals), with some animals effected at the next lower dose of 1 mg/kg/day (3/8 males). However, at the dose of 0.3 mg/kg, which was the high dose used in the definitive study, these opacities were not observed. The

reviewer believes that the ocular findings reported for the Jenloga labeling should be used in the same format for the ADHD labeling and as proposed by the sponsor in spite of the lack of an effect in the definitive juvenile study since the doses used in this study did not result in observing these findings.

Finally, in order to support safe use of clonidine in combination with stimulants in pediatric patients and to provide additional safety information for labeling, the sponsor must conduct a juvenile animal study of clonidine in combination with a stimulant as a post-marketing commitment (as communicated in the minutes of our 3/9/09 meeting).



## **12 Appendix/Attachments**

**Individual Sexual Maturity Data  
Males**

Animal Number	Age in Days
CYC1M 1	45
CYC1M 2	45
CYC1M 3	47
CYC1M 4	46
CYC1M 5	46
CYC1M 6	46
CYC1M 7	46
CYC1M 8	51
CYC1M 9	45
CYC1M 10	45
CYC1M 11	45
CYC1M 12	47
CYC1M 13	43
CYC1M 14	41
CYC1M 15	41
CYC1M 16	46
CYC1M 17	46
CYC1M 18	42
CYC1M 19	45
CYC1M 20	41
CYC1M 21	45
CYC1M 22	45
CYC1M 23	45
CYC1M 24	43
CYC1M 25	45
CYC2M 26	45
CYC2M 27	43
CYC2M 28	46
CYC2M 29	46
CYC2M 30	48
CYC2M 31	46
CYC2M 32	46
CYC2M 33	46
CYC2M 34	43
CYC2M 35	46
CYC2M 36	45
CYC2M 37	46
CYC2M 38	46
CYC2M 39	46
CYC2M 40	46
CYC2M 41	45
CYC2M 42	46
CYC2M 43	46
CYC2M 44	43
CYC2M 45	45

**Individual Sexual Maturity Data  
Males**

Animal Number	Age in Days
CYC2M 47	46
CYC2M 48	42
CYC2M 49	46
CYC2M 50	45
CYC3M 51	46
CYC3M 52	46
CYC3M 53	46
CYC3M 54	46
CYC3M 55	46
CYC3M 56	48
CYC3M 57	46
CYC3M 58	45
CYC3M 59	48
CYC3M 60	46
CYC3M 61	46
CYC3M 62	41
CYC3M 63	44
CYC3M 64	46
CYC3M 65	45
CYC3M 66	46
CYC3M 67	48
CYC3M 68	44
CYC3M 69	45
CYC3M 70	45
CYC3M 71	46
CYC3M 72	41
CYC3M 73	43
CYC3M 74	43
CYC3M 75	43
CYC4M 76	47
CYC4M 77	47
CYC4M 78	49
CYC4M 79	49
CYC4M 80	47
CYC4M 81	48
CYC4M 82	47
CYC4M 83	47
CYC4M 84	48
CYC4M 85	47
CYC4M 86	47
CYC4M 87	48
CYC4M 88	45
CYC4M 89	45
CYC4M 90	43

**Individual Sexual Maturity Data  
Males**

Animal Number		Age in Days
CYC4M	91	48
CYC4M	92	47
CYC4M	93	46
CYC4M	94	45
CYC4M	95	46
CYC4M	96	54
CYC4M	97	52
CYC4M	98	52
CYC4M	99	47
CYC4M	100	51

**Individual Sexual Maturity Data**  
**Females**

Animal Number	Age in Days
CYC1F 101	32
CYC1F 102	32
CYC1F 103	52
CYC1F 104	48
CYC1F 105	54
CYC1F 106	45
CYC1F 107	48
CYC1F 108	35
CYC1F 109	49
CYC1F 110	51
CYC1F 111	45
CYC1F 112	41
CYC1F 113	39
CYC1F 114	36
CYC1F 115	51
CYC1F 116	44
CYC1F 117	42
CYC1F 118	49
CYC1F 119	41
CYC1F 120	51
CYC1F 121	43
CYC1F 122	38
CYC1F 123	43
CYC1F 124	33
CYC1F 125	49
CYC2F 126	55
CYC2F 127	43
CYC2F 128	41
CYC2F 129	45
CYC2F 130	41
CYC2F 131	45
CYC2F 132	48
CYC2F 133	82
CYC2F 134	44
CYC2F 135	50
CYC2F 136	45
CYC2F 137	41
CYC2F 138	52
CYC2F 139	52
CYC2F 140	89
CYC2F 141	32
CYC2F 142	49
CYC2F 143	40
CYC2F 144	35
CYC2F 145	51

**Individual Sexual Maturity Data  
Females**

Animal Number	Age in Days
CYC2F 146	51
CYC2F 147	52
CYC2F 148	36
CYC2F 149	47
CYC2F 150	58
CYC3F 151	58
CYC3F 152	31
CYC3F 153	39
CYC3F 154	89
CYC3F 155	51
CYC3F 156	34
CYC3F 157	48
CYC3F 158	48
CYC3F 159	48
CYC3F 160	55
CYC3F 161	47
CYC3F 162	48
CYC3F 163	63
CYC3F 164	45
CYC3F 165	48
CYC3F 166	45
CYC3F 167	38
CYC3F 168	46
CYC3F 169	47
CYC3F 170	51
CYC3F 171	49
CYC3F 172	39
CYC3F 173	48
CYC3F 174	46
CYC3F 175	51
CYC4F 176	36
CYC4F 177	45
CYC4F 178	47
CYC4F 179	48
CYC4F 180	52
CYC4F 181	48
CYC4F 182	48
CYC4F 183	54
CYC4F 184	47
CYC4F 185	48
CYC4F 186	63
CYC4F 187	43
CYC4F 188	49
CYC4F 189	52

**Individual Sexual Maturity Data  
Females**

Animal Number	Age in Days
CYC4F 190	53
CYC4F 191	38
CYC4F 192	36
CYC4F 193	58
CYC4F 194	32
CYC4F 195	32
CYC4F 196	51
CYC4F 197	41
CYC4F 198	49
CYC4F 199	47
CYC4F 200	48

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

IKRAM M ELAYAN  
07/02/2010

LINDA H FOSSOM  
07/02/2010

Also, see the supervisory memo by Linda Fossom, Team Leader, for additional comments.



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number** 22,331 (Supplement 001, SD-15; Supplement 002, SD-16) ; SN-0019

**Drug Name:** CLONICEL® (clonidine HCl modified release)

**Indication(s):** ADHD (Attention Deficit Hyperactivity Disorder)

**Applicant:** Shionogi (initially, Addrenex)

**Dates:** Received Date: September 30, 2009, PDUFA Due Date: July 30, 2010.

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics I

**Statistical Reviewer:** Eiji Ishida, M.S.

**Concurring Reviewers:** Peiling Yang, Ph.D.  
Hsien Ming J. Hung, Ph.D.

**Medical Division:** DPP (Division of Psychiatric Products).

**Clinical Team:** Maju Mathews, M.D.  
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**Project Manager:** Hiren Patel, Pharm. D.

**Keywords:** Clinical studies; NDA review

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# **1. EXECUTIVE SUMMARY**

## **1.1 Conclusions and Recommendations<sup>1</sup>**

The efficacy assessments based on the primary efficacy analysis of data from the submitted phase III studies, CLON-301 and CLON-302, have shown evidence to support the sponsor's efficacy claim of a new treatment, CLONICEL (clonidine HCl modified release), in children and adolescents (6 to 17 years old) with ADHD. The sponsor's phase III studies, CLON-301 and CLON-302, provided statistical evidence that CLONICEL is efficacious, as a monotherapy and as an add-on to a psychostimulant, in the treatment of subjects (6-17 years-old) with ADHD.

## **1.2 Brief Overview of Clinical Studies**

The sponsor submitted two phase III studies, CLON-301 and CLON-302, to support the efficacy of two dosing regimens of CLONICEL (CLON), CLON 0.2 mg/day and CLON 0.4 mg/day, in children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD.

Study CLON-301 was an 8-week (56 days), multi-center (US alone), parallel-group, randomized, double-blind, placebo-controlled study. A total of 236 male and female subjects were randomly assigned in a 1:1:1 ratio to CLONICEL treatment, CLON 0.2 mg/day (N=78) or CLON 0.4 mg/day (N=80), or placebo (N=78). The majority of subjects (60.6%) completed the treatment phase. Dosing for the CLON groups started at 0.1 mg/day and a proper titration schedule was used to escalate subjects to their respective fixed dose. Subjects were maintained at their dose level for a minimum period of 2 weeks, from Week 4 through Week 5, before being gradually tapered down to 0.1 mg/day at the last week of treatment. The primary efficacy assessment was conducted based on the primary efficacy measure, the ADHDRS-IV total score obtained at Week 5.

Study CLON-302 was an 8-week (56 days), multi-center (US alone), parallel-group, randomized, double-blind, placebo-controlled study. A total of 198 male and female subjects were randomly assigned in a 1:1 ratio to one of the two groups: CLONICEL as an add-on to psychostimulant (CLON+STM) (N=102) or PLACEBO and a psychostimulant (CLON +STM) (N=96). The majority of subjects (83.3%) completed the treatment phase. Patients entering the study should have been on a stable regimen of approved stimulant medication of either methylphenidate or amphetamine (or their derivatives) for a minimum period of 4 weeks and could potentially benefit from the addition of an alpha adrenergic agonist as evidenced by a lack of adequate response to this stable regimen of stimulant medication. The CLON dose (or matching placebo) will be initiated at 0.1 mg/day and titrated up to a 0.4 mg/day (administered as 0.2 mg q12h) over a 3-week period. The dose will be maintained at this level for a period of 2 weeks, from Week 4 through Week 5, before being gradually tapered to 0.1 mg/day at the last week of treatment. The primary efficacy assessment was conducted based on the primary efficacy measure, the ADHDRS-IV total score obtained at Week 5.

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<sup>1</sup> Refer to Section 5.2

### 1.3 Statistical Issues and Findings<sup>2</sup>

The phase III studies, Study CLON-301 and Study CLON-302, established statistical evidence of a mean difference in the ADHDRS-IV total score at the study endpoint (Week 5) in favor of CLONICEL treatment against the placebo, both as a monotherapy and as an add-on to a psychostimulant.

The sponsor established statistical evidence to support the claim for the efficacy of CLONICEL, based on results from the pre-specified analysis LOCF ANCOVA (last observation carried forward analysis of covariance) as well as the pre-specified sensitivity analysis ANCOVA on Observed Cases. The dropout rates were around 40% and 17% respectively in these two studies. In order to explore the impact of the dropouts on efficacy findings, this reviewer performed a MMRM-based sensitivity analysis, which requires a milder assumption for the missing data mechanism. It was found that the result led to the same conclusion in supporting efficacy.

In the subgroup analysis, this reviewer observed differences in estimates of change from baseline scores among races in Study CLON-302, but not in Study CLON-301. In addition, this reviewer observed that the age groups (6-12 year-old and >12 year-old) did not show similar efficacy estimates in Study CLON-301, but in Study CLON-302. These differences, however, may be due to a chance or the fact that subgroups but the white had too small a sample size to statistically assess the estimated differences. Despite some apparent discrepancies in efficacy estimates for subgroups, overall evidence is strong to support the efficacy of the clonice treatment.

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<sup>2</sup> Refer to Section 5.1

## 2. INTRODUCTION

### 2.1 Overview

This review provides a statistical evaluation of CLONICEL (clonidine HCl modified release) as a monotherapy and as an add-on to a psychostimulant, indicated for children and adolescents (6 to 17 years old) with ADHD. The evaluation was based on the submitted data from two phase III studies: Studies CLON-301 and CLON-302.

CLONICEL is a patented oral dose, modified release formulation of the widely available generic drug clonidine hydrochloride USP. Clonidine HCl is a mesomeric imidazoline derivative, chemically described as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The modified release formulation is achieved by (b) (4)

(b) (4) The modified release period is targeted for a minimum of 12 hours to result in a twice daily dose regimen.

Clonidine is a centrally acting alpha<sub>2</sub> adrenergic agonist that has been used effectively since the early 70s to treat mild to moderate hypertension. Because it has a different mechanism of action than most other antihypertensive agents, it can be used alone or in combination therapy with other agents. Clonidine is currently approved in the US in 3 formulations: immediate release oral, transdermal patch, and epidural injection.

Several studies have documented the effectiveness and safety of orally administered clonidine in the treatment of hypertension. Positive data on safety and efficacy led Boehringer Ingelheim, the original maker of the clonidine brand Catapres, to file a new drug application (NDA) with FDA for hypertension in 1973. In its review, the FDA relied on 7 studies, 6 of which were deemed adequate and well controlled trials, usually randomizing patients to Catapres vs. Aldomet (methyldopa), another well established antihypertensive at the time.

In addition to hypertension, clonidine has been evaluated and used extensively for several other indications, including attention deficit hyperactivity disorder (ADHD), alcohol withdrawal, atrial fibrillation, tic disorders, menopausal flushing, smoking cessation, and ulcerative colitis. Clonidine became widely accepted in the early 1990s as a drug for treating a variety of symptoms and disorders related to ADHD in children and adults.

Two important clinical studies have recently been performed, both funded by the National Institutes of Health (NIH). The first was a randomized double-blind placebo-controlled parallel-group study of 16 weeks treatment with clonidine, methylphenidate (MPH) or the combination of both treatments in 136 children with Tourette's Syndrome and comorbid ADHD (TACT Study, Tourette Syndrome Study Group 2002). The two groups receiving clonidine (clonidine alone and clonidine plus MPH) showed statistically better improvement in the primary endpoint, the Conners' Abbreviated Symptom Questionnaire for Teachers (CASQ-Teacher) than the two groups not receiving clonidine (MPH alone and placebo).

The second NIH-funded study, the Clonidine in ADHD Trial (CAT Study, Palumbo et al., 2008), which was performed by a subset of investigators of the first study, evaluated 122 patients with

ADHD without chronic tic disorder using a study design very similar to that of the TACT study. Clonidine was not found to improve ADHD symptoms; however, subjects treated with clonidine had greater improvements on the Conner's Abbreviated Symptom Questionnaire for Parents and Children's Global Assessment.

The sponsor's discussions with clinicians who have used clonidine to treat ADHD were consistent in showing that while clonidine has been a useful medication for ADHD. However, significant problems with the traditionally available preparations (oral tablets and transdermal patches) have greatly limited its use. These problems have mostly involved the ease of administration and the control of side effects. The beneficial effects of a dose of oral clonidine appear to last only 3-4 hours in children with ADHD. This necessitates frequent dosing and causes roller coaster effects characterized by "peak" side effects of sedation and "trough" side effects of rebound hyper arousal. Clinical benefits from clonidine appear suddenly as it is rapidly absorbed, peaking sharply at about 45 to 60 minutes after ingestion. Effects fall off rapidly at about 4-5 hours after ingestion with a characteristic period of rebound hyper arousal. Children often report transient periods of drowsiness about 45 minutes to one hour after taking a dose, and may even fall asleep and nap for 10-15 minutes until the sedation passes. A rebound period can often be observed four to five hours after a dose characterized by hyperactivity, hyper emotionality, anxiety, aggressive behavior or emotional outbursts. This can occur in the middle of the night resulting in nightmares and insomnia.

An easy to administer clonidine formulation is needed that retains the efficacy of the current oral formulation in ADHD but has an improved safety profile similar to the patch formulation minus the dermatologic AEs and the poor adhesion. The CLONICEL clinical development program investigated the safety and efficacy of clonidine delivered from the modified release formulation of CLONICEL over a dose range that is commonly used in the treatment of ADHD.

## **2.2 Data Sources**

Initially, Addrenex submitted the NDA on November 15, 2009. The submission is located at the CDER's electronic document room: [\\fdswa150\NONECTD\N22331\S\\_001\2009-11-05](\\fdswa150\NONECTD\N22331\S_001\2009-11-05).

Due to a change in sponsorship to Shionogi, this new submission storage was created at the CDER's electronic document room: <\\Cdsub1\evsprod\NDA022331\0019\m5\datasets>.



### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 STUDY CLON-301

###### *Study title:*

The title of Study CLON-301 is given as “A phase III, dose response evaluation of the efficacy and safety of CLONICEL (clonidine HCl sustained release) vs. placebo in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)”.

###### *Primary objective:*

- To evaluate the efficacy of two dosing regimens of CLONICEL: 0.2 and 0.4 mg/day compared to placebo in the treatment of children and adolescents with ADHD
- To evaluate the safety of these dosing regimens compared to placebo in the treatment of children and adolescents with ADHD

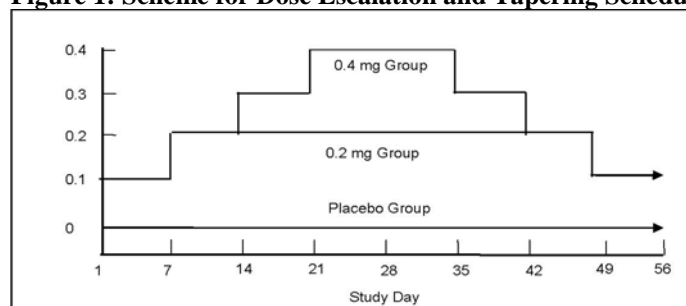
###### *Secondary objective:*

- To evaluate the efficacy of these dosing regimens in alleviating symptoms of sleep disturbance in this patient population
- To evaluate the efficacy of these dosing regimens in alleviating symptoms of aggression in this patient population
- To evaluate the population pharmacokinetics in children and adolescents receiving CLONICEL at these dosing regimens
- To correlate measures of efficacy and safety with genetic or other biologic markers

##### 3.1.1.1 Study Design

This was an 8-week (56 days), multi-center, parallel-group, randomized, double-blind, placebo-controlled study of the efficacy and safety of two dosing regimens of CLONICEL in children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD. Dosing for the CLON groups started at 0.1 mg/day and a proper titration schedule was used to escalate subjects to their respective fixed dose. Subjects were maintained at their dose level for a minimum period of 2 weeks before being gradually tapered down to 0.1 mg/day at the last week of treatment. Figure 1 shows the dose escalation and dose tapering schedule for the three treatment groups.

**Figure 1: Scheme for Dose Escalation and Tapering Schedule (CLON-301)**



[Source: Figure 1. of CLON 301 CSR (page 39)]

Treatment was discontinued for subjects who could not tolerate their assigned dose. Prior to initiating the 8-week treatment period, subjects completed a screening period of up to 2 weeks during which all screening assessments were performed and any current ADHD treatments discontinued. During the treatment period, subjects returned to the investigative site weekly to complete efficacy and safety assessments. Subjects discontinued study medication at the Week 8 visit but returned for a closeout safety visit one week later.

*Sample size calculation:*

The sample size calculation was based on comparing each active group to placebo on mean changes in ADHDRS-IV total scores from Baseline to the Week 5 (or last available) measure. The following assumptions were made:

Difference between active and placebo mean change scores = 8 points

Pooled standard deviation = 15

Alpha = 0.05

Power = 90%

Ratio of active/placebo = 1

Sample size calculations indicated that 75 patients per treatment group would be required to achieve statistical significance given the above assumptions.

### **3.1.1.2 Statistical Method and Analysis**

*Definition of study population in primary analysis:*

The study population will consist of 225 children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD of the hyperactive or combined inattentive/hyperactive subtypes will be enrolled, 75 per treatment group. The Intent to Treat (ITT) population was defined as all subjects who are randomized, took at least one dose of study drug, and provided at least one efficacy assessment post Baseline.

*Primary endpoint and analyses:*

The primary endpoint was the change from Baseline to Week 5 in the ADHDRS-IV scale total score. All primary statistical summaries and analyses were conducted using the ITT population. The primary analysis was based on ANCOVAs that model the change from baseline as a function of the baseline ADHDRS-IV total score, the study site, and the treatment group. Missing data was imputed by the Last Observation Carried Forward (LOCF) approach.

For study sites with fewer than 10 total subjects, the study sites were pooled. The pooling algorithm will match the largest site with fewer than 10 subjects with the smallest site until a pooled site with 10 or more subjects is obtained. The process continued with the remaining sites until all sites for analysis purposes included 10 or more subjects.

Confidence bounds presented will show two-sided 95% confidence limits for the average ADHDRS-IV total score difference between the two dosing regimens. A p-value of less than or

equal to 0.05 was deemed statistically significant. Any confidence bounds presented two-sided 95% confidence limits.

When comparing a given dose with placebo, the sponsor excluded the other dose group from the ANCOVA model. Since there were two comparisons (high dose vs. placebo and low dose vs. placebo), the sponsor referred to their primary analysis as “two independent ANCOVA’s”. However, they did not consider multiplicity adjustment for these two comparisons and declared a statistical significance for a nominal p-value of less than or equal to 0.05. This reviewer noted that in an email communication of statistical comments, dated on August 27, 2008, the sponsor was advised to prospectively propose a method for dealing with multiple comparisons due to the multiple doses, but apparently the sponsor did not address this.

The sponsor proposed to conduct two sensitivity analyses to investigate the sensitivity of the study results to other analysis methods and assumptions than the primary analysis method:

- 1) ANCOVA model with a covariate of baseline ADHDRS-IV total score, factors of treatment, study site, and the treatment  $\times$  site interaction term, based on LOCF data.
- 2) The same ANCOVA model as in the primary analysis based on completed scores at Week 5 (observed cases) without LOCF imputation.

#### *Secondary endpoints and analyses:*

Secondary measurements included Conners’ Parent Rating Scale Revised: Long Form (CPRS-L), Sleep Self Report questionnaire – Child’s Form (SSR-CF), Horacek Adrenergic Dysregulation Scale (HADS), Clinical Global Impressions-Severity (CGI-S), Clinical Global Impressions-Improvement (CGI-I), Parent Global Assessment (PGA). No key secondary endpoint was pre-specified.

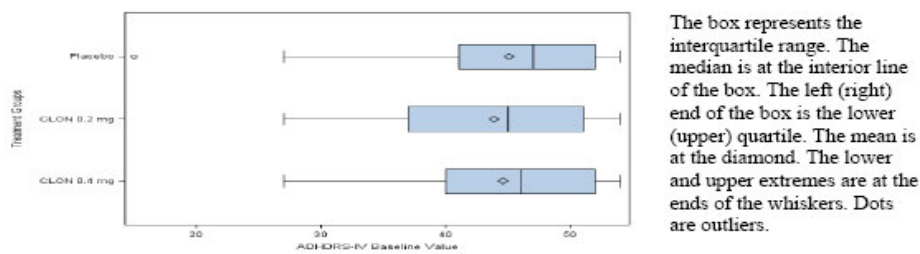
### **3.1.1.3 Efficacy Results**

#### **3.1.1.3.1 Subject Disposition and Baseline Demographic Characteristics**

##### *Baseline distributions of the treatment groups:*

Figure 2 displays box plots of baseline ADHDRS-IV total scores of each treatment group. A visual inspection of this figure along with Table 1 suggest that the Baseline ADHDRS-IV total scores for the clonidine 0.2-mg treatment group appeared slightly smaller than the other groups, but the difference may not be clinically relevant.

**Figure 2: Box-Whisker Plots: Baseline ADHDRS-IV total scores by treatment (CLON-301)**



[Source: Reviewer’s analysis]

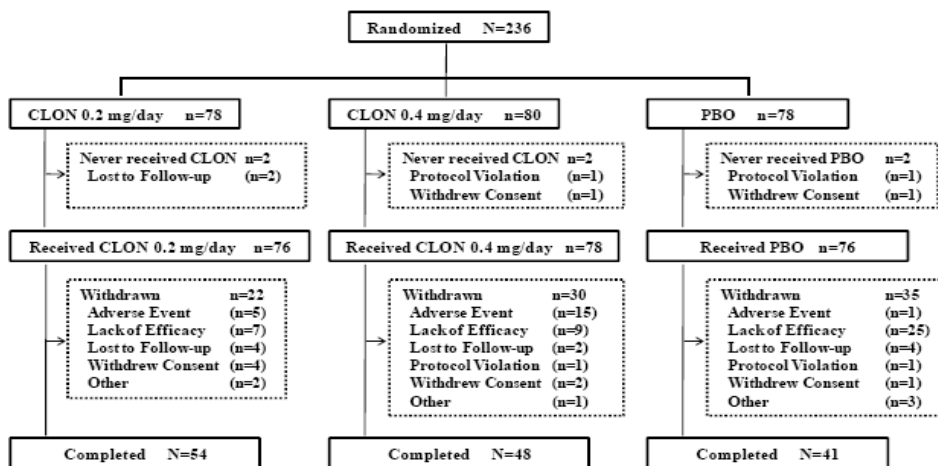
**Table 1: Baseline ADHDRS-IV total scores by treatment groups (CLON-301)**

Treatment	N	Mean	SD	Median
CLON 0.2 mg	74	43.8	7.47	45.0
CLON 0.4 mg	78	44.6	7.73	46.0
Placebo	76	45.0	8.53	47.0

[Source: Reviewer's analysis]

### Subject disposition:

A total of 236 male and female subjects were randomly assigned in a 1:1:1 ratio to CLONICEL treatment, CLON 0.2 mg/day (N=78) or CLON 0.4 mg/day (N=80), or placebo (N=78). As shown in Table 2, the majority of subjects (60.6%) completed the treatment phase. Figure 3 and Table 2 provide all the details of subject dispositions.

**Figure 3: Subjects Dispositions in CLON-301**

[Source: Figure 2 of CLON 301 CSR (page 63)]

**Table 2: Subject Dispositions in CLON-301**

Summary	Treatment Group			All Subjects
	Clonice1 0.2 mg	Clonice1 0.4 mg	Placebo	
Study Population				
All Randomized [1]	78	80	78	236
Intent-to-Treat (ITT) [2]	74	78	76	228
Safety	78	78	78	230
Subjects Completed Treatment Phase				
Yes	54 (69.2%)	48 (60.0%)	41 (52.6%)	143 (60.6%)
No	24 (30.8%)	32 (40.0%)	37 (47.4%)	93 (39.4%)
Reason for not Completing Treatment Phase				
Withdrawal Consent	4 (5.1%)	3 (3.8%)	2 (2.6%)	9 (3.8%)
Adverse Event	5 (6.4%)	15 (18.8%)	1 (1.3%)	21 (8.9%)
Lack of Efficacy	7 (9.0%)	9 (11.3%)	25 (32.1%)	41 (17.4%)
Lost to Follow-Up	8 (7.7%)	2 (2.5%)	4 (5.1%)	12 (5.1%)
Protocol Violation	0	2 (2.5%)	2 (2.6%)	4 (1.7%)
Other	2 (2.6%)	1 (1.3%)	3 (3.8%)	6 (2.5%)
Subjects Completed Follow-up Visit				
Yes	68 (84.6%)	68 (85.0%)	64 (82.1%)	198 (83.9%)
No	12 (15.4%)	12 (15.0%)	14 (17.9%)	38 (16.1%)
Reason for not Completing Follow-Up				
Withdrawal Consent	4 (5.1%)	3 (3.8%)	2 (2.6%)	9 (3.8%)
Adverse Event	0	2 (2.5%)	1 (1.3%)	3 (1.3%)
Lack of Efficacy	0	0	0	0
Lost to Follow-Up	6 (7.7%)	3 (3.8%)	8 (10.3%)	17 (7.2%)
Protocol Violation	0	0	0	0
Other	2 (2.6%)	4 (5.0%)	3 (3.8%)	9 (3.8%)

[Source: Table 14.1.1 of CLON 301 CSR (page 105)]

### Demographic characteristics:

As shown in Table 3, for all randomized subjects, the majority were male (72.4%) and White (59.2%). The mean subject age was 9.4 years (median 9.0 years), and most subjects were 6-12 years of age (82.5%). The mean body weight was 41.1 kg.

**Table 3: Subgroup (Gender, Age, Age group, Race, Weight) in CLON-301**

Summary	Treatment Group			All Subjects
	Clonice1 0.2 mg	Clonice1 0.4 mg	Placebo	
ITT Subjects	74	78	78	228
Gender				
Male	58 (78.4%)	55 (70.5%)	52 (66.4%)	165 (72.4%)
Female	16 (21.6%)	23 (29.5%)	24 (31.6%)	63 (27.6%)
Age (years)				
N	74	78	78	228
Mean (Std)	9.6 (2.94)	9.4 (2.89)	9.4 (2.86)	9.4 (2.89)
Median	9.0	9.0	8.5	9.0
Min, Max	6.0, 17.0	6.0, 17.0	6.0, 16.0	6.0, 17.0
Age				
6-12 Years	61 (82.4%)	65 (83.3%)	62 (81.6%)	188 (82.5%)
>12-17 Years	13 (17.6%)	13 (16.7%)	14 (18.4%)	40 (17.5%)
Race				
White	45 (60.8%)	46 (59.0%)	44 (57.9%)	135 (59.2%)
Black/African American	19 (25.7%)	20 (25.6%)	23 (30.3%)	62 (27.2%)
Hispanic or Latino	6 (8.1%)	7 (9.0%)	6 (7.9%)	19 (8.3%)
Other	4 (5.4%)	5 (6.4%)	3 (3.9%)	12 (5.3%)
Weight (kg)				
N	74	78	78	228
Mean (Std)	40.8 (20.59)	40.1 (18.33)	42.3 (17.83)	41.1 (18.87)
Median	33.7	34.4	36.9	34.8
Min, Max	20.8, 128.7	17.0, 106.1	20.4, 90.9	17.0, 128.7

[Source: Table 14.1.3 of CLON 301 CSR (page 110)]

### 3.1.1.3.2 Sponsor's Efficacy Analysis Results

#### Results from the primary variable:

Table 4 displays the sponsor's primary analysis results, summarizing the change scores from Baseline for ADHDRS-IV comparing each dosing group to placebo. The least-squares mean difference in each of the comparisons was statistically significantly different from zero at the 2-sided, 5% nominal significance level, in favor of the corresponding clonice1 dosing group.

**Table 4: Sponsor Primary Efficacy Analysis in CLON-301**

Primary analysis	Treatment Group	N	LS Means Model Estimate for Difference (Clonice1-Placebo) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value**
ANCOVA (LOCF)	Clonice1 0.2 mg	74	-8.49 (-12.05, -4.93)	< .0001
	Clonice1 0.4 mg	78	-8.99 (-12.66, -5.32)	< .0001
	Placebo	76	--	--

\* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA

\*\* p-values were obtained by "two independent ANCOVA's" (No multiplicity adjustment was performed).

[Source: Table 14.2.2 of CLON 301 CSR (page 117)]

The sponsor performed two sensitivity analyses. The analysis results can be found in Table 5 and Table 6. The results are consistent with those found in the primary analysis, and support the sponsor's efficacy claim. This reviewer confirmed the results.

**Table 5: Sponsor sensitivity analysis: using observed cases - ANCOVA (OC) CLON-301**

Sponsor sensitivity analysis: Using observed cases	Treatment Group	N	LS Means Model Estimate for Difference (Clonice1-Placebo) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value**
ANCOVA (OC)	Clonice1 0.2 mg	58	-8.78 (-12.53, -5.04)	< .0001
	Clonice1 0.4 mg	52	-12.23 (-16.44, -8.01)	< .0001
	Placebo	59	--	--

\* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA

\*\* p-values were obtained by "two independent ANCOVA's" (No multiplicity adjustment was performed).

[Source: Table 14.2.2 of CLON 301 CSR (page 117)]

**Table 6: Sponsor sensitivity analysis: Inclusion of an interaction of study site and treatment - ANCOVA (LOCF) in CLON-301**

Sponsor sensitivity analysis: Inclusion of an interaction of study site and treatment	Treatment Group	N	LS Means Model Estimate for Difference (Clonice1-Placebo) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value**
ANCOVA (LOCF)	Clonice1 0.2 mg	74	-7.58 (-11.37, -3.80)	< .0001
	Clonice1 0.4 mg	78	-8.19 (-12.12, -4.26)	< .0001
	Placebo	76	--	--

\* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA

\*\* p-values were obtained by "two independent ANCOVA's" (No multiplicity adjustment was performed).

[Source: Table 14.2.2 of CLON 301 CSR (page 117)]

### *Results of subscales of the ADHDRS-IV scale:*

The ADHDRS-IV scale, where the primary endpoint was derived, consists of two subscales: Inattention and Hyperactivity. The sponsor concluded statistically significant improvements favoring the CLONICEL treatment groups for both subscales. (See Table 7)

**Table 7: Change Scores for Subscales of the ADHDRS-IV Scale at Week 5 (LOCF) – CLON-301**

	TREATMENT GROUP		
	CLON 0.2 mg/day	CLON 0.4 mg/day	PBO
<b>Inattention Subscale, N</b>	74	78	76
Baseline, Mean (SD)	22.9 (3.87)	23.1 (3.81)	23.4 (4.32)
Change Score at Week 5, Mean (SD)	-7.7 (6.88)	-7.7 (7.10)	-3.4 (5.13)
p-value <sup>1</sup>	p<0.0001	p<0.0001	--
<b>Hyperactivity/Impulsivity, N</b>	74	78	76
Baseline, Mean (SD)	20.9 (5.31)	21.5 (5.04)	21.6 (5.59)
Change Score at Week 5, Mean (SD)	-7.9 (6.96)	-8.8 (7.26)	-4.1 (5.04)
p-value <sup>1</sup>	p<0.0001	p<0.0001	--

<sup>1</sup> Versus placebo p-value; obtained from the treatment parameters in an ANCOVA modeling change from Baseline as a function of Baseline, treatment, and pooled study site.

[Source: Synopsis Table 3 of CLON 301 CSR (page 9)]

### *Results of secondary endpoints:*

The sponsor concluded that the results of the secondary endpoints supported those of the primary endpoint and achieved statistical significance (p-value at least  $<0.05$ ). Statistical significance was found in pre-specified secondary endpoints, except for SSR-CF total score or derived subscales. This reviewer confirmed these results.

### *Sponsor's conclusion on efficacy:*

Both dosing regimens of CLONICEL, 0.2 mg/day and 0.4 mg/day (in divided AM and PM doses), were efficacious in alleviating the symptoms of ADHD in pediatric patients and well-tolerated for up to 8 weeks of treatment.

### Reviewer's Note:

[1] The sponsor did not consider multiplicity adjustment for the two doses compared with placebo. However, since the p-values were nearly zero, any reasonable multiple testing procedure would lead to the same conclusion.

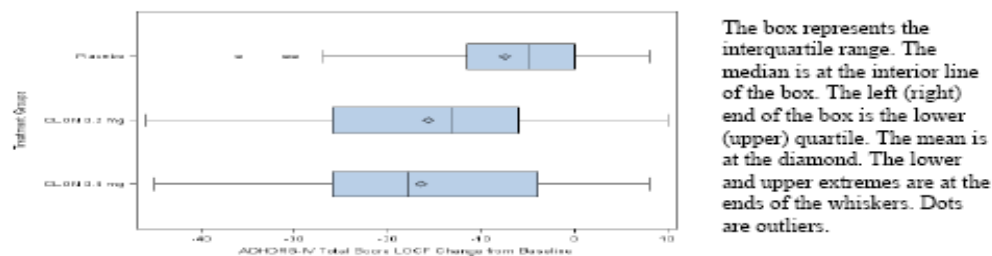
[2] The sponsor performed the primary analysis and the sensitivity analysis by excluding the irrelevant dose group from the ANCOVA model for each comparison. Typically, when comparing a given dose with placebo, all dose groups are included in the model. This approach takes more information into account and allows for implementation of multiple testing procedures (such as Dunnett's) that require correlation between comparisons. Since the p-values were very close to zero, the results were consistent whether excluding the irrelevant dose group from the model or not.

### **3.1.1.3.3 Reviewer's Assessments**

#### *Confirmation of sponsor's results of the primary analysis:*

This reviewer confirmed the sponsor's primary analysis results. As displayed in Figure 4, the box plots of the change from baseline in ADHDRS-IV total scores suggest a distributional separation of each treatment group from the placebo group. The distribution in the placebo group appears narrower than the other two clonicele treatment groups. Given the robustness of ANCOVA analysis, however the distributions of the change from baseline in ADHDRS-IV total scores seem to be fairly acceptable for an ANCOVA analysis. This reviewer created normal QQ plots of residual errors after model fitting, and did not find apparent indications of a violation of the distributional assumption, so the ANCOVA model appears fairly robust.

**Figure 4: Box-Whisker plots: Change from baseline in ADHDRS-IV total score by treatment (CLON-301)**



[Source: Reviewer's analysis]

### Reviewer's sensitivity analysis

This reviewer conducted a mixed model for repeated measures (MMRM) analysis as a sensitivity analysis, in order to look into the robustness of the sponsor's efficacy analysis result based on the LOCF ANCOVA. As in the sponsor's LOCF ANCOVA primary analysis, the MMRM model included baseline ADHDRS-IV total score as a fixed covariate, treatment group, study site, week and the treatment by week interaction as fixed factors. The method of estimation was restricted maximum likelihood (REML). The within subject covariance matrix was unstructured. The degree of freedom of the denominator was approximated by the Kenward-Roger's method. The results in Table 8 and Table 9 support the primary analysis results based on the LOCF ANCOVA analysis.

**Table 8: Sensitivity Analysis by MMRM (CLON 0.2 mg vs. Placebo) – CLON-301**

Visit	Placebo		Clonice1 0.2 mg		Clonice1 0.2 mg vs. Placebo	
	N	MEAN	N	MEAN	LS Mean	P-value*
Week 1	75	-3.9	72	-7.0	-3.2	0.016
Week 2	74	-4.5	72	-13.1	-8.3	< 0.0001
Week 3	70	-6.9	68	-15.7	-8.1	< 0.0001
Week 4	67	-6.9	62	-16.2	-8.7	< 0.0001
Week 5	59	-8.0	58	-16.5	-8.2	< 0.0001

\*No adjustment for multiplicity across visits was performed.

[Source: Reviewer's analysis]

**Table 9: Sensitivity Analysis by MMRM (CLON 0.4 mg vs. Placebo) – CLON-301**

Visit	Placebo		Clonice1 0.4 mg		Clonice1 0.4 mg vs. Placebo	
	N	MEAN	N	MEAN	LS Mean	P-value*
Week 1	75	-3.9	77	-6.5	-2.5	0.053
Week 2	74	-4.5	65	-14.2	-9.5	< 0.0001
Week 3	70	-6.9	69	-16.0	-8.4	< 0.0001
Week 4	67	-6.9	57	-17.9	-10.7	< 0.0001
Week 5	59	-8.0	52	-19.4	-11.1	< 0.0001

\*No adjustment for multiplicity across visits was performed.

[Source: Reviewer's analysis]

### 3.1.2 STUDY CLON-302

#### Study Title:

The title of Study CLON-301 is given as "A phase III evaluation of the efficacy and safety of CLONICEL (clonidine HCl sustained release) as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)."

#### Primary Objective:

- To evaluate the efficacy of CLONICEL administered as a flexible dose of 0.1 to 0.4 mg/day as add-on to a stable regimen of psychostimulant medication compared to



psychostimulant medication alone in the treatment of children and adolescents with ADHD

- To evaluate the safety of this dosing regimen as add-on to psychostimulant medication compared to psychostimulant medication alone in the treatment of children and adolescents with ADHD

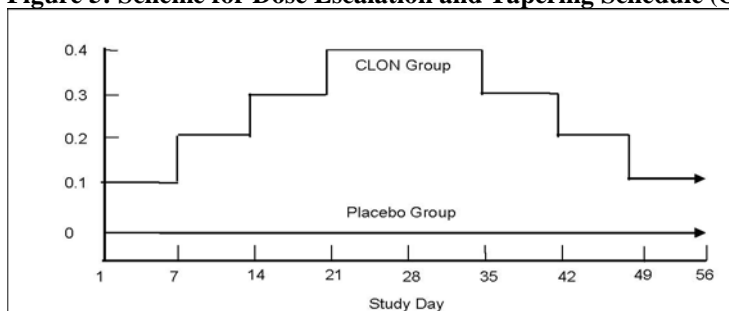
*Secondary Objective:*

- To evaluate the efficacy of the add-on therapy in alleviating symptoms of sleep disturbance in this patient population
- To evaluate the efficacy of the add-on therapy in alleviating symptoms of adrenergic dysregulation in this patient population
- To evaluate the population pharmacokinetics in children and adolescents receiving CLONICEL at this dosing regimen
- To correlate measures of efficacy and safety with genetic or other biologic markers

### 3.1.2.1 Study Design

This was an 8-week (56 days), multi-center, parallel-group, randomized, double-blind, placebo-controlled study of the efficacy and safety of a flexible dose of CLONICEL in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD. Subjects were randomly assigned to one of two groups: CLONICEL as add-on to a psychostimulant (CLON+STM) or a psychostimulant and Placebo (PBO+STM). Subjects entering the study should have been on a stable regimen of approved stimulant medication of either methylphenidate or amphetamine (or their derivatives) for a minimum period of 4 weeks and could potentially benefit from the addition of an alpha2 adrenergic agonist as evidenced by a lack of adequate response to this stable regimen of stimulant medication. The CLON dose (or matching placebo) was initiated at 0.1 mg/day and titrated up to a 0.4 mg/day (administered as 0.2 mg q12h) over a 3-week period. The dose was maintained at this level for a period of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. The Investigator could elect to keep a subject on a CLON dose lower than 0.4 mg/day or taper the dose earlier than scheduled in the case of adverse events. The investigator could also elect to change the dose of stimulant medication based on the profile of safety and efficacy observed, but changing the category of stimulant medication was not allowed. Subjects who could not tolerate a minimum CLON dose of 0.1 mg/day were discontinued. Figure 5 shows the dose escalation and dose tapering schedule for the two treatment groups.

**Figure 5: Scheme for Dose Escalation and Tapering Schedule (CLON-302)**



[Source: Figure 1. of CLON 302 CSR (page 41)]

Prior to initiating the 8-week treatment period, subjects completed a screening period (1 to 2 weeks) during which all screening assessments were performed including performance while on the current stimulant treatment regimen. During the treatment period, subjects returned to the investigative site weekly to complete efficacy and safety assessments. Subjects discontinued study medication at the Week 8 visit but returned for a closeout safety visit one week later.

*Sample size calculation:*

The sample size calculation was based on comparing the two treatment on mean changes in ADHDRS-IV scores from Baseline to the Week 5 (or last available) measure. The following assumptions were made:

Difference between active and placebo mean change scores = 7 points

Pooled standard deviation = 15

Alpha = 0.05

Power = 90%

Ratio of active/placebo = 1

Sample size calculations indicated that 100 patients per treatment group would be required to achieve statistical significance given the above assumptions.

### **3.1.2.2 Statistical Method and Analysis**

*Definition of study population in primary analysis:*

The study population will consist of 200 children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD of the hyperactive or combined inattentive/hyperactive subtypes will be enrolled, 100 per treatment group. The Intent to Treat (ITT) population was defined as all subjects who are randomized, took at least one dose of study drug, and provided at least one efficacy assessment post Baseline.

*Primary endpoint and analyses:*

The primary endpoint was the change from Baseline to Week 5 in the ADHDRS-IV scale total score. All primary statistical summaries and analyses were conducted using the ITT population. The primary analysis was based on ANCOVAs that model the change from baseline as a function of the baseline ADHDRS-IV total score, the study site, and the treatment group. Missing data was imputed by the Last Observation Carried Forward (LOCF) approach.

For study sites with fewer than 10 total subjects, the study sites were pooled. The pooling algorithm will match the largest site with fewer than 10 subjects with the smallest site until a pooled site with 10 or more subjects is obtained. The process continued with the remaining sites until all sites for analysis purposes included 10 or more subjects.

Confidence bounds presented will show two-sided 95% confidence limits for the average ADHDRS-IV total score difference between the two dosing regimens. A p-value of less than or

equal to 0.05 was deemed statistically significant. Any confidence bounds presented two-sided 95% confidence limits.

The sponsor proposed to conduct two sensitivity analyses to investigate the sensitivity of the study results to other analysis methods and assumptions than the primary analysis method:

- 1) ANCOVA model with a covariate of baseline ADHDRS-IV total score, factors of treatment, study site, and the treatment  $\times$  site interaction term, based on LOCF data.
- 2) The same ANCOVA model as in the primary analysis based on completed scores at Week 5 (observed cases) without LOCF imputation.

#### *Secondary efficacy endpoints and analyses:*

Secondary measurements included Conners' Parent Rating Scale Revised: Long Form (CPRS-L), Sleep Self Report questionnaire – Child's Form (SSR-CF), Horacek Adrenergic Dysregulation Scale (HADS), Clinical Global Impressions-Severity (CGI-S), Clinical Global Impressions-Improvement (CGI-I), Parent Global Assessment (PGA). No key secondary endpoint was pre-specified.

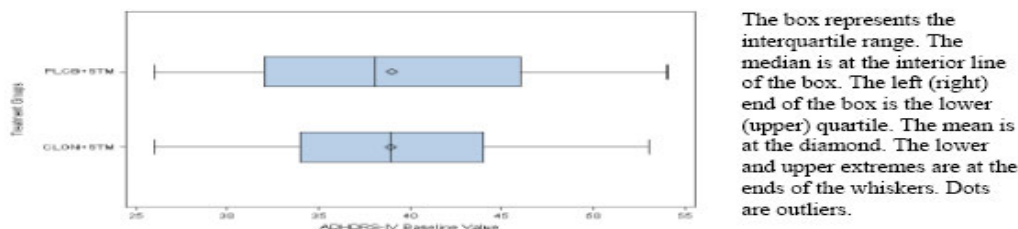
### **3.1.2.3 Efficacy Results**

#### **3.1.2.3.1 Subject Disposition and Baseline Demographic Characteristics**

##### *Baseline distributions of the treatment groups:*

Figure 6 displays box plots of baseline ADHDRS-IV total scores of each treatment group. A visual inspection of this figure along with Table 10 suggests that the distribution of Baseline ADHDRS-IV total scores for PBO +STM group is wider than that of the CLON +STM group, but their means and medians are similar. The difference in the distribution may not be clinically relevant.

**Figure 6: Box-Whisker Plots: Baseline ADHDRS-IV total scores by treatment (CLON-302)**



[Source: Reviewer's analysis]

**Table 10: Baseline ADHDRS-IV total scores by treatment groups (CLON-302)**

Treatment	N	Mean	SD	Median
CLON +STM	102	38.9	6.95	39.0
Placebo +STM	95	39.0	7.68	38.0

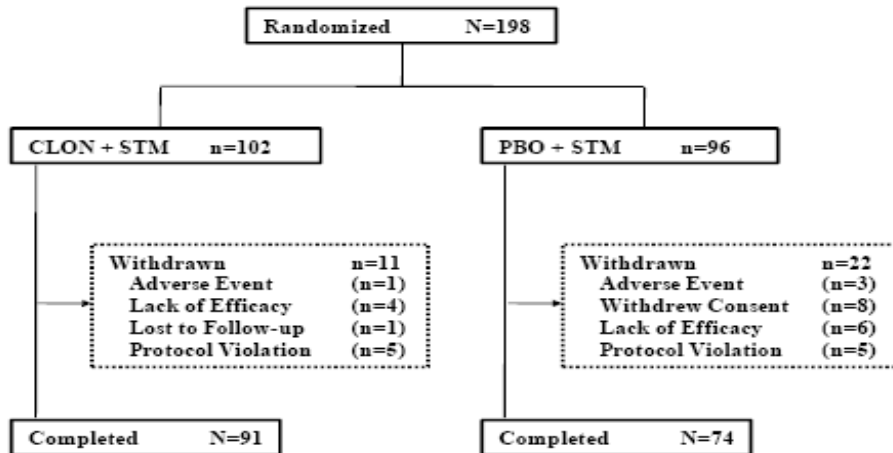
[Source: Reviewer's analysis]

##### *Subject disposition:*

A total of 200 subjects were planned for enrollment. Of the 243 subjects screened, 198 subjects were randomly assigned to study treatments (All Randomized population). All 198 subjects

were included in the Safety population (102 subjects in the CLON+STM and 96 in the PBO+STM treatment groups). One of the 198 subjects in the Safety population received at least one dose of study drug but had no post-baseline measurements. The remaining 197 subjects provided evaluable efficacy data and were included in the ITT population. Figure 7 and Table 11 provide all the details of subject dispositions.

**Figure 7: Subjects Dispositions in CLON-302**



[Source: Figure 2 of CLON 302 CSR (page 61)]

**Table 11: Subject Dispositions in CLON-302**

Summary	Treatment Group		All Subjects
	Clonice1 + STM	Placebo + STM	
Study Population			
All Randomized	102	96	198
Intent-to-Treat (ITT) [1]	102	95	197
Safety	102	96	198
Subjects Completed Treatment Phase			
Yes	91 (89.2%)	74 (77.1%)	165 (83.3%)
No	11 (10.8%)	22 (22.9%)	33 (16.7%)
Reason for not Completing Treatment Phase			
Withdrew Consent	0	8 (8.3%)	8 (4.0%)
Adverse Event	1 (1.0%)	3 (3.1%)	4 (2.0%)
Lack of Efficacy	4 (3.9%)	6 (6.3%)	10 (5.1%)
Lost to Follow-Up	1 (1.0%)	0	1 (0.5%)
Protocol Violation	5 (4.9%)	5 (5.2%)	10 (5.1%)
Other	0	0	0
Subjects Completed Follow-up Visit			
Yes	95 (93.1%)	77 (80.2%)	172 (86.9%)
No	7 (6.9%)	19 (19.8%)	26 (13.1%)
Reason for not Completing Follow-Up			
Withdrew Consent	2 (2.0%)	16 (16.7%)	18 (9.1%)
Adverse Event	0	1 (1.0%)	1 (0.5%)
Lack of Efficacy	0	0	0
Lost to Follow-Up	5 (4.9%)	0	5 (2.5%)
Protocol Violation	0	1 (1.0%)	1 (0.5%)
Other	0	1 (1.0%)	1 (0.5%)

[Source: Table 14.1.1 of CLON 302 CSR (page 108)]

### *Demographic characteristics:*

As shown in Table 12, for all randomized subjects, the majority were male (73.6%) and White (53.8%). The mean subject age was 10.5 years (median 10.0 years), and most subjects were 6-12 years of age (77.2%). The mean body weight was 39.6 kg.

**Table 12: Subgroup (Gender, Age, Age group, Race, Weight) in CLON-302**

Summary	Treatment Group		All Subjects
	Clonice1 + STM	Placebo + STM	
ITT Subjects	102	95	197
Gender			
Male	79 (77.5%)	66 (69.5%)	145 (73.6%)
Female	23 (22.5%)	29 (30.5%)	52 (26.4%)
Age (years)			
N	102	95	197
Mean (Std)	10.4 (2.50)	10.5 (2.53)	10.5 (2.50)
Median	10.0	10.0	10.0
Min, Max	6.0, 17.0	6.0, 16.0	6.0, 17.0
Age			
6-12 Years	77 (75.5%)	75 (78.9%)	152 (77.2%)
>12-17 Years	25 (24.5%)	20 (21.1%)	45 (22.8%)
Race			
White	49 (48.0%)	57 (60.0%)	106 (53.8%)
Black/African American	35 (34.3%)	19 (20.0%)	54 (27.4%)
Hispanic or Latino	11 (10.8%)	11 (11.6%)	22 (11.2%)
Other	7 (6.9%)	8 (8.4%)	15 (7.6%)
Weight (kg)			
N	100	93	193
Mean (Std)	40.2 (18.57)	38.9 (13.57)	39.6 (16.33)
Median	36.4	35.7	35.9
Min, Max	18.8, 112.6	20.0, 76.8	18.8, 112.6

[Source: Table 14.1.3 of CLON 302 CSR (page 115)]

### 3.1.2.3.2 Sponsor's Efficacy Analysis Results

*Results from the primary variable:*

Table 13 displays the sponsor's primary analysis results, summarizing the change scores from Baseline for ADHDRS-IV comparing the CLON+STM to the PBO+STM treatment group. The least-squares mean difference in the comparison was statistically significantly different from zero at the 2-sided, 5% nominal significance level, in favor of the CLON+STM treatment group.

**Table 13: Sponsor Primary Efficacy Analysis in CLON-302**

Primary analysis	Treatment Group	N	LS Means Estimate of Difference (CLON+STM – PBO+STM) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value
ANCOVA (LOCF)	Clonice1 +STM	102	-4.48 (-7.83, -1.13)	0.0091
	Placebo +STM	95	--	--

\* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA

[Source: Table 14.2.2 of CLON 302 CSR (page 129)]

**Table 14: Sponsor sensitivity analysis: using observed cases - ANCOVA (OC) in CLON-302**

Sponsor sensitivity analysis: Using observed cases	Treatment Group	N	LS Means Model Estimate for Difference (Clonice1+STM – Placebo+STM) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value
ANCOVA (OC)	Clonice1 +STM	92	-4.12 (-7.77, -0.47)	0.0273
	Placebo +STM	75	--	--

\* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA

[Source: Table 14.2.2 of CLON 302 CSR (page 129)]

The sponsor performed two sensitivity analyses. The analysis results can be found in Table 14 and Table 15. The results are consistent with those found in the primary analysis, and support the sponsor's efficacy claim. This reviewer confirmed the results.

**Table 15: Sponsor sensitivity analysis: Inclusion of an interaction of study site and treatment - ANCOVA (LOCF) in CLON-302**

Sponsor sensitivity analysis: Including an interaction of study site and treatment	Treatment Group	N	LS Means Model Estimate for Difference (Clonice1+STM vs. Placebo+STM) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value
ANCOVA (LOCF)	Clonice1 +STM	102	-4.97 (-8.38, -1.56)	0.0045
	Placebo +STM	95	--	--

\* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA  
[Source: Table 14.2.2 of CLON 302 CSR (page 129)]

#### *Results of subscales of the ADHDRS-IV scale:*

The ADHDRS-IV scale, where the primary endpoint was derived, consists of two subscales: Inattention and Hyperactivity. The sponsor concluded statistically significant improvements favoring the CLONICEL treatment groups for both subscales, Inattention and Hyperactivity, of the ADHDRS-IV scale. (See Table 16)

**Table 16: Change Scores for Subscales of the ADHDRS-IV Scale at Week 5 (LOCF) – CLON-302**

	TREATMENT GROUP	
	CLON+STM	PBO+STM
<b>Inattention Subscale, N</b>	102	95
Baseline, Mean (SD)	20.7 (4.22)	20.8 (4.21)
Change Score at Week 5, Mean (SD)	-7.8 (6.81)	-5.8 (6.85)
p-value <sup>1</sup>	p=0.0169	--
<b>Hyperactivity/Impulsivity, N</b>	102	95
Baseline, Mean (SD)	18.2 (4.94)	18.2 (5.14)
Change Score at Week 5, Mean (SD)	-7.9 (6.70)	-5.8 (6.32)
p-value <sup>1</sup>	p=0.0143	--

<sup>1</sup> Versus placebo p-value; obtained from the treatment parameters in an ANCOVA modeling change from Baseline as a function of Baseline, treatment, and pooled study site.  
[Source: Synopsis Table 3 of CLON 301 CSR (page 9)]

#### *Results of secondary endpoints:*

The sponsor concluded that most of the results of the secondary efficacy analyses supported those of the primary efficacy analysis and achieved statistical significance (p-value at least <0.05). Statistical significance was found in pre-specified secondary efficacy endpoint, except for the HADS, CPRS-L oppositional subscale, and SSR-CF scale total score and all subscales. This reviewer confirmed the results.

#### *Sponsor's conclusion on efficacy:*

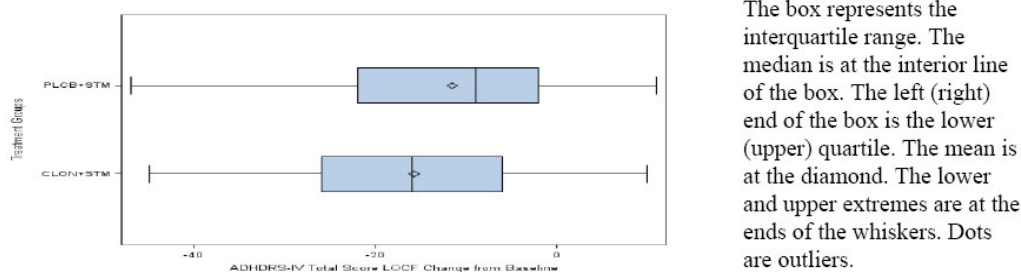
CLONICEL (clonidine HCl modified release), as add-on therapy to ADHD psychostimulants, was efficacious in alleviating symptoms in children and adolescents with ADHD who lacked adequate response on a stable regimen of stimulant medication alone.

### 3.1.2.3.3 Reviewer's Assessments

*Confirmation of sponsor's results of the primary efficacy analysis:*

This reviewer confirmed the sponsor's primary efficacy analysis. As displayed in Figure 8, in each of the two treatment groups, a box plot of the change from baseline ADHDRS-IV total scores suggests a distributional separation of the CLON +STM treatment group from the PBO +STM treatment group. Both the distributions of the change from baseline ADHDRS-IV total scores are determined to be fairly acceptable for an ANCOVA analysis. This reviewer created a normal QQ plot for each treatment group, and confirmed that there is no indication of a violation of the distributional assumption, considering that the ANCOVA model is fairly robust for the assumption of the normality of the distribution of the dependent variable.

**Figure 8: Box-Whisker plots: Change from baseline in ADHDRS-IV total score by treatment (CLON-302)**



[Source: Reviewer's analysis]

*Reviewer's sensitivity analysis:*

This reviewer conducted a mixed model for repeated measures (MMRM) analysis as a sensitivity analysis, in order to look into the robustness of the sponsor's efficacy analysis result based on the LOCF ANCOVA. As in the sponsor's LOCF ANCOVA primary analysis, the MMRM model included baseline ADHDRS-IV total score as a fixed covariate, treatment group, study site, week and the treatment by week interaction as fixed factors. The method of estimation was restricted maximum likelihood (REML). The within subject covariance matrix was unstructured. The degree of freedom of the denominator was approximated by the Kenward-Roger's method. The results in Table 17 support the primary analysis results based on the LOCF ANCOVA analysis.

**Table 17: Sensitivity Analysis by MMRM (CLON+ STM vs. PBO+STM) – CLON 302**

Visit	Placebo + STM		Clonice1 +STM		Clonice1 +STM vs. Placebo + STM	
	N	Mean	N	Mean	LS Mean	P-value*
Week 1	93	-4.6	100	-4.3	0.3	0.7575
Week 2	85	-8.6	97	-11.5	-2.9	0.0563
Week 3	91	-10.4	96	-14.1	-3.7	0.0281
Week 4	81	-12.6	93	-17.2	-4.9	0.0048
Week 5	75	-13.3	92	-16.9	-3.9	0.0274

[Source: Reviewer's analysis]

## 3.2 Evaluation of Safety

*(The evaluation of safety is deferred to the clinical team.)*

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section all the subgroup analyses were exploratory for the purpose of assessing the consistency across subgroups.

### 4.1 Gender, Race and Age

#### 4.1.1 STUDY CLON-301

##### 4.1.1.1 Gender

The sponsor conducted an analysis on the ADHDRS-IV primary endpoint by including the factor of gender as a potential predictor of the response in the ANCOVA model. The ANCOVAs were fit modeling the change from baseline as a function of the baseline ADHDRS-IV total score, the treatment group, gender and the interaction of the treatment and gender. The sponsor's interpretations of this analysis are as follows:

In the analysis of gender, the overall treatment effect for CLONICEL relative to placebo was not affected by gender, but there were statistically significant main effects for gender. As Table 14.2.17 shows, the effects do not relate to the overall treatment performance of CLONICEL relative to placebo which is substantial in both genders. However, as shown in the estimated mean response by gender and treatment in Table 14.2.17, the trend between the treatment arms is reversed for CLONICEL 0.2 mg and CLONICEL 0.4 mg between males and females.

**Table 18: Gender subgroup analysis results in CLON-301**

Gender	Variable	ADHDRS-IV Total score (Observed)						ADHDRS-IV Total score (LOCF)	
		Clon 0.2 mg		Clon 0.4 mg		Placebo		Clon 0.2 mg vs. Placebo	Clon 0.4 mg vs. Placebo
		N	MEAN (SD)	N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB	DIFFERENCE in LSMEAN of CFB
Female	Baseline	16	41.5 (7.28)	23	44.83 (8.04)	24	45.08 (7.58)	-9.48	-12.77
	CFB Mean from Placebo	16	-17.63 (13.52)	16	-21.69 (10.46)	19	-9.84 (11.14)		
Male	Baseline	58	44.48 (7.45)	55	44.49 (7.67)	52	45.02 (9.00)	-8.31	-7.64
	CFB Mean from Placebo	42	-16.02 (11.63)	36	-18.44 (13.66)	40	-7.10 (8.07)		
Overall	Baseline	74	43.8 (7.47)	78	44.6 (7.73)	76	45.0 (8.53)	-8.49	-9.13
	CFB Mean from Placebo	58	-16.5 (12.08)	52	-19.4 (12.75)	59	-8.0 (9.16)		

\* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.

[Source: Reviewer's analysis]

This reviewer conducted a gender-based subgroup analysis for the primary analysis data. The analysis results appear in Table 18. The ANCOVA model with a covariate of the baseline ADHDRS-IV total score and a factor of the treatment group was fit on each of the subgroup (male and female). The observed treatment effects appeared comparable between genders in both the treatment comparisons (CLON 0.2-mg vs. Placebo and CLON 0.4-mg vs. Placebo), except that the female CLON 0.4-mg group had a numerically larger treatment effect (-12.77).



#### 4.1.1.2 Race

The sponsor conducted a subgroup analysis on the ADHDRS-IV primary endpoint by including the factor of race as potential predictors of response in the endpoint with an ANCOVA model analogous to that for the gender subgroup analysis. The sponsor's interpretations of this analysis are as follows:

In the analysis of race (White, Black/African American, Hispanic, Other), the overall treatment effect for CLONICEL relative to placebo was not affected by race; there were not statistically significant effects for race or a race by treatment interaction. As shown in the least square means model estimates for race and treatment in Table 14.2.17, the effects of CLONICEL relative to placebo was substantial in Whites compared with Black/African Americans and Other races.

There are not many patients in each subgroup except for the white. The observed treatment effects in the White appear similar to the overall treatment effects for each treatment group, as summarized in this reviewer's results (Table 19).

**Table 19: Race subgroup analysis results in CLON-301**

Race	Variable	ADHDRS-IV Total score (Observed)						ADHDRS-IV Total score (LOCF)	
		Clon 0.2 mg		Clon 0.4 mg		Placebo		Clon 0.2 mg vs. Placebo	Clon 0.4 mg vs. Placebo
		N	MEAN (SD)	N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB	DIFFERENCE in LSMEAN of CFB
Black	Baseline	19	44.9 (8.89)	20	47.0 (6.50)	23	46.9 (8.82)	-6.04	-8.48
	CFB Mean from Placebo	13	-14.9 (12.62)	14	-19.3 (11.54)	20	-9.3 (11.11)		
White	Baseline	45	43.1 (7.24)	46	43.3 (8.29)	44	45.2 (8.29)	-9.13	-9.20
	CFB Mean from Placebo	37	-16.0 (12.29)	32	-18.9 (13.33)	30	-7.3 (8.43)		
Hispanic	Baseline	6	46.3 (5.61)	7	45.7 (6.45)	6	42.5 (6.72)	-12.65	-13.11
	CFB Mean from Placebo	5	-20.2 (12.38)	4	-20.8 (17.08)	6	-7.8 (8.82)		
Other	Baseline	4	43.0 (5.89)	5	45.0 (7.97)	3	34.0 (6.24)	-11.28	-9.43
	CFB Mean from Placebo	3	-22.3 (8.50)	2	-26.0 (8.49)	3	-6.3 (3.05)		
Overall	Baseline	74	43.8 (7.47)	78	44.6 (7.73)	76	45.0 (8.53)	-8.49	-9.13
	CFB Mean from Placebo	58	-16.5 (12.08)	52	-19.4 (12.75)	59	-8.0 (9.16)		

\* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.

[Source: Reviewer's analysis]

#### 4.1.1.3 Age

The sponsor performed their subgroup analysis on the ADHDRS-IV primary endpoint by including the covariate of age as potential predictors of response, with an ANCOVA model analogous to that for their gender subgroup analysis. The sponsor's interpretations of this analysis are as follows:

Age was evaluated as a continuous variable. The main effects for treatment were greater than were observed in the primary efficacy model. The age by treatment interaction was a significant factor. CLONICEL group age slopes were positive while the placebo slope was slightly negative. For the mean overall age, 9.4 years, the mean for the groups was -15.9, -16.4, and -7.4 for CLONICEL 0.2 mg, CLONICEL 0.4 mg, and placebo, respectively.

According to the sponsor's report, the interaction of treatment and age was significant and concluded that the treatment effect might differ according to the age of the subject.

This reviewer explored the age impact by dichotomizing the age into two subgroups: 6-12 year-old, and >12 year-old. In each subgroup, the ANCOVA with a covariate of baseline score and a factor of treatment was applied. The results, as summarized in Table 20, suggest that the 6-12 year-old subgroup was the contributor of the overall efficacy evidence, while the >12 year-old was not. In both comparisons, the difference of the least-square means was much smaller for the >12 year-old subgroup than for the 6-12 year-old group. This, however, may be due to the small number of subjects of this subgroup, and thus there is no information in the data enough to draw any conclusion on the efficacy of the >12 year-old subgroup.

**Table 20: Age subgroup analysis results in CLON-301**

Age group	Variable	ADHDRS-IV Total score (Observed)						ADHDRS-IV Total score (LOCF)	
		Clon 0.2 mg		Clon 0.4 mg		Placebo		Clon 0.2 mg vs. Placebo	Clon 0.4 mg vs. Placebo
		N	MEAN (SD)	N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB	DIFFERENCE in LSMEAN of CFB
6-12 year-old	Baseline	61	45.1 (6.93)	65	45.9 (7.07)	62	46.2 (8.0)	-10.62	-10.80
	CFB Mean from Placebo	46	-18.0 (12.49)	40	-21.0 (12.52)	49	-6.8 (8.43)		
>12 year-old	Baseline	13	38.2 (7.54)	13	38.0 (7.74)	14	39.7 (9.06)	-1.53	-1.69
	CFB Mean from Placebo	12	-10.5 (8.32)	12	-14.3 (12.67)	10	-13.9 (10.74)		
Overall	Baseline	74	43.8 (7.47)	78	44.6 (7.73)	76	45.0 (8.53)	-8.49	-9.13
	CFB Mean from Placebo	58	-16.5 (12.08)	52	-19.4 (12.75)	59	-8.0 (9.16)		

\* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.

[Source: Reviewer's analysis]

## 4.1.2 STUDY CLON-302

### 4.1.2.1 Gender

The sponsor conducted an analysis on the ADHDRS-IV primary endpoint by including the factor of gender as a potential predictor of the response in the endpoint. The ANCOVAs were fit modeling the change from baseline as a function of the baseline ADHDRS-IV total score, the treatment group, gender and the interaction of the treatment and gender. The sponsor's interpretations of this analysis are as follows:

In the analysis of gender, the overall treatment effect for CLONICEL relative to placebo was not affected by gender; there were no statistically significant effects for gender or a gender by treatment interaction. The least squares means for the treatments adjusted for gender were -16.4 and -11.2 for CLON+STM and PBO+STM, respectively, and the treatment difference was highly significant ( $p=0.0087$ ).

The sponsor found that the gender and the interaction of gender and treatment were not statistically significant in the specified ANCOVA model, and concluded that the overall treatment effect for CLONICEL relative to placebo was not affected by gender.

This reviewer conducted a gender-based subgroup analysis for the primary analysis data. The ANCOVA model with a covariate of the baseline ADHDRS-IV total score and a factor of the treatment group was fit on each of the subgroup (male and female). The observed treatment effects appeared consistent in favoring the combination therapy. (See Table 21)

**Table 21: Gender subgroup analysis in CLON-302**

Gender	Variable	ADHDRS-IV Total score (Observed)				ADHDRS-IV Total score (LOCF)
		Clon +STM		Placebo +STM		Clon +STM vs. Placebo +STM
		N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB
Female	Baseline	23	38.9 (7.92)	29	37.6 (8.25)	-6.8
	CFB Mean from Placebo	22	-17.4 (14.55)	21	-12.2 (14.09)	
Male	Baseline	79	38.9 (6.70)	57	39.6 (7.39)	-3.1
	CFB Mean from Placebo	70	-16.8 (11.51)	44	-13.7 (10.98)	
Overall	Baseline	102	38.9 (6.95)	95	39.0 (7.68)	-4.5
	CFB Mean from Placebo	92	-15.7 (12.08)	75	-11.5 (12.75)	

\* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.

[Source: Reviewer's analysis]

#### 4.1.2.2 Race

The sponsor performed a subgroup analysis on the ADHDRS-IV primary endpoint by including the factor of race as potential predictors of response. The ANCOVAs were fit modeling the change from baseline as a function of the baseline ADHDRS-IV total score, the treatment group, race and the interaction of the treatment and race. The sponsor's interpretations of the analysis are as follows:

In the analysis of race, the ANOVA tests for homogeneity of race and race/treatment interaction were not significant. However, inspection of the least squares means and model estimates show that the effect of CLONICEL relative to placebo was most substantial in Whites compared to Other races (Hispanic/Latino and other) and Black/African American subjects. The overall least squares mean average treatment responses were -15.7 and -12.4 for CLON+STM and PBO+STM, respectively ( $p=0.0888$ ). The pair-wise p-value for Whites was statistically significant on its own ( $p=0.0397$ ) with estimated means of -17.1 and -10.2 for CLON+STM and PBO+STM, respectively. There was a reasonable number of Blacks/African Americans and Other Races in this study and the proportion of Whites in the CLON+STM group (48.0%) was actually lower than in the PBO+STM group (60.0%) primarily as a result of having more Blacks/African Americans in the CLON+STM group, though the test for overall homogeneity of the race distributions was not statistically significant ( $p=0.1547$ ). This imbalance may explain the lack of statistical significance in the average pair-wise treatment comparison.

The essential part of the sponsor's interpretations is that no other race had a greater impact on the outcome of the primary efficacy analysis than the white.

**Table 22: Race subgroup analysis in CLON-302**

Race	Variable	ADHDRS-IV Total score (Observed)				ADHDRS-IV Total score (LOCF)
		Clon +STM		Placebo +STM		Clon +STM vs. Placebo +STM
		N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB
Black	Baseline	35	39.7 (6.04)	19	41.7 (7.22)	-0.3
	CFB Mean from Placebo	29	-15.3 (13.22)	14	-15.1 (11.57)	
White	Baseline	49	38.7 (7.39)	57	38.4 (7.52)	-7.0
	CFB Mean from Placebo	45	-18.3 (11.41)	44	-11.9 (10.94)	
Hispanic	Baseline	11	39.4 (7.92)	11	36.7 (9.43)	-0.6
	CFB Mean from Placebo	11	-13.9 (14.96)	9	-14.1 (11.48)	
Other	Baseline	7	35.6 (6.90)	8	40.0 (6.76)	-7.5
	CFB Mean from Placebo	7	-19.7 (8.24)	8	-16.8 (17.85)	
Overall	Baseline	102	38.9 (6.95)	95	39.0 (7.68)	-4.5
	CFB Mean from Placebo	92	-15.7 (12.08)	75	-11.5 (12.75)	

\* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline. [Source: Reviewer's analysis]

This reviewer applied the primary analysis to each subgroup of race: the white, the black, the Hispanic, and the other (see Table 22). The white accounts for the largest proportion of the race, and the observed treatment effect for this subgroup was in favor of the clonice group. For the black, they appear similar between treatment groups. It is noted that the black in the placebo group seem to have numerically considerable improvement. The reason is unclear, but it might be explained by the effect contributed by the use of stimulant or the chance because of the sample size in this subgroup.

#### 4.1.2.3 Age

The sponsor performed their subgroup analysis on the ADHDRS-IV primary endpoint by including the covariate of age as potential predictors of response. The ANCOVAs were fit modeling the change from baseline as a function of the baseline ADHDRS-IV total score, the treatment group, age and the interaction of the treatment and age. The sponsor's interpretations of this analysis are as follows:

Age was evaluated as a continuous variable. Age and the age by treatment interaction were not significant factors. Slopes indicated that the PBO+STM improved with increasing age (slope = -0.41), while the overall slope for CLON+STM was close to zero (-0.03). There was a large difference in the intercepts with CLON+STM having a -8.29 difference relative to PBO+STM associated with the treatment parameter. As noted above, the p-value for the overall least squares mean treatment comparison adjusted for age was statistically significant (p=0.0143). For the mean overall age, 10.5 years, the means were -15.8 and -11.5 for CLON+STM and PBO+STM, respectively.

The sponsor found that the age and the interaction of age and treatment were not statistically significant in the specified ANCOVA model. This reviewer confirmed the analysis results and has no further comments to the sponsor's interpretations shown above.

This reviewer explored the age impact by dichotomizing the age into two subgroups: 6-12, and >12. In each subgroup, the ANCOVA with a covariate of baseline score and a factor of treatment was applied. The results, as summarized in Table 23, appear consistent between these two subgroups.

**Table 23: Age subgroup analysis in CLON-302**

Age group	Variable	ADHDRS-IV Total score (Observed)				ADHDRS-IV Total score (LOCF)
		Clon +STM		Placebo +STM		Clon +STM vs. Placebo +STM
		N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB
6-12 Years	Baseline	77	39.3 (6.85)	75	39.5 (7.69)	-3.8
	CFB Mean from Placebo	70	-16.51 (12.29)	62	-13.4 (12.27)	
>12 Years	Baseline	25	37.7 (7.2)	20	36.9 (7.47)	-5.8
	CFB Mean from Placebo	22	-18.2 (12.17)	13	-12.8 (10.26)	
Overall	Baseline	102	38.9 (6.95)	95	39.0 (7.68)	-4.5
	CFB Mean from Placebo	92	-15.7 (12.08)	75	-11.5 (12.75)	

\* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.

[Source: Reviewer's analysis]

## 4.2 Other Special/Subgroup Populations

### 4.2.1 STUDY CLON-302: Psychostimulant subgroup

The sponsor conducted their subgroup analysis for the stimulant based subgroups (Amphetamine or Methylphenidate). The results are provided in Table 14.2.1.3 (observed data) and Table 14.2.1.4 (LOCF data) of the study report. Means and standard deviations of observed baseline scores and observed (and LOCF) changes from baseline in ADHDRS-IV total score at all the visits (Screening, Baseline, Week 1- Week5) are provided in these tables. The sponsor also conducted a model-based analysis; the same ANCOVA model as in the primary efficacy analysis, with an additional categorical variable of stimulants. These results are also provided in Table 14.2.1.3 (observed data) and Table 14.2.1.4 (LOCF data) of the study report.

The sponsor found that there were no statistically significant differences between the CLON+STM treatment group and PBO+STM treatment group at Week 5, but attributed this to the small sample sizes. This reviewer agrees. These corresponding results along with essential statistics are provided in Table 24. The small difference between the subgroups in magnitude of each of the LS mean estimates (-4.2 for Amphetamine and -3.4 for Methylphenidate) does not seem to suggest any inconsistency that may affect the interpretations of the overall primary efficacy result.

**Table 24: Sponsor subgroup analysis by Psychostimulant (Amphetamine/Methylphenidate) in CLON-302**

Stimulant group	Variable	ADHDRS-IV Total score (Observed)				ADHDRS-IV Total score (LOCF)
		Clon +STM		Placebo +STM		Clon +STM vs. Placebo +STM
		N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB
Amphetamine	Baseline	42	39.3 (6.60)	35	38.9 (6.67)	-4.2
	CFB Mean from Placebo	41	-18.6 (12.44)	30	-14.6 (10.88)	
Methylphenidate	Baseline	60	38.6 (7.22)	60	39.0 (8.26)	-3.4
	CFB Mean from Placebo	51	-15.6 (11.99)	45	-12.4 (12.50)	
Overall	Baseline	102	38.9 (6.95)	95	39.0 (7.68)	-4.5
	CFB Mean from Placebo	92	-15.7 (12.08)	75	-11.5 (12.75)	

\* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.

[Source: Reviewer's analysis]

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

The phase III studies, Study CLON-301 and Study CLON-302, established statistical evidence of a mean difference in the ADHDRS-IV total score at the study endpoint (Week 5) in favor of CLONICEL treatment against the placebo, both as a monotherapy and as an add-on to a psychostimulant.

The sponsor established statistical evidence to support the claim for the efficacy of CLONICEL, based on results from the pre-specified analysis LOCF ANCOVA (last observation carried forward analysis of covariance) as well as the pre-specified sensitivity analysis ANCOVA on Observed Cases. The dropout rates were around 40% and 17% respectively in these two studies. In order to explore the impact of the dropouts on efficacy findings, this reviewer performed a MMRM-based sensitivity analysis, which requires a milder assumption for the missing data mechanism. It was found that the result led to the same conclusion in supporting efficacy.

In the subgroup analysis, this reviewer observed differences in estimates of change from baseline scores among races in Study CLON-302, but not in Study CLON-301. In addition, this reviewer observed that the age groups (6-12 year-old and >12 year-old) did not show similar efficacy estimates in Study CLON-301. These differences, however, may be due to a chance or the fact that subgroups but the white had too small a sample size to statistically assess the estimated differences. Despite some apparent discrepancies in efficacy estimates for subgroups, overall evidence is strong to support the efficacy of the clonice treatment.

### **5.2 Conclusions and Recommendations**

The sponsor's phase III studies, CLON-301 and CLON-302, provided statistical evidence that CLONICEL is efficacious, as a monotherapy and as an add-on to a psychostimulant, in the treatment of subjects (6-17 years-old) with ADHD.

## **SIGNATURES/DISTRIBUTION LIST**

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Date: June 18, 2010

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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06/21/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

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

# OFFICE of CLINICAL PHARMACOLOGY

## Efficacy Supplement

### Pharmacometrics review

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PRODUCT (Generic Name):	Clonidine HCL
PRODUCT (Brand Name):	Kapvay
DOSAGE FORM:	Tablets
DOSAGE STRENGTH:	0.1 mg tablet
NDA:	22331
NDA TYPE:	505(b)(2) Submission
SUBMISSION DATE:	September 29, 2009
SPONSOR:	Addrenex Pharmaceuticals
REVIEWER	Andre Jackson

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#### REVIEW OF CLONIDINE HCL TABLET FOR ADHD

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## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1. Do the firm's data support the firm's statements in the label that somnolence appeared to be independent of clonidine dose or concentration?
2. To assess if the blood pressure measurements indicate the occurrence of hypotension in the subjects since the primary indication for clonidine is that of an antihypertensive agent?
3. Do the firm's data support the firm's statements in the label related to clonidine drug interactions with psycho-stimulants?
4. Does exposure response help to explain the lack of efficacy in adolescents when compared to younger children?

#### 1.1.1

1. Does the firm's data support the firm's statements in the label that somnolence appeared to be independent of clonidine dose or concentration?

Data submitted by the firm clearly show clonidine is associated with higher incidence of somnolence compared to placebo although there was no clear relationship to dose. The lack of a clear dose response may be due to the titration design. Most of the somnolence

in the high dose group (0.4 mg/day) happened around 2 weeks when the patients were taking 0.2 mg day during the titration phase.

2. To assess if the blood pressure measurements indicate the occurrence of hypotension in the subjects since the primary indication for clonidine is that of an antihypertensive agent?

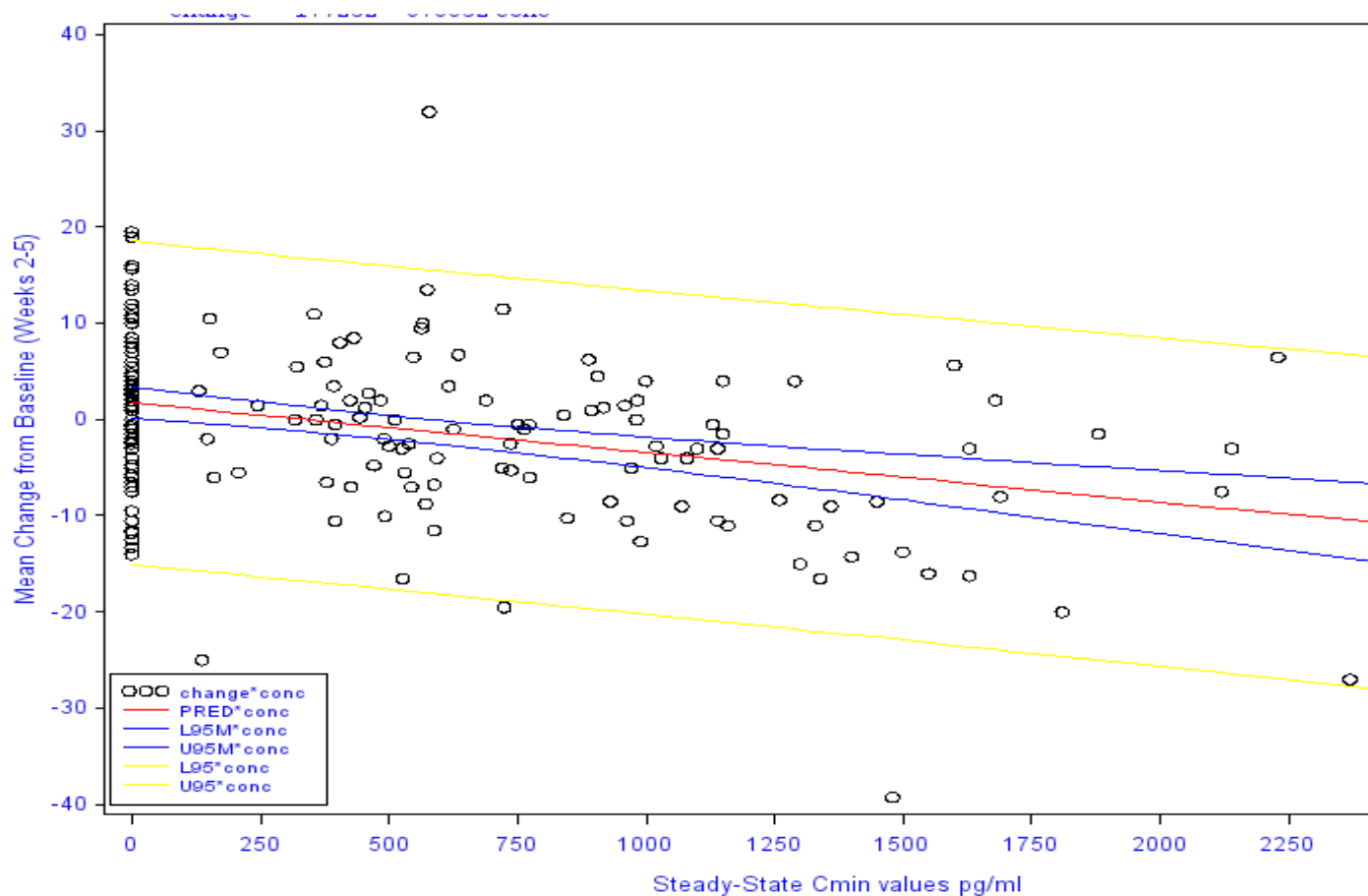
The firm conducted two studies, a fixed dose study 301 and adjunctive therapy study 302 which was variable doses of clonidine added to subjects previously receiving the stimulants methylphenidate or amphetamine.

Analysis of the systolic and diastolic changes in blood pressure from baseline from weeks 2-5 during the fixed dose phase of dosing of Study 301 indicated larger reduction in blood pressure with larger exposure. The reductions were less than those observed in the previous adult study in mild and moderate hypertensives, i.e., Study 201.

Figure 1 presents the regression of change in systolic blood pressure vs concentration for weeks 2-5 during fixed dosing and Figure 2 for diastolic blood pressure weeks 2-5. Table 1 presents the observed reductions in blood pressure for adult study 201 and the current study 301.

**Figure 1. Significant Exposure-Response Relationship for Systolic Blood Pressure  
for fixed dose study 301**

$$\text{Change} = 1.7252 - 0.0052 * \text{conc} \quad p < 0.0001$$



**Figure 2. Significant Exposure-Response Relationship for Diastolic Blood Pressure  
for fixed dose study 301**

$$\text{Change} = 1.325 - 0.0046 * \text{conc} \quad p < 0.0001$$

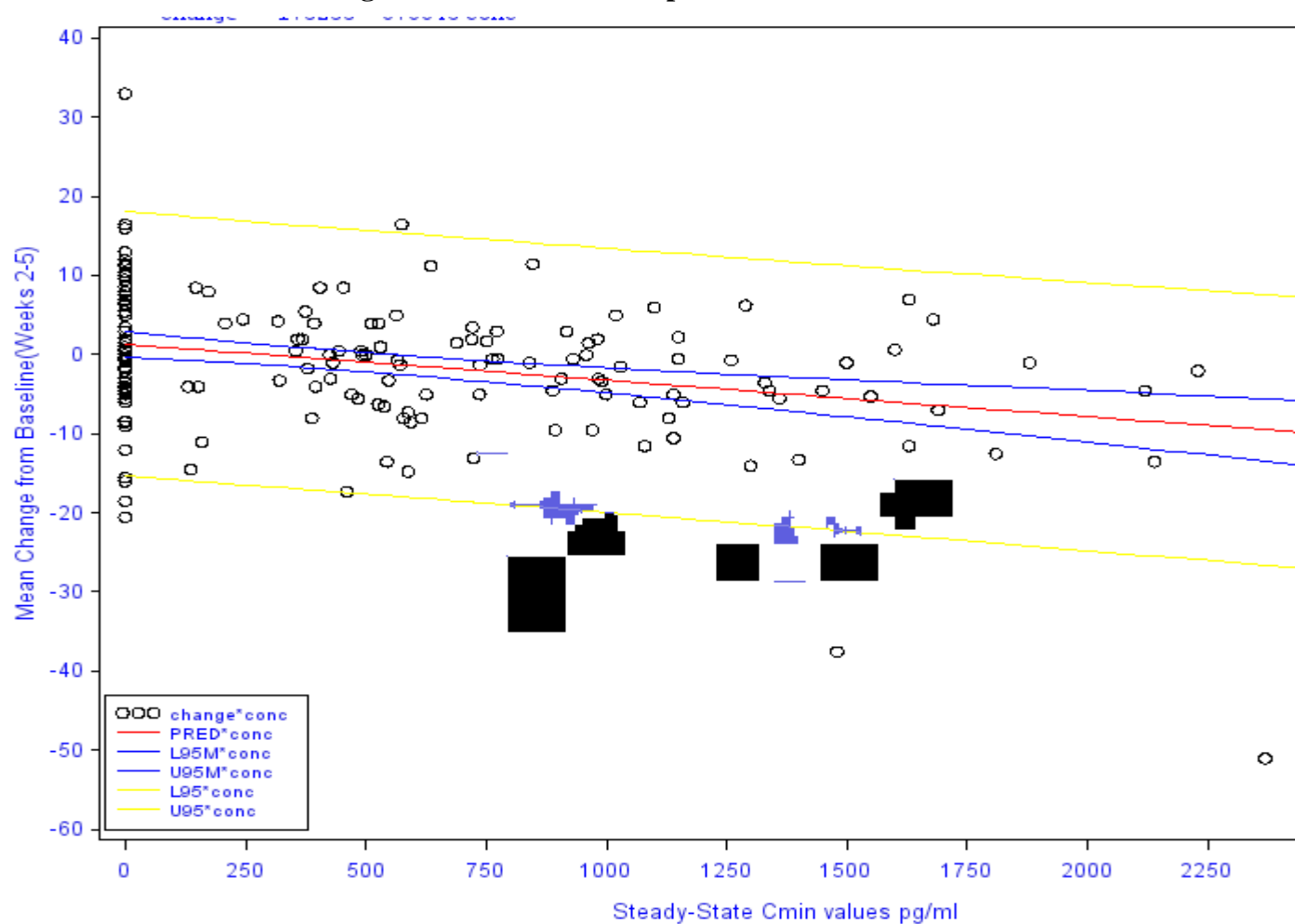


Table 1. Change in Blood Pressure from baseline in adult study 201 with mild to moderate hypertensive patients compared to normal adolescents and children in Study 301. Doses are bid for both studies.

Study 201-Day 26-Hour 11			Study 301-Weeks 2-5		
Reduction from Baseline Systolic BP (mmHg)			Reduction from Baseline Systolic BP (mmHg)		
0.2 mg	0.4 mg	0.6 mg	0.2 mg	0.4 mg	---
10.8	21.3	19.6	1-1.5	5-6	
Reduction from Baseline Diastolic BP (mmHg)			Reduction from Baseline Diastolic BP (mmHg)		
0.2 mg	0.4 mg	0.6 mg	0.2 mg	0.4 mg	---
6.3	10.6	17	2	4-5	

3. Do the firm's data support the firm's statements in the label related to clonidine drug interactions with psycho-stimulants?

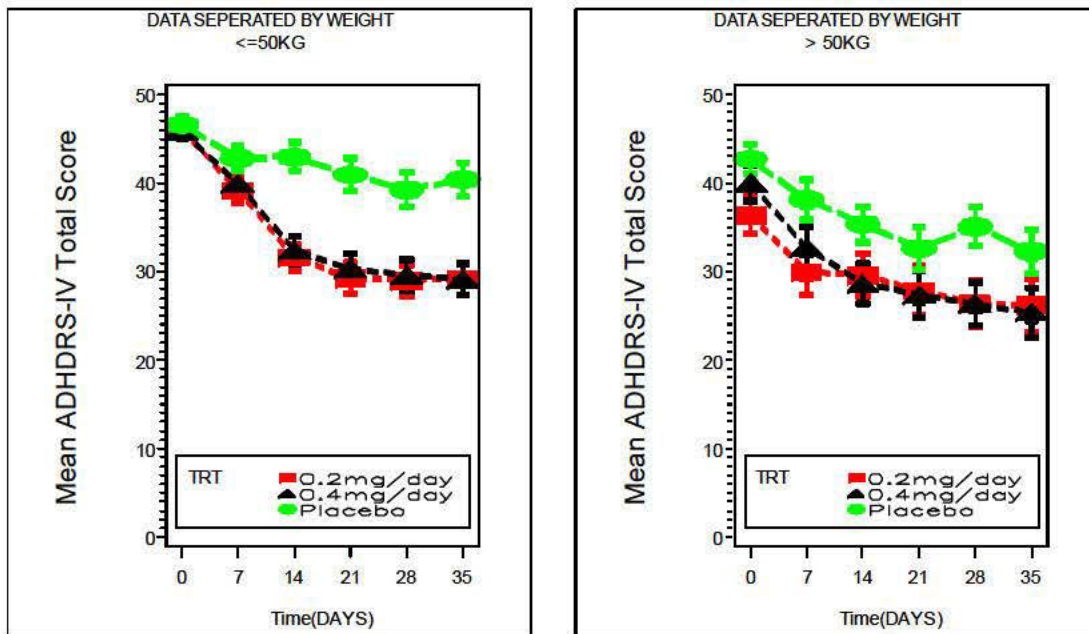
The study was designed for subjects entering the study to have been on a stable regimen of approved stimulant medication of either methylphenidate or amphetamine (or their derivatives) for a minimum period of 4 weeks. The aim was to determine if these subjects could potentially benefit from the addition of an alpha2 adrenergic agonist as evidenced by a lack of adequate response to the stable regimen of stimulant medication.

The clonidine dose (or matching placebo) was initiated at 0.1 mg/day and titrated up to a 0.4 mg/day (administered as 0.2 mg q12h) over a 3-week period. Since the drug was titrated the concern for a drug-drug interaction was minimized and if observed the dose could be tapered. The administered dose was maintained at a level for a period of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. This tapering could be done if a drug-drug interaction was observed.

4. Does exposure response help to explain the lack of efficacy in adolescents when compared to younger children?



**Figure 3. Change in the primary Clinical endpoint ‘Mean ADHDRS IV Total Score’ as a function of time for subjects separated by weight.**



The results show that the children above 50 kg in weight have a much lower response to Clonidine as determined by the ADHDRS-IV (attention deficit hyperactivity disorder rating scale) score than lighter children. The lack of response is mainly due to a larger placebo effect in the heavier children.

## 1.2 Recommendations

All children and adolescents should only receive the 0.2 mg/day dose unless they fail to respond.

## 1.3 Label Statements

Firm's Proposed Label

### Multiple-dose Pharmacokinetics in Children and Adolescents

(b) (4)

## FDA Label

### **Multiple-dose Pharmacokinetics in Children and Adolescents**

Plasma clonidine concentrations in children and adolescents (0.1 mg bid and 0.2 mg bid) with ADHD are greater than those of adults with hypertension with children and adolescents receiving higher doses on a mg/kg basis. Body weight normalized clearance (CL/F) in children and adolescents was higher than CL/F observed in adults with hypertension. Clonidine concentrations in plasma increased with increases in dose over the dose range of 0.2 to 0.4 mg/day. Clonidine CL/F was independent of dose administered over the 0.2 to 0.4 mg/day dose range. Clonidine CL/F appeared to decrease slightly with increases in age over the range of 6 to 17 years, and females had a 23% at lower CL/F than males. The incidence of “sedation-like” AEs (somnolence and fatigue) appeared to be independent of clonidine dose or concentration within the studied dose range in a titration study. Results from the add-on study showed that clonidine CL/F was 11% higher in patients who were receiving stimulant therapy with methylphenidate and 44% lower in those receiving amphetamine compared to subjects not on adjunctive therapy.

## **2 PERTINENT REGULATORY BACKGROUND**

### **REGULATORY BACKGROUND**

The effectiveness and safety of orally administered clonidine in the treatment of hypertension has been documented and approved by the FDA in NDA 22331 for mild and moderate hypertensive adults. Despite the usefulness of clonidine in the treatment of hypertension, the regimen of administration required by the pharmacokinetic profile of the drug resulted in quite wide fluctuations in plasma concentrations for the IR formulation bid regimen, even at steady state. It has been established that many of the AEs observed during oral clonidine administration were related to its high peak plasma concentrations. The pharmacokinetic profile and relationship between plasma levels and AEs necessitated frequent dosing and resulted in a “roller coaster” effect characterized by “peak” AE of sedation and “trough” AE of rebound hypertension.

In addition to hypertension, clonidine has been evaluated and used extensively for several other indications, including attention deficit hyperactivity disorder (ADHD), alcohol withdrawal, atrial fibrillation, tic disorders, menopausal flushing, smoking cessation, and ulcerative colitis. The current submission is a 505b(2) submission. All of the relevant

pharmacokinetic studies were conducted and submitted for review to the Division of Cardioresenal drug products. The main focus of this submission will be safety and effectiveness of clonidine in adolescents at two fixed bid doses of 0.2 mg and 0.4 mg.

For this submission the firm has conducted two studies relevant to OCP:

1. Study 301-dose response evaluation of the efficacy and safety of CLONICEL® (clonidine HCl ) vs. placebo in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)
2. Study 302- A phase III evaluation of the efficacy and safety of CLONICEL® (clonidine HCl ) as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD).

## 2.1 Sponsors' Analysis

[\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1\\_AJ\Sponsor Data and Reports](#)

Document: Results of Sponsor.doc-OCP Review of Sponsors Data

## 2.2 Summary of Firm's Data Related to Label

The major assumption related to all the pharmacokinetic data was that based upon study (CLON-201)-study in adults with hypertension, the fluctuation index for CloniceL is relatively low, averaging 34%. Since the same mg dose was given to adults, adolescents and children, the lower body weights in children resulted in higher doses on a µg/kg basis. As shown in Table 2, the mean daily doses in children were 5.66 and 5.86 µg/kg for the 0.2 mg dose, and 10.74 and 12.22 µg/kg for the 0.4 mg dose.

Table 2. Dosing Information Summary for the PK Populations for CLON-301 and CLON-302

Statistic		CLON-301		CLON-302			
		0.2 mg	0.4 mg	0.1 mg	0.2 mg	0.3 mg	0.4 mg
Subjects	N	57	51	1	7	20	52
Average	Mean	0.20	0.38	0.10	0.19	0.31	0.39
Daily Dose	SD	0.00	0.04	NC	0.02	0.02	0.01
(mg)	Minimum	0.20	0.20	0.10	0.16	0.27	0.36
	Median	0.20	0.40	0.10	0.20	0.30	0.39
	Maximum	0.20	0.40	0.10	0.20	0.34	0.40
Weight	Mean	5.66	10.74	2.51	5.86	8.25	12.22
Normalized	SD	2.25	4.50	NC	2.93	3.66	3.55
Dose (µg/kg)	Minimum	1.53	3.28	2.51	2.31	2.72	3.64
	Median	5.83	10.26	2.51	6.69	7.94	12.46
	Maximum	9.57	19.90	2.51	8.81	15.08	20.00

In contrast, the mean weight normalized doses in adults were substantially lower, averaging 1.20, 2.24, and 3.36 µg/kg for the 0.2 mg, 0.4 mg, and 0.6 mg doses, respectively.

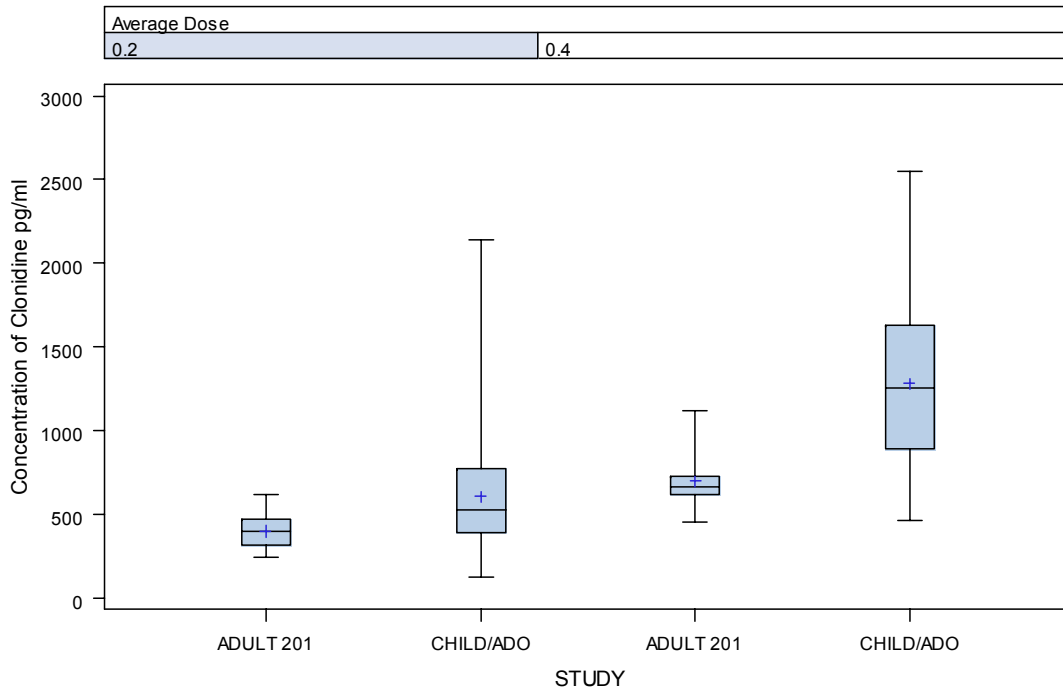
The OCP review for adult study 201 can be found at the following location.

<http://darrrts.fda.gov:7777/darrrts/ViewDocument?documentId=090140af8013545a>

The observed clonidine C<sub>MIN</sub> concentrations for the doses studied in children and adolescents (i.e., 0.2 mg and 0.4 mg-Study 301 ) resulted in larger clonidine C<sub>min</sub> values than those observed at the same 0.2mg and 0.4 mg doses in mild and moderate hypertensive adults, as shown in Figure 4.

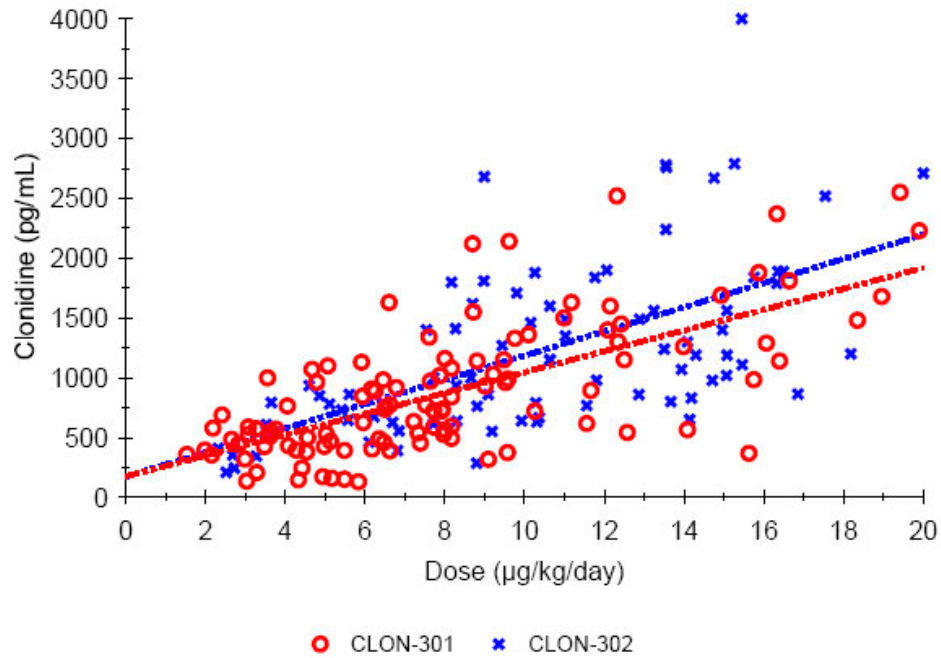
Figure 4. Clonidine C<sub>min</sub> Concentrations by Study and Treatment for CLON-301-Children and adolescents fixed dose, and CLON-201-Adults with hypertension

**Comparison of Trough Plasma Levels Adults vs Adolescents and Children**  
Doses of 0.2 0.4 mg



The plasma levels increased with dose for studies 301 and 302 as seen in Figure 5.

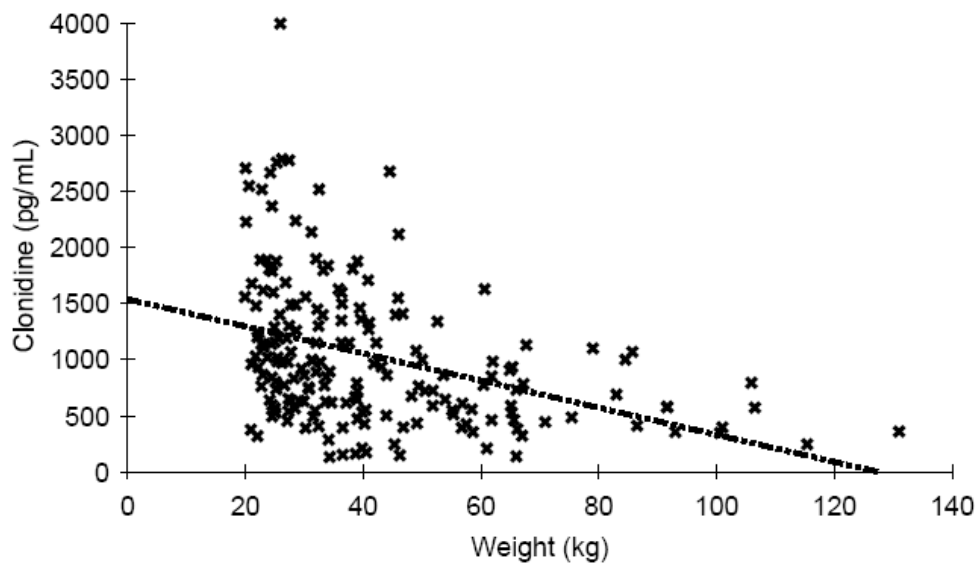
Figure 5. Plasma Clonidine Concentration vs Dose for CLON-301 and CLON-302



The results indicate that the plasma clonidine concentrations were proportional to dose.

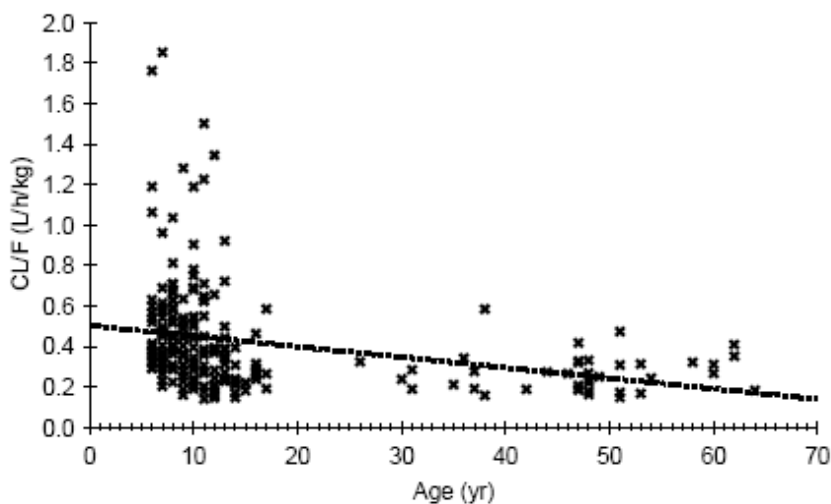
Weight was an important covariate with the fixed dose used in these studies, therefore one observes much larger exposure for lighter subjects, Figure 6.

Figure 6. Plasma Clonidine Concentration vs Body Weight



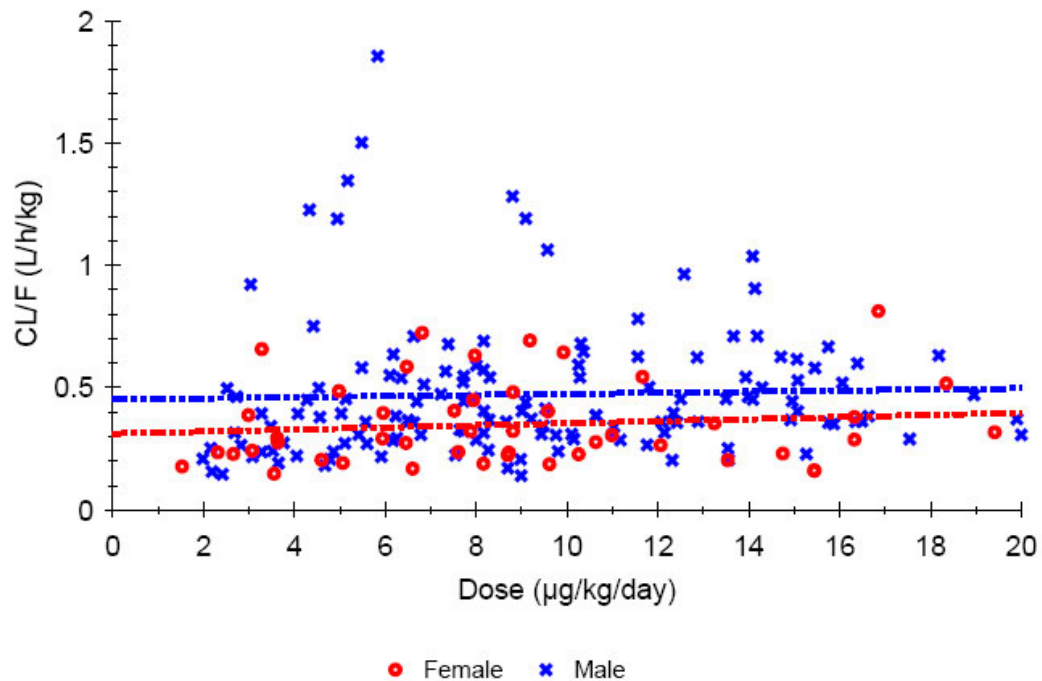
Further analysis of the CL/F vs age in Figure 7, showed a decrease with age which probably reflects the decrease in renal excretion related to age since the compound is primarily renally excreted.

Figure 7. Clonidine Weight Normalized CL/F vs Age for CLON-301, CLON-302 and CLON-201



The effects of gender on clonidine CL/F are displayed graphically in Figure 8.

Figure 8. Clonidine CL/F vs Dose by Gender for CLON-301 and CLON-302



The results seem to show a higher clearance in males than females. Overall, in both studies combined, the median CL/F was 0.393 L/h/kg for males and 0.294 L/h/kg for females, a 25% lower value for females.

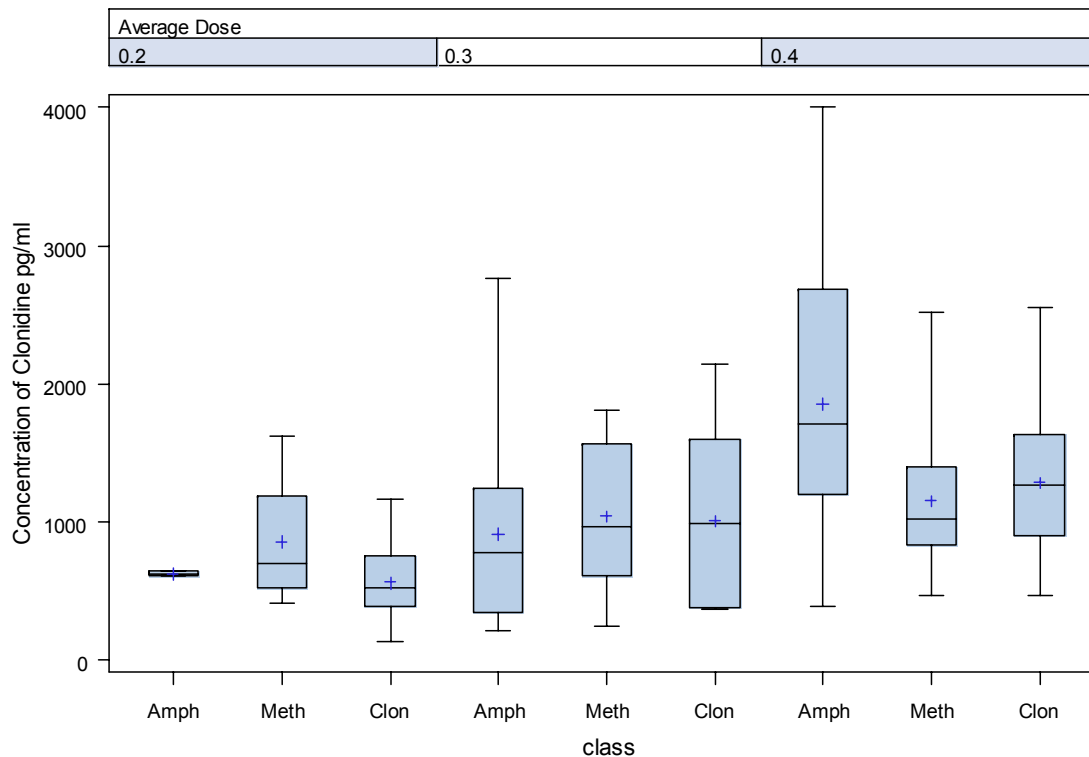
### ***Effects of Concomitant Psychostimulant Therapy***

CLON-302 required that subjects be on a stable regimen of a stimulant drug for treatment of their ADHD. Of the total of 80 subjects in CLON-302, 35 were receiving amphetamine and 45 were being treated with methylphenidate as stimulant therapy for ADHD. The box plot in Figure 9 shows, the median steady-state clonidine concentration alone for clonidine and when co-administered with amphetamine and when administered with methylphenidate. Compared to clonidine alone there was a 44% increase in exposure for amphetamine(Clonidine-1284 pg/ml; Clonidine+amphetamine-1857 pg/ml; Clonidine + methylphenidate-1151 pg/ml) and an 11% decrease in exposure for methylphenidate.

Figure 9. Effect of Concomitant Stimulant Administration on Steady-state Clonidine Concentrations

## COMPARISON OF TROUGH PLASMA LEVELS

DOSES OF 0.2 0.3 0.4 MG



Two of the most common adverse events in both studies, with a notably higher incidence in the active treatment groups versus placebo were the “sedation-like” adverse events of somnolence (which includes sedation), and fatigue (which includes lethargy).

Table 3. Treatment Emergent Adverse Events with 5% or Greater Incidence in any active Treatment Group and at least Twice the Incidence of Placebo (Safety Population) Relationship Between AE Incidence and Clonidine Dose and Concentration for CLON-301.



	TREATMENT GROUP		
	CLON 0.2 mg/day N=76	CLON 0.4 mg/day N=78	PBO N=76
PREFERRED TERM	Subjects n (%)	Subjects n (%)	Subjects n (%)
Somnolence	30 (39.5)	24 (30.8)	5 (6.6)
Fatigue	12 (15.8)	10 (12.8)	1 (1.3)
Irritability	7 (9.2)	6 (7.7)	3 (3.9)
Pharyngolaryngeal pain	6 (7.9)	6 (7.7)	3 (3.9)
Body Temperature Increased	4 (5.3)	2 (2.6)	2 (2.6)
Insomnia	4 (5.3)	5 (6.4)	1 (1.3)
Ear Pain	4 (5.3)	0	1 (1.3)
Emotional Disorder	3 (3.9)	4 (5.1)	1 (1.3)
Nightmare	3 (3.9)	7 (9.0)	0
Constipation	1 (1.3)	5 (6.4)	0
Dry Mouth	0	4 (5.1)	1 (1.3)
Data Source: Table 14.3.1.2			

Reviewer's Comments:

(b) (4)  
In addition, exposure response related to adverse events and efficacy will be explored by the reviewer.

### 3 REVIEWER'S ANALYSIS

#### 3.1 Introduction

The reviewer's analysis is being done to further delineate exposure response for blood pressure and somnolence in the children. In addition the impact of weight on efficacy will be investigated since large weight led to lower exposure for clonidine.

#### 3.2 Objectives

Analysis objectives are:

1. To determine if the data presented by the firm support that somnolence appeared to be independent of clonidine dose or concentration.
2. To assess if the blood pressure measurements indicate the occurrence of hypotension in the children and adolescents since the approved indication for clonidine is that of an antihypertensive agent.
3. To evaluate if the firm's data support the label related to clonidine drug interactions with psycho-stimulants.

4. To determine if exposure response helps to explain the lack of efficacy in adolescents when compared to younger children.

### 3.3 Methods

#### 3.3.1 Data Sets

Name of Dataset	Link to EDR Study 301
adhdrs.xpt	<a href="\\cdsesub1\evsprod\NDA022331\0014\m5\datasets\120day\listings">\\cdsesub1\evsprod\NDA022331\0014\m5\datasets\120day\listings</a> Primary efficacy endpoint scores
Vsl.xpt	<a href="\\cdsesub1\evsprod\NDA022331\0014\m5\datasets\120day\listings">\\cdsesub1\evsprod\NDA022331\0014\m5\datasets\120day\listings</a> Blood pressure values for study 301
Adef.sas7bdat	<a href="\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports\STUDY301">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports\STUDY301</a> Somnolence data for study 301
Adae.sas7bdat	<a href="\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports\STUDY301">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports\STUDY301</a> Adverse events study 301
Sas.sas7bdat	<a href="\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports\STUDY301">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports\STUDY301</a> Plasma data for study 301
Yvar_new.csv	<a href="\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports\STUDY301">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports\STUDY301</a> Data for exposure vs dose by weight

Name of Dataset	Link to EDR Study 302
adtx.xpt	<a href="\\cdsesub1\evsprod\NDA022331\0019\m5\datasets\302\tabulations">\\cdsesub1\evsprod\NDA022331\0019\m5\datasets\302\tabulations</a> Identify subjects taking placebo
vsl.xpt	<a href="\\cdsesub1\evsprod\NDA022331\0019\m5\datasets\302\tabulations">\\cdsesub1\evsprod\NDA022331\0019\m5\datasets\302\tabulations</a> Blood pressure values for Study 302

Studyclon302_fda.csv	<a href="\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Shared Analysis Data\STUDY302">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Shared Analysis Data\STUDY302</a> Plasma data for study 302
StimplusClon.xls	<a href="\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Shared Analysis Data\STUDY302">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Shared Analysis Data\STUDY302</a> Adjunctive therapy mean plasma values for clonidine, clonidine + amphetamine, and clonidine + methylphenidate

Name of Dataset	Link to EDR Study 201
PLCONC_STUDY201.XPT	<a href="\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Shared Analysis Data\STUDY201">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Shared Analysis Data\STUDY201</a> Plasma concentrations for adult study 201
STUDY201_PLAS.csv	<a href="\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Shared Analysis Data\STUDY201">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Shared Analysis Data\STUDY201</a> Median plasma concentrations for adult study 201

### 3.3.2 Software

SAS 9.2 was used for statistical and graphical analysis of the data.

### 3.3.3 Models

No PK models were used to analyze this data.

### 3.4 Results

Figures 1- Figure 2 in Section 1.1.1 clearly show an exposure response for blood pressure reduction for the fixed dose Study 301.

Figure 3 in section 1.1.1 shows that effect was based upon weight with children < 50 kg having a lower ADHD Rating Scale (Attention Deficit Hyperactivity Disorder) compared to placebo.

## 4 LISTING OF ANALYSES CODES AND OUTPUT FILES

PD_STDY301_PM4-12.sas	Analysis of study	<a href="\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER</a>
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	301 efficacy vs dose	<a href="#">Analyses\SAS</a>
SIDEBYSIDE_GR_CLON_4-12.sas	SAS code for efficacy vs dose graph	<a href="#">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\SAS</a>
rank_new1dias.sas rank_new1sys.sas	SAS code for BP vs exposure	<a href="#">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\SAS</a>
DDIgraph.sas	Analysis of study 302 drug interaction	<a href="#">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\SAS</a>
XPTIMPORT.sas	Import 201 study data	<a href="#">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\SAS</a>

File Name	Description	Location in \\cdsnas\pharmacometrics\
DIASBPCHANGE.png	Diastolic Blood Pressure vs Clonidine Steady-state concentrations-Fixed dose Study 301	<a href="#">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Graphs STUDY301</a>
SYSBPCHANGE.png	Systolic Blood Pressure vs Clonidine Steady-state concentrations-Fixed dose Study 301	<a href="#">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Graphs STUDY301</a>
302SGPlot1_DBP.png	Adhdrs Score vs dose by Subject weight	<a href="#">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Graphs STUDY301</a>
DDICLON.png	Steady-state clonidine levels alone and in the presence of amphetamine and methyphenidate in Study 302	<a href="#">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Clonidine_NDA22331S1_AJ\ER Analyses\Graphs STUDY302</a>

Conclusions:

Submission Number

DCTM\_ARP.doc

1. Clonidine is associated with a higher incidence of somnolence but there is a lack of dose response due to the titration design.
2. There was a decrease in blood pressure in children and adolescents taking 0.1 mg or 0.2 mg of Clonidine bid.
3. There appeared to be a 44% increase in clonidine exposure with amphetamines and an 11% decrease in exposure for clonidine with methylphenidate in children and adolescents taking clonidine as adjunctive therapy compared to the presence of no interacting drug.
4. Children greater than 50kg showed less response to clonidine because of a larger placebo effect in this patient group.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

/s/

ANDRE J JACKSON  
07/14/2010

RAMAN K BAWEJA  
07/14/2010

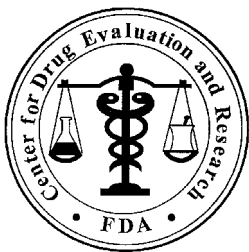
YANING WANG  
07/14/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**OTHER REVIEW(S)**



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: August 29, 2010

To: Thomas Laughren, MD, Director  
Division of Psychiatry Products

Through: Kristina A. Toliver, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis  
(DMEPA)

From: Lori Cantin, RPh, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis  
(DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Kapvay (Clonidine Hydrochloride) Extended-Release Tablets  
0.1 mg and 0.2 mg

Application Type/Number: NDA 022331/S-001 and S-002

Sponsor: Shionogi Pharma, Inc.

OSE RCM #: 2010-1154



## **1 INTRODUCTION**

This review responds to a request from the Division of Psychiatry Products (DPP) for assessment of the proposed labels and labeling for Kapvay (Clonidine Hydrochloride) Extended-release Tablets. Labels and labeling for this product were submitted as part of efficacy supplements 001 and 002 for NDA 022331. These efficacy supplements provide for monotherapy and add-on therapy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

## **2 REGULATORY HISTORY**

DMEPA reviewed the container labels submitted by the Applicant on June 21, 2010 (see Appendix A) and the insert labeling submitted on July 9, 2010. We provided recommendations on the container labels and insert labeling in order to minimize the potential for medication errors (See Appendix C). DPP forwarded our container label and insert labeling recommendations to the Applicant on July 22, 2010. Subsequently the Applicant submitted revised container labels and insert labeling on August 5, 2010. The revised labels and labeling are the subject of this review.

## **3 METHODS AND MATERIALS**

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels (see Appendices A and B), and insert labeling (no image) submitted August 5, 2010. There is no carton labeling for this product.

- Container Labels (Trade and Professional Sample)
  - 0.1 mg (8-count, 60-count, and 180-count)
  - 0.2 mg (8-count, 60-count, and 180-count)
- Insert Labeling (no image)

## **4 RECOMMENDATIONS**

We acknowledge that the Applicant addressed all of the recommendations concerning the container labels and one of the recommendations concerning the insert labeling in their August 5, 2010 submission. However, since not all of our recommendations regarding the insert labeling were addressed we continue to note areas of needed improvement in order to minimize the potential for medication errors. Recommendations provided on the insert labeling at labeling meetings, along with any additional recommendations on the insert labeling are provided in Section 4.1 Comments to the Division.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sandra Griffith, at 301-796-2445.

### **4.1 COMMENTS TO THE DIVISION**

1. We recommend that a statement be added to Section 17.4 (Patient Counseling Information, Dosing) to inform patients and healthcare practitioners that Kapvay must be swallowed whole, and never crushed, cut, or chewed.

2. In the DOSAGE AND ADMINISTRATION section and DOSAGE FORMS AND STRENGTHS section of the FULL PRESCRIBING INFORMATION we recommend revising the statements [REDACTED] (b) (4) to “*Tradename tablets must be swallowed whole and never crushed, cut, or chewed.*”
3. In the DOSAGE AND ADMINISTRATION section of the FULL PRESCRIBING INFORMATION we recommend revising the statement, [REDACTED] (b) (4) ”
4. Revise all relevant sections of the package insert labeling to indicate that the dosage form for this product is an extended-release tablet.

2 Pages of Draft Labeling have been Withheld in Full immediately following this page.

Appendix C: Insert Labeling and Container Label comments sent to the Applicant that were satisfied in the August 5, 2010 submission

#### COMMENTS TO THE DIVISION

DOSAGE AND ADMINISTRATION sections in the HIGHLIGHTS OF PRESCRIBING INFORMATION and FULL PRESCRIBING INFORMATION: We recommend that the sentence, (b) (4) be revised to specify the FDA-approved dosage information for this product. For example:

Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals (b) (4) until the desired response is achieved. (b) (4), as depicted below (2.1).

#### COMMENTS TO THE APPLICANT

##### Container Labels

1. The established name appears to be less than ½ the size of the proprietary name. Additionally, the (b) (4) used for the established name is difficult to see against the white background of the container label. Ensure the established name is at least ½ the size of the proprietary name, and that the established name has a prominence commensurate with the prominence with which the proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features as per 21 CFR 201.10(g)(2).
2. Revise the dosage form statement on the container labels from (b) (4) to “Extended-Release Tablets.”
3. The 0.1 mg strength and 0.2 mg strength are presented in a blue and a green color block, respectively. (b) (4)
4. Decrease the prominence of the graphic on the principal display panel to ensure the product strength and proprietary and established names are the most prominent information. Additionally, the font in the “Rx only” statement should be debolded.
5. Include instructions that state the product “must be swallowed whole and never crushed, cut, or chewed”. The manufacturer and distributor information can be modified if needed to make space for this statement.
6. On the container labels for Kapvay 0.1 mg and 0.2 mg tablets, we recommend revising the statement, (b) (4) to “Do not use Kapvay interchangeably with other clonidine products.”

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

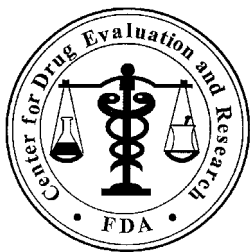
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

KRISTINA C ARNWINE on behalf of LORI G CANTIN  
08/29/2010

KRISTINA C ARNWINE  
08/29/2010

DENISE P TOYER  
08/29/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 6, 2010

To: Thomas Laughren, M.D., Director  
Division of Psychiatry Products (DPP)  
Office of New Drugs (OND)

Through: Mark I. Avigan, M.D., C.M., Director  
Division of Pharmacovigilance (DPV) I

From: Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader  
Division of Pharmacovigilance I  
and  
Mitchell V. Mathis, M.D., Deputy Director  
Division of Psychiatry Products  
Office of New Drugs

Subject: Death with the concomitant use of clonidine or guanfacine and  
amphetamine/dextroamphetamine or dexamethylphenidate or  
dextroamphetamine or lisdexamfetamine or methylphenidate

Drug Name(s): Clonidine, guanfacine, amphetamine/dextroamphetamine,  
dexamethylphenidate, dextroamphetamine, lisdexamfetamine,  
methylphenidate

Application Type/Number: See Appendix A

Applicant/sponsor: See Appendix A

OSE RCM #: 2010-1046

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## **EXECUTIVE SUMMARY**

The purpose of this review is to determine whether the current labels for methylphenidate and dexamethylphenidate products, which have a drug interaction statement cautioning clinicians about serious adverse events that may occur with concomitant use of methylphenidate (a psychostimulant) and clonidine (an  $\alpha_2$  adrenergic agonist), require updating. This drug interaction caution first appeared in labeling in 2000 with the approval of Concerta. The statement was apparently based upon four case reports of seriously life-threatening adverse reactions or death with the combination of stimulants and clonidine, despite the fact that these cases were reviewed by DPP at the time with a conclusion that there was no clear relationship between death and the combination of methylphenidate and clonidine. Nonetheless, the cautionary statement about a potential drug-drug interaction appeared in the Concerta label in 2000 and after that appeared in the other methylphenidate labels without an apparent critical review of cases.

This issue has public health importance because stimulants and clonidine are often used in standard-of-care psychiatry practice to treat attention deficit hyperactivity disorder (ADHD). This has been an off-label clinical practice for many years, but recently DPP has had applications for the use of  $\alpha_2$ -adrenergic agonists for the monotherapy and adjunctive (to stimulants) treatment of ADHD. DPP currently asks sponsors of selective  $\alpha_2$ -adrenergic agonists that they be studied as adjuncts to stimulants in new drug applications seeking the indication of the treatment of ADHD, because it is common clinical practice to use members of these two drug classes together.

Therefore, the Division of Psychiatry Products (DPP) requested that the Division of Pharmacovigilance I (DPV I) search the Adverse Event Reporting System (AERS) database for cases of death associated with the concomitant use of selective  $\alpha_2$  adrenergic agonists (clonidine or guanfacine) and stimulants (methylphenidate, dexamethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts).

In addition to the AERS search, DPP has evaluated controlled clinical trial data from applications for the  $\alpha_2$ -adrenergic agonists submitted for the indication of adjunctive (to stimulants) treatment of ADHD.

This joint effort identified only one new case of death in the AERS database, which reported the concomitant use of clonidine and methylphenidate, and no cases of serious and unexpected adverse events from the clinical trials data

Based on the data reviewed, in the absence of published or other data that points to risk for adverse events, we recommend updating the current methylphenidate and dexamethylphenidate labels to remove the drug interaction statement regarding methylphenidate and clonidine..

## **1 INTRODUCTION**

The purpose of this review is to determine whether the current labels for the methylphenidate and dexamethylphenidate products, which have a drug interaction statement warning clinicians about serious adverse events that may occur with concomitant use of methylphenidate and clonidine, require updating. DPP requested that DPV I search the AERS database for cases of death associated with the concomitant use of  $\alpha$  agonists (clonidine or guanfacine) and stimulants (methylphenidate, dexamethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts). Additionally, DPP requested that we specifically focus on cases of death that did not report co-existing physical disorders known or suspected to be associated with death, or



deaths with known causes unrelated to an underlying medical condition (e.g. accidental deaths, homicides, motor vehicle accident, natural disease progression, overdoses, or suicides).

## 1.1 BACKGROUND

In 2000, Concerta® (methylphenidate hydrochloride) received FDA approval; this approval marked the first time that a methylphenidate label included a statement regarding a potential drug interaction between methylphenidate and clonidine. This potential drug interaction was first reported in 1995 in a broadcast from National Public Radio, followed by an article in the literature that described four reports from the FDA AERS database of life-threatening or fatal cases associated with the concomitant use of methylphenidate and clonidine.<sup>1</sup> The author concluded that the cases were not convincing of a drug interaction between clonidine and methylphenidate. However, due to the limited number of existing reports and the lack of data from controlled clinical trials, it was impossible to prove the interaction did not exist.

Current literature and practice guidelines support the concomitant use of stimulants and alpha agonist agents to treat attention deficit hyperactivity disorder (ADHD), and there is no clear evidence of death associated with the combination.<sup>2</sup> There is some belief that clonidine has synergistic effects when used with stimulants in reducing behavioral symptoms of ADHD, which ultimately can result in a reduction in the stimulant dose when these medications are used concomitantly.<sup>3</sup>

## 1.2 REGULATORY HISTORY

The methylphenidate-clonidine drug interaction statement was added to the various methylphenidate and dexamethylphenidate product labels at different times (see Table 1 below for a summary of the additions).

<b>Table 1. Timeline for the labeling addition of the methylphenidate-clonidine drug interaction statement</b>		
<b>Date of the addition</b>	<b>Product name</b>	<b>Reason for addition</b>
August 1, 2000	Concerta (methylphenidate)	Drug approval
April 3, 2001	Metadate CD (methylphenidate)	Drug approval
November 13, 2001	Focalin (dexamethylphenidate)	Drug approval
January 11, 2002	Ritalin IR and Ritalin SR (methylphenidate)	Changes Being Effected supplement submitted by Novartis
June 5, 2002	Ritalin LA (methylphenidate)	Drug approval
May 26, 2005	Focalin XR (dexamethylphenidate)	Drug approval
April 6, 2006	Daytrana (methylphenidate)	Drug approval

## 1.3 RELEVANT PREVIOUS DPV REVIEWS

- May 17, 1995<sup>4</sup>- The purpose of this review was to identify cases of drug interactions between clonidine and methylphenidate in children in response to a report of sudden



death in an 8-year old female treated with both products. Five serious reports were retrieved where clonidine and methylphenidate were used concomitantly. Two of these cases reported death with the first reporting an underlying cardiac issue and the second reporting a sudden death. There was limited information in the cases identified to draw any conclusions as to a potential drug interaction between clonidine and methylphenidate.

- June 11, 1997<sup>5</sup>. The purpose of this consult was to identify cases of deaths in children on clonidine therapy. Three additional cases of death in association with concomitant clonidine and methylphenidate use were identified. The author stated that these three cases were potentially not attributable to drug administration based on other factors described in the cases. Once again, the author concluded that the data did not provide substantial evidence of an interaction between clonidine and methylphenidate.
- August 22, 2000<sup>6</sup>- The purpose of this consult was to identify cases of serious cardiovascular events and sudden death when used concomitantly with psychostimulants (methylphenidate, pemoline, amphetamine, dextroamphetamine, or methamphetamine). Since the previous review in 1997, no new cases of sudden death or serious cardiovascular events were identified in patients on concomitant clonidine-psychostimulant therapy. No conclusions were made regarding the potential for a drug interaction between clonidine and the psychostimulants.

## 1.4 PRODUCT LABELING

The current methylphenidate and dextromethylphenidate product labels contain the following language regarding a possible drug interaction with clonidine.<sup>7,8</sup>

### Drug Interactions

*Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.*

Due to a lack of support for an association with the combined use of clonidine and methylphenidate and serious adverse events, including death, the Catapres (clonidine hydrochloride) label, approved on April 7, 2010, no longer contains the following language<sup>9,10</sup>:

### Drug Interactions

*Serious adverse events, including death, have been reported in concomitant use with methylphenidate, although no causality for the combination has been established. The safety of using clonidine in combination with methylphenidate has not been systematically evaluated.*

The product labels for dextroamphetamine, guanfacine, lisdexamfetamine, and the mixed amphetamine salts do not have this drug interaction statement.

## 2 METHODS AND MATERIALS

### 2.1 CASE DEFINITION

We only included cases of death in association with the concomitant use of a stimulant and an alpha agonist that did not report a co-existing medical disorder known or suspected to be

associated with death or a death with a known cause unrelated to an underlying medical condition (e.g. accidental deaths, homicides, motor vehicle accident, natural disease progression, overdoses, or suicides).

## 2.2 AERS SELECTION OF CASES

DPV searched the AERS database on April 6, 2010 for all reports with an outcome of **death** utilizing the drug interaction tool for the following drug combinations:

- Clonidine and dexamethylphenidate (n=0)
- Clonidine and methylphenidate (n=32)
- Clonidine and mixed amphetamine salts (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate) + dextroamphetamine sulfate + lisdexamfetamine (n=10)

AND

- Guanfacine and dexamethylphenidate (n=0)
- Guanfacine and methylphenidate (n=5)
- Guanfacine and mixed amphetamine salts (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate) + dextroamphetamine sulfate + lisdexamfetamine (n=1)

**\*\*All associated trade names and active ingredients were included in our searches.**

The AERS search retrieved 48 reports for all six searches combined. Of these reports, 47 were not included for further discussion for the following reasons:

- Duplicate reports (19)
- The case reported a co-existing medical condition/disorder known or suspected to be associated with death {e.g., multi-organ failure, life-threatening infection, natural disease progression} (11)
- The case reported a death with a known cause unrelated to an underlying medical condition {e.g. accidental deaths, motor vehicle accident, overdoses, or suicides} (10)
- Mistake in reporting- the patient was not taking clonidine (1)
- Case mistakenly captured in the search- the patient was on clonidine alone (1)

Additionally, there were five cases captured in our search reporting death in association with the clonidine-methylphenidate combination that were previously described in other DPV reviews and/or the literature; therefore, they were not included for discussion in this review. Of note, only one of these cases met the case definition for inclusion in this review (ISR# 4960351). Appendix B contains narrative summaries of these five cases.

The remaining one unique case met the inclusion criteria based on the case definition, and was therefore, included for further review and discussion.

## **2.3 CLINICAL TRIAL DATA**

### **2.3.1 Clonidine and Psychostimulants**

DPP reviewed the adverse event data submitted as part of pending NDA 22331 from the controlled trials looking at the combination of clonidine and psychostimulants. This application is seeking the indications of monotherapy and adjunctive therapy (to stimulants) for a slightly modified release formulation of clonidine hydrochloride in children and adolescents with ADHD.

### **2.3.2 Guanfacine and Psychostimulants**

DPP reviewed the adverse event data submitted as part of pending NDA supplement 22037 S-2 from the controlled trials looking at the combination of guanfacine and psychostimulants. This supplement is seeking the indication of adjunctive therapy (to stimulants) for a long-acting formulation of guanfacine.

## **2.4 LITERATURE SEARCH**

DPV performed a PubMed search in an attempt to identify additional case reports of death in association with the concomitant use of alpha agonists (clonidine or guanfacine) and stimulants (methylphenidate, dexamethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts).

## **3 RESULTS**

### **3.1 ADVERSE EVENTS CASES**

Below is the narrative summary of the one case of death associated with the concomitant use of methylphenidate and clonidine, which met the case definition described in section 2.1.

**ISR #6391595; US, 2009-** A 15-year old female “suddenly fell to the ground while running” and died from “unknown causes” during treatment with both methylphenidate and clonidine (doses and durations unknown). An autopsy performed at 11.6 hours after her death reported a normal heart weight of 250 g, and the toxicology screen reported the presence of methylphenidate hydrochloride (ritalinic acid) in the blood at 240 ng/ml (normal range unknown). No further case details were provided. This case was also reported in the literature.<sup>11</sup>

### **3.2 CLINICAL TRIAL DATA**

Clinical trial data are unlikely to have a sufficient number of serious and rare adverse events to have any meaningful impact on this issue, but the clinical trial data available for review were nevertheless examined for safety signals of serious adverse events.

#### **3.2.1 Clonidine and Psychostimulants**

In an adjunctive treatment study, 154 patients received clonidine along with a psychostimulant (methylphenidate or amphetamine). There were no deaths in this study. There were three serious adverse events, but none of these are considered related to study drugs, and they were not life-threatening. In general, most common adverse events were consistent with the known properties of alpha<sub>2</sub>-adrenergic agonists: somnolence/fatigue.

### 3.2.2 Guanfacine and Psychostimulants

In the adjunctive treatment study, 302 patients received guanfacine along with a psychostimulant (methylphenidate or amphetamine). There were no deaths in this study. There were three serious adverse events, two were unrelated to study drugs, and the third was syncope in a 9-year-old, which may be related to the pharmacodynamic effects of guanfacine. This third patient was judged by the investigators to have syncope unrelated to guanfacine and completed the study without changing his dose and with no more syncopal events.

### 3.3 LITERATURE SEARCH

The search of PubMed did not identify any additional case reports of death in association with the concomitant use of alpha agonists (clonidine or guanfacine) and stimulants (methylphenidate, dextromethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts).

## 4 DISCUSSION

### 4.1 ADVERSE EVENT CASES

There are very few cases of death in people receiving the combination of a stimulant and alpha agonist in both the AERS database and the literature. Only one new case of death was identified in the AERS database associated with the concomitant use of methylphenidate and clonidine<sup>‡</sup>. This case provided very limited details and the cause of death was listed as unknown. While it is of course true that the absence of reporting does not necessarily mean the absence of a signal and that AERS data is subject to under-reporting, the fact remains that there is but one new case since 1997. FDA does not receive all adverse event reports that may potentially occur with a product. Many factors can influence the reporting of an event, including the length of time a product has been marketed, and publicity surrounding an event. Having said this, in 1995, there was a significant amount of publicity surrounding this issue in the news and literature, and yet FDA did not experience stimulated reporting.

To date, there has been no clear elaboration of a mechanism for the potential drug interaction when methylphenidate and clonidine are used together. There is one hypothesis described in the literature, which focuses primarily on the timing of administration of both agents: methylphenidate early in the day to treat ADHD, and clonidine at night to minimize stimulant use and to promote sleep. When clonidine is administered in the evening and methylphenidate is administered in the morning, the potential exists for a patient to experience a rebound increase in blood pressure from trough concentrations of clonidine in the morning added to the potential increase in blood pressure from morning stimulant dosing; this combined effect may ultimately result in an elevated blood pressure.<sup>2</sup> An elevated blood pressure, however, would not by itself lead to serious adverse events in most cases, and the cardiovascular adverse events typically associated with clonidine therapy have been seen primarily in patients with pre-existing myocardial impairments and/or who are concomitantly using sympatholytic agents.<sup>12</sup>

In clinical practice, the use of concomitant methylphenidate and clonidine for the management of ADHD in children and adolescents has been increasingly popular since 1992.<sup>2</sup> Based on a concurrency analysis performed as part of this review, there is a substantial amount of concurrent dispensing of clonidine or guanfacine with psychostimulants to pediatric patients. The proportion of patients who received a clonidine or guanfacine prescription dispensed

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<sup>‡</sup> There was another case previously identified and described in 1994, which meets our current case definition, and is summarized in Appendix B- ISR#4960351.

concurrently with a stimulant product in the study group was approximately 12-13% and 34-36%, respectively, during the study period (utilization trends are further described in the concurrency analysis)<sup>13</sup> Despite the fact that the concomitant use of these drugs has increased over the years, and that there has been increasing acceptance of combination therapy to treat ADHD in the medical community, there is still an absence of reports that would support an association for a potential serious drug interaction.

Considering all of these factors, at this time there does not appear to be a drug interaction signal associated with the concomitant use of a stimulant and alpha agonist.

## **4.2 CLINICAL TRIAL DATA**

Overall, the review of the controlled trial adverse event data did not identify any new potential safety concerns associated with the concomitant use of clonidine or guanfacine with psychostimulants. There were relatively few serious adverse events and none that were obviously drug-related.

## **5 CONCLUSION**

There is a lack of the evidence in the available AERS data and in the controlled clinical trial data to support an association for a potential drug interaction between stimulants and alpha agonists.

## **6 RECOMMENDATIONS**

Based on the data reviewed, in the absence of published or other data that points to risk for adverse events, we recommend updating the current methylphenidate and dexamethylphenidate labels to remove the drug interaction statement regarding methylphenidate and clonidine.

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## 8 APPENDICES

### 8.1 APPENDIX A- APPLICATION NUMBERS AND SPONSORS

DRUG (Active Ingredient)	APPLICATION NUMBER	SPONSOR
Clonidine	17407, 18891, 22499, 22500, 76157, 70317, 70923, 70924, 70925, 70963, 70974, 70975, 70976, 71783, 71784, 71785, 77901, 78099, 78895, 91104, 20615, 22331	Boehringer Ingelheim, Tris, Aveva, Mylan, Mutual, Watson, Actavis, Dava, Vintage, Impax, Unichem, Pharmaforce, Bioniche, Shionogi
Dexmethylphenidate	21278, 21802, 77107	Novartis, Teva
Dextroamphetamine sulfate	17078, 40361, 40365, 40367, 40436, 40776, 76137, 76353	SmithKline Beecham, Barr, KV, Mallinckrodt, Outlook, Barr
Guanfacine	22037, 19032, 74145, 74673, 74796, 75109	Shire, Promius, Watson, Mikah, Mylan, Amneal
Lisdexamfetamine	21977	Shire
Methylphenidate	21121, 21514, 21259, 40306, 89601, 21419, 21475, 75629, 10187, 21284, 18029, 40220, 40300, 40321, 40410, 75450, 85799, 86428, 86429	Johnson & Johnson, Shire, UCB, Mallinckrodt, Novartis, Watson, Actavis Elizabeth,
Mixed amphetamine salts (Amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate)	11522, 21303, 40422, 40439, 40440, 40444, 40472	Duramed, Shire, Barr, Sandoz, Mallinckrodt, Corepharma, Teva

## **8.2 APPENDIX B- NARRATIVE SUMMARIES OF THE FIVE PREVIOUSLY DESCRIBED DEATH CASES**

**ISR# 4960351, Foreign, 2006-** A 8-year old female experienced sudden death after using methylphenidate 25 mg daily for almost three years and clonidine 225 mcg daily for four months, both for unknown indications. At both four weeks and one week prior to her death, she received general anesthetics for unknown reasons resulting in two episodes of vomiting, from which she recovered. The autopsy reported the results as normal. (This case was originally reported to the AERS database in 1994 ISR# 1502861 and also described in the literature).

**ISR# 1557196, US, 1995-** A 7-year old male with a history of premature birth (~34 weeks gestation), cardiac abnormalities, and ADHD died while using both methylphenidate and clonidine (doses and durations unknown). He complained of “feeling ill” while at school and was pronounced dead within two hours of his initial complaint. The autopsy revealed “an enlarged, dilated heart showing no evidence of congenital malformation but with considerable fibrosis of the mitral papillary muscles and patchy fibrosis of other areas of the myocardium.” The medical examiner stated that the patient’s “cardiac abnormalities were sufficient to cause death regardless of the presence or absence of any therapeutic drug regimen.”

**ISR# 1842653, US, 1996-** A 4-year old female with a history of ADHD treated with methylphenidate 25 mg daily and clonidine (dose unknown) was found to have died in her sleep after complaining of a stomachache before bed. The autopsy revealed supra-therapeutic levels of clonidine (12 ng/ml) with no other significant findings. The manner of death was ruled as accidental with the most likely mechanism of toxicity being “a cardiac conduction system dysfunction and a lethal cardiac dysrhythmia.”

**ISR# 3240724, US, 1999-** A 10-year old male with a history of unexplained exercise-related syncope was on methylphenidate 20 mg daily for four years and transdermal clonidine 0.2 mg for approximately two months. He became dizzy after playing in a pool and collapsed. CPR was unsuccessful. An autopsy report noted normal blood levels of clonidine and the most likely cause of death to be “a congenital cardiac malformation capable of causing transient ischemia and arrhythmia.”

**ISR# 1651122, US, 1995-** A 9-year old male treated with clonidine, methylphenidate and fluoxetine (doses, durations unknown) complained of “flu-like symptoms”, experienced three grand mal seizures, and died. The coroner’s report revealed elevated levels of fluoxetine and its metabolite, norfluoxetine on the order of 2-3 times greater than what is seen during routine treatment. Genetic testing was performed, which revealed a genetic defect at the cytochrome P450 CYP2D locus causing impaired fluoxetine metabolism.



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-17407	ORIG-1	BOEHRINGER INGELHEIM	CATAPRES
NDA-18891	ORIG-1	BOEHRINGER INGELHEIM	CATAPRES TTS
NDA-22499	ORIG-1	TRIS PHARMA INC	CLONIDINE POLISTIREX ER ORAL SUSPENSION
NDA-22500	ORIG-1	TRIS PHARMA INC	CLONIDINE POLISTIREX ER ORAL TABLETS
ANDA-76157	ORIG-1	AVEVA DRUG DELIVERY SYSTEMS INC	CLONIDINE
ANDA-70317	ORIG-1	MYLAN PHARMACEUTICA LS INC	CLONIDINE HYDROCHLORIDE
ANDA-70923	ORIG-1	MUTUAL PHARMACEUTICA L CO INC	CLONIDINE HYDROCHLORIDE
ANDA-70924	ORIG-1	MUTUAL PHARMACEUTICA L CO INC	CLONIDINE HYDROCHLORIDE
ANDA-70925	ORIG-1	MUTUAL PHARMACEUTICA L CO INC	CLONIDINE HYDROCHLORIDE
ANDA-70963	ORIG-1	WATSON LABORATORIES INC	CLONIDINE HYDROCHLORIDE
ANDA-70974	ORIG-1	ACTAVIS ELIZABETH LLC	CLONIDINE HYDROCHLORIDE
ANDA-70975	ORIG-1	ACTAVIS ELIZABETH LLC	CLONIDINE HYDROCHLORIDE
ANDA-70976	ORIG-1	ACTAVIS ELIZABETH LLC	CLONIDINE HYDROCHLORIDE
ANDA-71783	ORIG-1	DAVA PHARMACEUTICA LS INC	CLONIDINE HYDROCHLORIDE
ANDA-71784	ORIG-1	DAVA PHARMACEUTICA LS INC	CLONIDINE HYDROCHLORIDE
ANDA-71785	ORIG-1	DAVA PHARMACEUTICA LS INC	CLONIDINE HYDROCHLORIDE
ANDA-77901	ORIG-1	VINTAGE PHARMACEUTICA LS LLC	CLONIDINE HYDROCHLORIDE
ANDA-78099	ORIG-1	IMPAX LABORATORIES INC	CLONIDINE HYDROCHLORIDE
ANDA-78895	ORIG-1	UNICHEM LABORATORIES LTD	CLONIDINE HYDROCHLORIDE

ANDA-91104	ORIG-1	PHARMAFORCE INC	CLONIDINE HYDROCHLORIDE
NDA-20615	ORIG-1	BIONICHE PHARMA USA LLC	DURACLON
NDA-21278	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	FOCALIN Tablets
NDA-21802	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	Focalin XR Extended-Release capsules
ANDA-77107	ORIG-1	TEVA PHARMACEUTICA LS USA	DEXMETHYLPHENIDATE HYDROCHLORIDE
NDA-17078	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	DEXEDRINE Spansule Capsules
ANDA-40361	ORIG-1	BARR LABORATORIES INC	DEXTROAMPHETAMINE SULFATE
ANDA-40365	ORIG-1	KV PHARMACEUTICA L CO	DEXTROAMPHETAMINE SULFATE
ANDA-40367	ORIG-1	KV PHARMACEUTICA L CO	DEXTROAMPHETAMINE SULFATE
ANDA-40436	ORIG-1	MALLINCKRODT INC	DEXTROAMPHETAMINE SULFATE
ANDA-40776	ORIG-1	OUTLOOK PHARMACEUTICA LS INC	DEXTROAMPHETAMINE SULFATE
ANDA-76137	ORIG-1	BARR LABORATORIES INC	DEXTROAMPHETAMINE SULFATE
ANDA-76353	ORIG-1	MALLINCKRODT INC	DEXTROAMPHETAMINE SULFATE
NDA-22037	ORIG-1	SHIRE DEVELOPMENT INC	INTUNIV: Guanfacine SR; tablet form
NDA-19032	ORIG-1	PROMIUS PHARMA LLC	TENEX
ANDA-74145	ORIG-1	WATSON LABORATORIES INC	GUANFACINE HYDROCHLORIDE
ANDA-74673	ORIG-1	MIKAH PHARMA LLC	GUANFACINE HYDROCHLORIDE
ANDA-74796	ORIG-1	MYLAN PHARMACEUTICA LS INC	GUANFACINE HYDROCHLORIDE
NDA-21977	ORIG-1	SHIRE DEVELOPMENT INC	VYVANSE (LISDEXAMFETAMINE DIMESYLATE)

NDA-21121	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA L INC	CONCERTA Extended-Release Tablets
NDA-21514	ORIG-1	SHIRE DEVELOPMENT INC	Daytrana System
NDA-21259	ORIG-1	UCB INC	Metadate CD Extended-Release capsules
ANDA-40306	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-89601	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
NDA-21419	ORIG-1	MALLINCKRODT INC	Methylin Solution Oral Solution
NDA-21475	ORIG-1	MALLINCKRODT INC	METHYLIN CHEWABLE TABLETS.
ANDA-75629	ORIG-1	MALLINCKRODT INC	METHYLPHENIDATE HYDROCHLORIDE
NDA-10187	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	Ritalin Tablets
NDA-21284	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	Ritalin LA ) Extended-Release Capsules
NDA-18029	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	Ritalin SR ) Sustained-Release Tablets
ANDA-40220	ORIG-1	WATSON LABORATORIES INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-40300	ORIG-1	MALLINCKRODT INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-40321	ORIG-1	ACTAVIS ELIZABETH LLC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-40410	ORIG-1	WATSON LABORATORIES INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-75450	ORIG-1	ACTAVIS ELIZABETH LLC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-85799	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-86428	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-86429	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
NDA-11522	ORIG-1	TEVA WOMENS HEALTH INC	Adderall amphetamine product) tablets
NDA-21303	ORIG-1	SHIRE DEVELOPMENT INC	ADDERALL XR CAPSULES amphetamine product) Extended- Release

ANDA-40422	ORIG-1	BARR LABORATORIES INC	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
ANDA-40439	ORIG-1	SANDOZ INC	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
ANDA-40440	ORIG-1	MALLINCKRODT INC	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
ANDA-40444	ORIG-1	COREPHARMA LLC	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
ANDA-40472	ORIG-1	TEVA PHARMACEUTICA LS USA	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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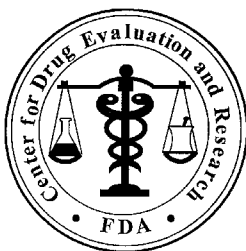
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**Department of Health and Human Services  
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amphetamine/dextroamphetamine, lisdexamfetamine, d-amphetamine,  
methylphenidate, and dexmethylphenidate

Drug Name(s): Clonidine or Guanfacine

Application Type/Number: Multiple

Applicant/sponsor: Multiple

OSE RCM #: 2010-753

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## EXECUTIVE SUMMARY

The Division of Psychiatry Products is reviewing the statement in methylphenidate labels regarding the drug-drug interaction between clonidine and methylphenidate. In support of these efforts, this review from the Division of Epidemiology (DEPI) provides a concurrency analysis of stimulant products (amphetamine/dextroamphetamines and methylphenidates) and alpha blockers (clonidine or guanfacine).

We examined the *nationally projected* estimates of the annual number of patients who filled an outpatient retail pharmacy prescription for clonidine or guanfacine products concurrent with stimulants by age during the years 2006-2009. We conducted a concurrency analysis utilizing the Wolters Kluwer Health's Concurrent Product Analyzer (WKCPA).

- Overall, the proportion of patients who received a guanfacine prescription dispensed concurrently with a stimulant product was higher compared to the proportion of patients who received a clonidine prescription dispensed concurrently with a stimulant product.
- There is a substantial amount of concurrent dispensing for clonidine and stimulants, as well as guanfacine and stimulants among the pediatric population. The largest proportion of concurrent use was among patients aged 0-12 years old.
- The majority of pediatric patients on stimulants were not on concurrent therapy with an alpha blocker; however, at least 21% of pediatric patients on clonidine or guanfacine were on therapy with a stimulant agent concurrently.
- Clonidine
  - Concurrent use with clonidine based on the number of patients filling a prescription for a stimulant product was approximately 4-5% throughout the study period. Among the stimulant products, the greatest frequency of concurrency occurred with dexamethylphenidate products followed by methylphenidate products.
  - Approximately 29-46% of pediatric patients aged 0-12 years old receiving clonidine also concurrently received a stimulant agent.
- Guanfacine
  - Concurrent use with guanfacine based on the number of patients filling a prescription for a stimulant product was approximately 1% of throughout the study period. Among the stimulant products, the greatest frequency of concurrency occurred with dexamethylphenidate products followed by lisdexamfetamine products.
  - Approximately 21-38% of pediatric patients aged 0-12 years old receiving guanfacine also concurrently received a stimulant agent.

## 1 INTRODUCTION

The Division of Psychiatry Products (DPP) is reviewing the statement in methylphenidate labels regarding the drug-drug interaction between clonidine and methylphenidate. The statement states that "Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established; the safety of using methylphenidate in combination with

clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.” Therefore, DPP would like to identify if there is indeed a signal for this drug-drug interaction causing serious adverse events. If a signal does not exist, DPP would like to remove this statement from methylphenidate labels. In support of this, DPP requested an estimate of the amount of concurrent use of alpha blockers, clonidine or guanfacine, by age (0-11 years, 13-17 years, and 18+ years) over the last 4 years with a list of selected stimulant products of interest: amphetamine/dextroamphetamine (amphetamine salt cmb, Adderall XR<sup>®</sup>, Adderall<sup>®</sup>, amphetamine salt cmb SR), methylphenidate (Concerta<sup>®</sup>, methylphenidate, methylin<sup>®</sup>, Metadate CD<sup>®</sup>, Ritalin LA<sup>®</sup>, Daytrana<sup>®</sup>, Methylin ER<sup>®</sup>, methylphenidate SR, Ritalin<sup>®</sup>, Ritalin SR<sup>®</sup>, Metadate ER<sup>®</sup>), lisdexamfetamine (Vyvanse<sup>®</sup>), dexamethylphenidate (Focalin XR<sup>®</sup>, Focalin<sup>®</sup>, dexamethylphenidate), d-amphetamine (dextroamphetamine, Dexedrine<sup>®</sup>, Dexedrine Spansules<sup>®</sup>, Dextrostat<sup>®</sup>).

## **2 METHODS AND MATERIALS**

### **2.1 DATA SOURCES USED AND CONCURRENCY METHODOLOGY**

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

The Wolters Kluwer Concurrency Product Analyzer (WKCPA) tool (see Appendix 2 for full database description) was used to examine the annual proportion of patients who filled a prescription from outpatient retail pharmacies for an alpha blocker (clonidine or guanfacine) with stimulant products (amphetamine/dextroamphetamine or lisdexamfetamine or d-amphetamine and clonidine with methylphenidate or dexamethylphenidate) for years 2006 through 2009.

An episode of concurrency is identified when an alpha blocker prescription overlaps with the days supply for a dispensed prescription in the stimulant group. Therapy days are calculated by adding the number of *days supply* to the time of prescription dispensing. A grace period of 30 days is allowed for the days supply time window to adjust for delays in prescription filling. Thus, the total days of therapy for a claim with 30 days supply would be 60 days when including the 30 day grace period. The number of *days supply* is estimated by dividing the number of tablets or capsules dispensed by the number of tablets or capsules consumed per day. We applied a conservative definition of concurrency as overlapping days supply with a 30 day grace period added. We obtained nationally projected counts of concurrent therapy patients in this study.

### **2.2 PRODUCTS INCLUDED**

Products in the alpha blocker group included: guanfacine (Tenex<sup>®</sup>, Intuniv<sup>®</sup>), clonidine (Catapres<sup>®</sup>, Catapres-TTS 1<sup>®</sup>, Catapres-TTS 2<sup>®</sup>, Catapres-TTS 3<sup>®</sup>).

Products in the stimulant group included: amphetamine/dextroamphetamine (amphetamine salt cmb, Adderall XR<sup>®</sup>, Adderall<sup>®</sup>, amphetamine salt cmb SR), methylphenidate (Concerta<sup>®</sup>, methylphenidate, methylin<sup>®</sup>, Metadate CD<sup>®</sup>, Ritalin LA<sup>®</sup>, Daytrana<sup>®</sup>, Methylin ER<sup>®</sup>, methylphenidate SR, Ritalin<sup>®</sup>, Ritalin SR<sup>®</sup>, Metadate ER<sup>®</sup>), lisdexamfetamine (Vyvanse<sup>®</sup>), dexamethylphenidate (Focalin XR<sup>®</sup>, Focalin<sup>®</sup>, dexamethylphenidate), d-amphetamine (dextroamphetamine, Dexedrine<sup>®</sup>, Dexedrine Spansules<sup>®</sup>, Dextrostat<sup>®</sup>).



### 3 RESULTS

#### 3.1 CONCURRENCY BETWEEN GUANFACINE AND SELECTED STIMULANTS

The estimated nationally projected number of patients determined to have concurrent therapy with guanfacine and stimulants is presented in Table 1 in Appendix 1. Overall, the number of patients receiving a prescription for guanfacine increased by 42% from year 2006 (213,306 patients) to year 2009 (303,753 patients), and the number of patients receiving a prescription for stimulants increased by 32% from year 2006 (7.2 million patients) to year 2009 (9.5 million patients). The proportion of patients who received a guanfacine prescription dispensed concurrently with a stimulant product in the study group increased from 34% in year 2006 to 36% during year 2009. When determining the concurrency based on the number of patients filling a prescription for a stimulant product, approximately 1% of patients concurrently received a prescription for guanfacine throughout the study period. Among the stimulant products, the greatest frequency of concurrency occurred with dexamethylphenidate products followed by lisdexamfetamine products.

##### 3.1.1 *Concurrency Between Guanfacine and Amphetamine/Dextroamphetamine*

Table 2 in Appendix 1 shows the nationally projected number of patients determined to have concurrent therapy with guanfacine and amphetamine/dextroamphetamine products. Patients aged 0-12 year's old receiving a guanfacine prescription increased from approximately 82,000 during year 2006 to 150,000 during year 2009. The proportion of pediatric patients aged 0-12 years who received a guanfacine prescription dispensed concurrently with amphetamine/dextroamphetamine product was around 21-25% throughout the study period. When determining the concurrency based on the number of patients filling a prescription for amphetamine/dextroamphetamine products, approximately 2% of patients aged 0-12 years concurrently received a prescription for guanfacine throughout the study period.

For pediatric patients aged 13-17 years old, the proportion of guanfacine concurrency with amphetamine/dextroamphetamine product ranged between 21-23%. When determining the concurrency based on the number of patients filling a prescription for amphetamine/dextroamphetamine products, approximately 1% of patients aged 13-17 years concurrently received a prescription for guanfacine throughout the study period.

For patients aged 18 years and greater, approximately 3-4% of patients filling a guanfacine prescription concurrently filled a prescription for an amphetamine/dextroamphetamine product. When determining the concurrency based on the number of patients filling a prescription for amphetamine/dextroamphetamine products, less than 1% of patients aged 18 years and greater concurrently received a prescription for guanfacine throughout the study period.

##### 3.1.2 *Concurrency Between Guanfacine and Methylphenidate*

Table 3 in Appendix 1 describes the nationally projected number of patients determined to have concurrent therapy with guanfacine and a methylphenidate containing agent. The proportion of pediatric patients aged 0-12 years who received a guanfacine prescription dispensed concurrently with a methylphenidate product was 33-38% throughout the study period. When determining the concurrency based on the number of patients filling a prescription for methylphenidate products, approximately 2% of patients aged 0-12 years concurrently received a prescription for guanfacine throughout the study period.

The proportion of concurrency with methylphenidate products for pediatric patients aged 13-17 years decreased from 33% in year 2006 to 23% in year 2009. When determining the concurrency based on the number of patients filling a prescription for methylphenidate products, approximately 1% of patients aged 13-17 years concurrently received a prescription for guanfacine throughout the study period.

For patients aged 18 years and greater, approximately 3% of patients filling a guanfacine prescription concurrently filled a prescription for a methylphenidate product. When determining the concurrency based on the number of patients filling a prescription for methylphenidate products, less than 1% of patients aged 18 years and greater concurrently received a prescription for guanfacine throughout the study period.

### **3.2 CONCURRENCY BETWEEN CLONIDINE AND SELECTED STIMULANTS**

The number of nationally projected number of patients determined to have concurrent therapy with clonidine and stimulants is presented in Table 4 in Appendix 1. Overall, the number of patients receiving a prescription for clonidine increased by 16% from year 2006 (2.8 million patients) to year 2009 (3.2 million patients), and the number of patients receiving a prescription for stimulants increased by 32% from year 2006 (7.2 million patients) to year 2009 (9.5 million patients). The proportion of patients who received a clonidine prescription dispensed concurrently with a stimulant product in the study group was approximately 12-13% during the study period. When determining the concurrency based on the number of patients filling a prescription for a stimulant product, approximately 4-5% of patients concurrently received a prescription for clonidine throughout the study period. Among the stimulant products, the greatest frequency of concurrency occurred with dexamethylphenidate products followed by methylphenidate products.

#### **3.2.1 *Concurrency Between Clonidine and Amphetamine/Dextroamphetamine***

Table 5 in Appendix 1 shows the nationally projected number of patients determined to have concurrent therapy with clonidine and amphetamine/dextroamphetamine products. Patients aged 0-12 years old receiving a clonidine prescription increased from approximately 312,000 during year 2006 to 437,000 during year 2009. The proportion of pediatric patients aged 0-12 years who received a clonidine prescription dispensed concurrently with amphetamine/dextroamphetamine product was around 29-35% throughout the study period. When determining the concurrency based on the number of patients filling a prescription for amphetamine/dextroamphetamine products, approximately 9-10% of patients aged 0-12 years concurrently received a prescription for clonidine throughout the study period.

For pediatric patients aged 13-17 years old, the proportion of clonidine concurrency with amphetamine/dextroamphetamine product ranged between 25-27% throughout the study period. When determining the concurrency based on the number of patients filling a prescription for amphetamine/dextroamphetamine products, approximately 3-5% of patients aged 13-17 years concurrently received a prescription for clonidine throughout the study period.

For patients aged 18 years and greater, less than 1% of patients filling a clonidine prescription concurrently filled a prescription for an amphetamine/dextroamphetamine product. When determining the concurrency based on the number of patients filling a prescription for amphetamine/dextroamphetamine products, less than 1% of patients aged 18 years and greater concurrently received a prescription for clonidine throughout the study period.

### **3.2.2 Concurrency Between Clonidine and Methylphenidate**

Table 6 in Appendix 1 shows the nationally projected number of patients determined to have concurrent therapy with clonidine and methylphenidate products. Patients aged 0-12 years old receiving a clonidine prescription increased from approximately 316,000 during year 2006 to 440,000 during year 2009. The proportion of pediatric patients aged 0-12 years who received a clonidine prescription dispensed concurrently with a methylphenidate product was around 42-46% throughout the study period. When determining the concurrency based on the number of patients filling a prescription for amphetamine/dextroamphetamine products, approximately 9% of patients aged 0-12 years concurrently received a prescription for clonidine throughout the study period.

For pediatric patients aged 13-17 years old, the proportion of concurrency with methylphenidate product decreased from 37% in year 2006 to 28% in year 2009. When determining the concurrency based on the number of patients filling a prescription for methylphenidate products, approximately 4-5% of patients aged 13-17 years concurrently received a prescription for clonidine throughout the study period.

For patients aged 18 years and greater, less than 1% of patients filling a clonidine prescription concurrently filled a prescription for a methylphenidate product. When determining the concurrency based on the number of patients filling a prescription for methylphenidate products, approximately 1% of patients aged 18 years and greater concurrently received a prescription for clonidine throughout the study period.

## **4 DISCUSSION**

The findings from this review should be interpreted in the context of the known limitations of the databases used. When examining concurrency, several assumptions are made: (1) a patient is taking the prescription(s) as recommended; and (2) the days supply for a prescription is recorded to reflect how the patient is actually taking the prescription. Patients who receive prescriptions with the instructions of “as needed” will tend to have a pharmacist days supply assigned that assumes the patient will take the maximum dose possible. This may lead to an underestimate of the length of time that these as needed medications will actually last for a patient.

WKCPA did not capture data from mail order pharmacies. Mail order pharmacies typically dispense chronic use meds in larger quantities than retail pharmacies. We therefore believe that the omission of mail order data may underestimate the days of concurrent therapy.

## **5 CONCLUSIONS**

Our analysis found substantial amounts of concurrent dispensing for clonidine and stimulants, as well as guanfacine and stimulants among the pediatric population. The largest proportion of concurrent use was among patients aged 0-12 years old with the proportion of concurrent patients nearing one half for clonidine and stimulants, as compared to around a third for guanfacine with stimulants.

Further characterization of the concurrent therapy use such as whether concurrent therapy is prescribed by the same or different physicians and the impact of mail order pharmacies will require further analysis requiring dataset extraction.

## **CONCURRENCE**

**Laura Governale**  
**Team Leader**  
**Division of Epidemiology (DEPI)**

**Amarilys Vega, M D, MPH**  
**Deputy Director**  
**Division of Epidemiology (DEPI)**

## APPENDIX 2: DATABASE DESCRIPTIONS

### ***Wolters Kluwer Concurrent Product Analyzer:***

Data used in CPA are derived from Wolters Kluwer prescription and medical claims databases. CPA integrates activity from a variety of sources, including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups, physician offices, and outpatient treatment centers. Wolters Kluwer receives over 1.4 billion prescription claims annually, 292 million medical claims, representing over 128.9 million unique patients. Approximately 18.9 million patients have both medical and prescription activity in the database.

CPA allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period. The data are projected to a national level.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

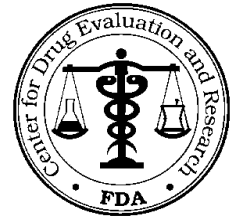
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/s/

HINA S MEHTA  
06/25/2010

LAURA A GOVERNALE  
06/25/2010  
Drug use data cleared

AMARILYS VEGA  
07/01/2010



# Memorandum

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## Pre-Decisional Agency Information

**Date:** June 23, 2010

**To:** Hiren Patel, Pharm.D., M.S.  
Regulatory Project Manager, DPP

**From:** Amy Toscano, Pharm.D., CPA  
Regulatory Review Officer, DDMAC

**Subject:** DDMAC comments on TRADENAME® (clonidine HCl) tablets PI  
NDA 22-331/S-001/S-002

---

DDMAC has reviewed the labeling provided by DPP on June 22, 2010, and offers the following comments, which are provided directly on the marked up version of the label attached below.

Thank you for the opportunity to comment on this proposed labeling.

If you have any questions or concerns regarding these comments, please contact us.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

AMY TOSCANO  
06/24/2010



**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Division of Drug Marketing, Advertising, and Communications**

## **Memorandum**

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**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Date:** June 18, 2010

**To:** Hiren Patel, Pharm.D.  
Regulatory Health Project Manager  
DPP

**CC:** Barbara Fuller, RN, MSN, CWOCN  
Patient Labeling Reviewer  
DRISK

LaShawn Griffiths, RN, MSHS-PH, BSN  
Patient Labeling Reviewer, Acting Team Leader  
DRISK

Amy Toscano, Pharm.D., CPA  
Regulatory Review Officer  
DDMAC

**From:** Susannah Hubert, MPH  
Regulatory Review Officer  
DDMAC

**Subject:** DDMAC comments on TRADENAME (clonidine hydrochloride)  
Tablets Medication Guide  
NDA 022331

---

DDMAC has reviewed the proposed revised Medication Guide for TRADENAME (clonidine hydrochloride), which includes the following two labeling supplements:

- 022331/S-001: Efficacy supplement to support an indication for monotherapy treatment of attention deficit/hyperactivity disorder (ADHD)
- 022331/S-002: Efficacy supplement to support an indication for add-on therapy to stimulant medication in the treatment of ADHD

DDMAC reviewed the Medication Guide provided by DRISK on June 11, 2010, and offers the following comments, which are provided directly on the marked up

version of the labeling attached below. DDMAC comments on the proposed PI will be provided under separate cover.

Thank you for the opportunity to comment on this proposed labeling.

If you have any questions or concerns regarding these comments, please contact us.

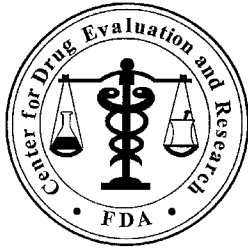
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immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

SUSANNAH HUBERT  
06/18/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 15, 2010

To: Thomas Laughren, MD, Director  
**Division of Psychiatry Products**

Through: Mary Willy, PhD, Deputy Director  
**Division of Risk Management (DRISK)**  
LaShawn Griffiths, RN, MSHS-PH, BSN  
Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Barbara Fuller, RN, MSN, CWOCN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Information)

Drug Name(s): TRADENAME (clonidine hydrochloride) Tablets

Application  
Type/Number: NDA 22-331

Submission Number: S-001, S-002

Applicant/sponsor: Shionogi Pharma, Inc.

OSE RCM #: 2010-170

## **1 INTRODUCTION**

Shionogi Pharma, Inc. submitted two Efficacy Supplements (S-001, S-002) on September 29, 2009. The Efficacy Supplements provides for two new indications for (clonidine hydrochloride): monotherapy treatment of attention deficit/hyperactivity disorder (ADHD) and add-on therapy to stimulant medication in the treatment of ADHD. In September 2009 the modified release clonidine hydrochloride tablets were approved for the treatment of hypertension in adults under the trade name JENLOGA (2009).

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Information (PPI) for TRADENAME (clonidine hydrochloride). Please let us know if DPP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## **2 MATERIAL REVIEWED**

- Draft TRADENAME (clonidine hydrochloride) Tablets Prescribing Information (PI) submitted April 2, 2010 and revised by the Review Division throughout the current review cycle and received by DRISK on June 2, 2010.
- Draft TRADENAME (clonidine hydrochloride) Tablets Patient Information (PPI) submitted on April 2, 2010 and received by DRISK on June 2, 2010.

## **3 RESULTS OF REVIEW**

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the Regulations as specified in 21 CFR 208.20
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/  
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BARBARA A FULLER  
06/15/2010  
DRISK review of clonidine hydrochloride tablets PPI

MARY E WILLY  
06/15/2010  
I concur

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

DATE: April 30, 2009

TO: Hiren D. Patel, PharmD, Regulatory Project Manager  
Maju Matthews, MD, Medical Officer  
Jing Zhang, M.D., Medical Officer  
Division of Psychiatry Products, HFD-130

THROUGH: Tejashri Purohit-Sheth, MD  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Anthony Orencia, MD, FACP  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-331

APPLICANT: Addrenex Pharmaceuticals, Inc. (now Shinogi Pharmaceuticals)

DRUG: modified release clonidine hydrochloride (CLONICEL®)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: (1) treatment of Attention Deficit/Hyperactivity Disorder  
(monotherapy), (2) add-on therapy to stimulant medication in the treatment of ADHD

CONSULTATION REQUEST DATE: November 17, 2009

DIVISION ACTION GOAL DATE: May 31, 2010

PDUFA DATE: July 30, 2010

## **I. BACKGROUND:**

Longitudinal and cross-sectional studies provide evidence that the majority of adolescents with ADHD continue to show significant ADHD-associated impairment as adults. Persistence of ADHD-associated behavior into adulthood carries a high risk of anxiety disorders, oppositional and antisocial personality disorders, and continued high incidence of substance abuse. Treatment options for ADHD include stimulant medications, non-stimulant medications, and non-pharmacological interventions. Clonidine has gained greater utilization in the early 1990s as a drug for treating symptoms and disorders related to ADHD in children and adults. Part of the rationale for this drug development is to administer a clonidine formulation easily that retains the efficacy of the current oral formulation in ADHD, but has an improved safety profile similar to the patch formulation without the dermatologic formulation problems.

Two pivotal studies, CLON-301 and CLON-302 were submitted in support of the application and were inspected for data validation.

### **Protocol CLON-301 (monotherapy, fixed-dose study):**

Protocol CLON-301 was an 8-week, multi-center, parallel-group, randomized, double-blind, placebo-controlled study of the efficacy and safety of two dosing regimens (0.2 mg/day or 0.4 mg/day) of CLONIXEL in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD. Dosing for the CLON groups began at 0.1 mg/day and a proper titration schedule was used to escalate patients to their respective fixed dose. Subjects were maintained at their dose level for a minimum period of 2 weeks before being gradually tapered down to 0.1 mg/day at the last week of treatment. This was a multi-center study conducted in the United States with 19 centers involved. The first study subject enrolled on October 22, 2007 and the last subject completed on August 6, 2008.

The primary objectives for Protocol CLON-301 were to evaluate (1) the efficacy of two dosing regimens of CLONIXEL: 0.2 and 0.4 mg/day sustained release (SR) tablets compared to placebo in the treatment of children and adolescents with ADHD, and (2) the safety of these dosing regimens compared to placebo in the treatment of children and adolescents with ADHD. The primary efficacy endpoint was the ADHD-RS-IV total score, based on evaluating the change from baseline at 5 weeks.

### **Protocol CLON-302 (add-on therapy, flexible dose study):**

Protocol CLON-302 was an 8-week, multi-center, parallel-group, randomized, double-blind, placebo-controlled study of the efficacy and safety of a flexible dose of CLONIXEL in children and adolescents (aged 6 to 17 years) who met DSM-IV criteria for ADHD. Subjects were randomly assigned to one of two groups: CLONIXEL as add-on to a psychostimulant or a psychostimulant alone.

The CLON dose (or matching placebo) was initiated at 0.1 mg/day and titrated up to a 0.4 mg/day (administered as 0.2 mg q12h) over a three-week period. The dose was maintained at this level for a period of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. This was a multi-center study conducted in the United States with 24 centers involved. The first patient's visit was recorded on March 10, 2008 and the last patient visit was recorded on February 3, 2009.



The primary objectives for Protocol CLON-2 (Revision: November 20, 2007) were to evaluate (1) the efficacy of CLONICEL administered as a flexible dose of 0.1 to 0.4 mg/day as add-on to a stable regimen of psychostimulant medication compared to psychostimulant medication alone in the treatment of children and adolescents with ADHD, and (b) the safety of this dosing regimen as add-on to psychostimulant medication compared to psychostimulant medication alone in the treatment of children and adolescents with ADHD. The primary efficacy analysis was the comparison between treatment groups on change scores from Baseline to the Week 5 measure (or discontinuation measure if earlier than Week 5) of the ADHDRS-IV scale total score.

Clinical inspection sites were selected, by virtue of being large enrollment centers, and drove the primary efficacy results. Further, the sites also had high treatment responders which would have a significant impact in drug approval decision-making process. Although clonidine is not a new chemical entity, this is a novel formulation (sustained release) for adolescents aged 6-17 years in the treatment of attention deficit/hyperactivity disorder.

## II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Rakesh Jain, M.D., /Site #06	Lake Jackson, TX	CLON-301	January 19-February 4, 2010	April 2, 2010	No Action Indicated (NAI)
Kamalesh K. Pai, M.D./ Site #09	Jacksonville, FL	CLON-301	February 8-11, 2010	March 16, 2010	NAI
Andrew J. Cutler, M.D./Site #30	Bradenton, FL	CLON-302	January 21-26,2010	February 16, 2010	NAI
Matthew Brams, M.D./Site #32	Houston, TX	CLON-302	January 12-20, 2010	March 22, 2010	Field classification: Referred to Center. No FDA Form 483 issued.  DSI classification: VAI

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

## **PROTOCOL CLON-301**

**1. Rakesh Jain, M.D., /Site #06**  
**461 This Way**  
**Lack Jackson, TX 77566**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from January 18 to February 4, 2010. A total of 48 subjects were screened, enrolled and randomized; 48 subjects completed the study. There were no deaths or SAEs reported. An audit of 24 enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

**b. Limitations of inspection**

None.

**c. General observations/commentary**

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision.**

The data, in support of clinical efficacy and safety at this clinical site, appears acceptable for this specific indication.

**2. Kamallesh K. Pai/Site #09**  
**6867 Southpointe Drive North, Suite 101**  
**Jacksonville, FL 32216**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from February 8 to 11, 2010. There were 33 subjects were screened, 27 subjects were enrolled and 20 subjects completed the study. No deaths or SAEs were reported. A review of 25 subject records for informed consent, and 8 study subjects for other aspects of the trial (e.g., primary efficacy endpoint, adverse event reporting, taking prohibited medications) was conducted.

**b. Limitations of inspection**

None.

**c. General observations/commentary:**

Verification of source data for efficacy endpoints, subject eligibility, test article accountability, monitoring record completions, and protocol-specified procedures for blinding and randomization were assessed. There were no issues related to under-reporting of adverse event data. No discrepancies between source and case report form or data listings provided in the NDA were noted.

At the end of the inspection, the ORA investigator issued a single item Form FDA 483. Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative, and did not meet exemptions in 21 CFR 50, parts 23 and 24, respectively. Specifically, the certification under Florida state law for the Information and Consent For Parents/Guardians, and the Addendum Consent for Genetics Study For Parents/Guardians were not obtained from the parent during the consenting process for study Subjects #906, #909, #925 and #927.

Dr. Pai responded in a letter on February 15, 2010, enclosing specimens of the signed consent forms with the actual signatures blocked out. He mentioned that the consent forms for the above subjects were fully signed by the parent of the child or adolescent, "as demonstrated in the psychiatric evaluation conducted by the consenting physician," albeit acknowledging that a check box indicating who signed the form was not marked as the ORA investigator found. Although regulatory deficiency may be found under state law, this finding was considered not substantive in nature to be subject to federal regulations.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

Study appears to have been conducted adequately, albeit with a minor deficiency. Data appear reliable to support the ADHD indication.

**PROTOCOL CLON-302**

**1. Andrew J. Cutler, M.D., /Site #30**

**3914 State Rd. 64 East**

**Bradenton, FL 34208**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from January 21 to 26, 2010. There were 17 subjects screened, 15 subjects enrolled and 13 subjects completed the study. No deaths or SAEs were reported. An audit of the 10 enrolled subjects was conducted.

**b. Limitations of inspection**

None.

**c. General observations/commentary:**

Verification of source data for efficacy endpoints, subject eligibility, informed consent, test article accountability, monitoring record completions, and protocol-specified procedures for blinding and randomization were assessed. There were no issues related to under-reporting of adverse event data. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

The study appears to have been conducted adequately, and in compliance with Good Clinical Practices (GCP). Data appear reliable in support of the ADHD indication.

**2. Matthew Brams, M.D., /Site #32**

**550 Westcott, Suite 310**

**Houston, TX 77007**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from January 12 to 20, 2010. There were 25 subjects screened, 22 subjects were enrolled, and 15 subjects completed the study. No deaths or SAEs were reported. An audit of the 100% enrolled subjects was conducted.

**b. Limitations of inspection**

None. Although there was initial refusal to copy patient identification data, information sheets subsequently were collected individually to allow patient identification, by full name and birth dates with the assigned patient identification numbers.

**c. General observations/commentary:**

Verification of source data for efficacy endpoints, subject eligibility, informed consent, test article accountability, monitoring record completions, and protocol-specified procedures for blinding and randomization were assessed. There were no issues related to under-reporting of adverse event data.

Although no Form FDA 483 was issued at the close of the inspection, the inspection did identify that the clinical research investigation was not conducted according to the investigational plan [21 CFR 312.60]. Specifically, per Protocol CLON-302 Section 7.4.4, the principal investigator or qualified designee were responsible for dispensing medications and for maintaining detailed record of drug receipt, use, and disposition. The firm's Bayou City Research (b) (6) not listed on Form FDA 1572, dispensed and maintained drug disposition records, without major task down delegation of research responsibilities. Additionally, the CLON-302 Site Personnel Responsibility Log lists a research staff member not trained by sponsor to conduct work under this protocol.

The ORA field investigator also noted other protocol deviations such as: inconsistent ratings of survey scale by child's parent, or lack of dose titration (e.g., up titration, or static drug dosing) for the investigational drug by patient's responsible guardian per protocol dose schedules. These observations, however, were not considered significant

protocol violations, and patient's safety did not appear to be compromised. Based upon DSI's review, this inspection was reclassified as a Voluntary Action Indicated (VAI). A regulatory correspondence letter will be sent to the Principal Investigator.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

Although some violations were noted, these are considered isolated occurrences, and unlikely to importantly impact data reliability. Study appears to have been conducted adequately, and in compliance with Good Clinical Practices (GCP). Data appear reliable to support the ADHD indication.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Four U.S. clinical investigator sites, two per study protocol, were inspected in support of this application, for Protocols CLON-301 (monotherapy indication) and CLON-302 (add-on therapy indication), respectively, with the proposed indication of symptomatic treatment of adolescents with Attention Deficit/Hyperactivity Disorder. No discrepancies were noted with the data listings provided in the NDA and source documents. Inspection findings documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Data appear acceptable for the proposed indication.

*{See appended electronic signature page}*

Anthony Orenca, M.D.  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

/s/

ANTHONY J ORENCIA  
05/03/2010

TEJASHRI S PUROHIT-SHETH  
05/03/2010

FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications



Memorandum

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**Date:** April 9, 2010

**From:** Cynthia Collins - Regulatory Review Officer, DDMAC

**Through:** Thomas Abrams - Director, DDMAC  
Mark Askine - Associate Director, DDMAC  
Kristin Davis - Deputy Director, DDMAC  
Amie O'Donoghue - Social Science Analyst, DDMAC  
Marissa Chaet Brykman - Regulatory Counsel, DDMAC  
Stephanie Victor - Regulatory Review Officer, DDMAC  
Kendra Jones - Regulatory Review Officer, DDMAC  
Michael Wade - DDMAC

**To:** Carol Holquist - Director, DMEPA

**Cc:** Todd Bridges - Team Leader, DMEPA  
Kristina Arnwine Toliver - Team Leader, DMEPA  
Lori Cantin - Safety Evaluator, DMEPA  
Chris Wheeler - Safety Regulatory Project Manager/Team Leader, OSE  
Sandra Griffith - Safety Regulatory Project Manager, OSE

**Subject:** **Proprietary Name Rebuttal Response**  
NDA 022331 (b) (4) (clonidine hydrochloride)  
Shionogi Pharma, Inc.

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## History

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the proposed proprietary name (b) (4) on December 31, 2009, and objected to the use of the proposed trade name from a promotional perspective. The objection was as follows:

DDMAC objects to the proposed trade name (b) (4) because it overstates and guarantees the efficacy of the drug product. (b) (4) can be broken down into two parts, (b) (4) and (b) (4). The pronunciation of these two parts sounds like, (b) (4). The word (b) (4) can be defined as (b) (4) (<http://www.merriam-webster.com/dictionary/> (b) (4) accessed 12/29/09). The proposed indication for this drug is for the treatment of ADHD, which is characterized by inattention, hyperactivity, and impulsiveness. Therefore, the proposed trade name is misleading because it overstates and guarantees the efficacy of the drug by suggesting that the drug will cause patients to be more (b) (4). In the absence of substantial clinical evidence to support this implication, we object to the proposed trade name.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

The Division of Medication Error Prevention and Analysis (DMEPA) communicated the above information to the sponsor Shionogi Pharma, Inc. (Shionogi) on March 8, 2010. In a rebuttal submitted on March 18, 2010, Shionogi requested that the Agency re-evaluate the proposed trade name (b) (4). This rebuttal was provided to DDMAC on March 24, 2010. DDMAC has reviewed this rebuttal and offers the following comments.

## Review

The March 18, 2010, letter from Shionogi requesting reconsideration of the proposed proprietary name (b) (4) includes the following arguments:

"Given the reasons stated for the rejection. . . we wish to present some recent FDA-approved products that could be tied to similar claims:

- Intuniv® might suggest being "in tune" OR "intuitive" for its Attention Deficit Hyperactivity Disorder (ADHD) indication
- Adcirca® might suggest "add circulation" for its pulmonary arterial hypertension indication
- Intelence® might suggest "intelligence" for its HIV indication
- Savella® might suggest "save" for its fibromyalgia indication
- Effient® might suggest "efficient" for its acute coronary syndrome indication

Citing your reference, [www.meriam-webster.com](http://www.meriam-webster.com), the definitions for "intelligence", "efficient", "save" and "intuitive" are unambiguous. . . . And as with the interpretation of (b) (4) and (b) (4) to mean (b) (4) Adcirca and Intinuv can be broken down similarly to be interpreted as "add circulation"; and "in tune", respectively.

The owners of the brand names listed above would surely present similar rationale, despite the fact that their names can either be directly translated or interpreted as improving a patient's quality of life based on the positive connotations of the direct meaning of embedded words within them or common sounding words embedded within them.

In addition your letter states that: "in the absence of substantial clinical evidence to support this implication, we object to the proposed proprietary name." With respect to that, we feel that the clinical data submitted as part of our NDA demonstrates precisely that; that the product causes patients to be more (b) (4). . . and therefore we do not feel the name to be misleading."



The March 18, 2010, letter from Shionogi also includes a request to consider the alternate proposed proprietary name (b) (4) for the product; however, the alternate name request was withdrawn in a March 22, 2010 letter from Shionogi.

## Summary

DDMAC has considered Shionogi Pharma Inc.'s response dated March 18, 2010, and is not persuaded. DDMAC maintains the position that the proposed proprietary name (b) (4) suggests the phrase (b) (4) which misleadingly implies that treatment with (b) (4) is guaranteed to cause patients to be more (b) (4). We are not aware of substantial evidence to support such an absolute effect. Without substantial evidence to support such a treatment response, the proposed trade name misleadingly overstates the efficacy of the drug.

As stated previously, please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

CYNTHIA S COLLINS  
04/22/2010

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022331 BLA#	NDA Supplement #:S-001; S-002 BLA STN #	Efficacy Supplement Type SE1 (new indication)
Proprietary Name: Pending review by DMEPPA Established/Proper Name: clonidine hydrochloride modified release tablets Dosage Form: tablets Strengths: 0.1mg; 0.2 mg		
Applicant: Shionogi Pharma Inc. Agent for Applicant (if applicable):		
Date of Application: September 29, 2009 Date of Receipt: September 30, 2009 Date clock started after UN:		
PDUFA Goal Date: July 30, 2010		Action Goal Date (if different):
Filing Date: November 29, 2009		Date of Filing Meeting: November 6, 2009
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): 1) <u>Monotherapy</u> : CLONICEL <sup>®</sup> (modified release clonidine hydrochloride) is indicated in the treatment of attention deficit/hyperactivity disorder (ADHD).  2) <u>Add-on Therapy</u> : CLONICEL <sup>®</sup> (modified release clonidine hydrochloride) is also indicated as add-on therapy to stimulant medication in the treatment of ADHD.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a>            and refer to Appendix A for further information.</i>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response:	



<input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s):				
<b>Goal Dates/Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?	X			
<i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names correct in tracking system?	X			
<i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?	X			
<i>If not, ask the document room staff to make the appropriate entries.</i>				
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application:  <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><b><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></b></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears</p> <p><input type="checkbox"/> In arrears</p>
<p><b><i>Note:</i></b> 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</p>	

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?			X	
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>	X			
<b>If yes, please list below:</b>				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
N022331	Clonicef (clonidine)	NP	9-29-12	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>		X		
<b>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b>			X	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)	X			
<b>If yes, # years requested:</b> 3				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				



Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input checked="" type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	CRFs, Datasets, Annotated Labeling			
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
If electronic submission, does it follow the eCTD guidance <sup>1</sup> ? If not, explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p><input type="checkbox"/> legible  <input type="checkbox"/> English (or translated into English)  <input type="checkbox"/> pagination  <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	X			
<p><b>Controlled substance/Product with abuse potential:</b>            Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p>		X		
<p><b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>				

<b>Forms and Certifications</b>				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included.</i></p> <p><b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?		X		
<b>Patent Information</b> (NDAs/NDA efficacy supplements only)	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the <b>APPLICANT</b>, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?		X		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature? ( <i>Certification is not required for supplements if submitted in the original application</i> )	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				



<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>		X		

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA</b>, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p><b>If studies or full waiver not included</b>, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p><b>If a request for full waiver/partial waiver/deferral is included</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?  <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		X		
<b>OTC Labeling</b>	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input checked="" type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	X			

Are annotated specifications submitted for all stock keeping units (SKUs)?	X			
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	X			
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
<b>Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			DSI – 11/17/09
<i>If yes, specify consult(s) and date(s) sent:</i>				

<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> March 9, 2009	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

<sup>1</sup><http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>



# ATTACHMENT

## MEMO OF FILING MEETING

**DATE:** November 6, 2009

**BLA/NDA/Supp #:** 022331/Supplements 001 and 002

**PROPRIETARY NAME:** Pending review by DMEPPA

**ESTABLISHED/PROPER NAME:** clonidine hydrochloride tablets

**DOSAGE FORM/STRENGTH:** 0.1 mg

**APPLICANT:** Addrenex Pharmaceuticals

### PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

- 1) Monotherapy: CLONICEL<sup>®</sup> (modified release clonidine hydrochloride) is indicated in the treatment of attention deficit/hyperactivity disorder (ADHD).
- 2) Add-on Therapy: CLONICEL<sup>®</sup> (modified release clonidine hydrochloride) is also indicated as add-on therapy to stimulant medication in the treatment of ADHD.

**BACKGROUND:** The sponsor is seeking claims for both monotherapy and adjunctive therapy for the treatment of ADHD.

### REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Hiren Patel	Y
	CPMS/TL:	Paul David/Renmeet Grewal	N
Cross-Discipline Team Leader (CDTL)	Jing Zhang		Y
Clinical	Reviewer:	Maju Mathews	Y
	TL:	Jing Zhang	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Andre Jackson	Y
	TL:	Raman Baweja	Y
Biostatistics	Reviewer:	Eiji Ishida	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ikram Elayan	Y
	TL:	Linda Fossom	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:	Nallaperum Chidambaram	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Anthony Orenca	Y
	TL:		

Other reviewers		
Other attendees	Yaning Wang	Y

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter



<b>Comments:</b>	
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<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs/BLA supplements only)</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
<b>Signatory Authority:</b> Hiren Patel  <b>21<sup>st</sup> Century Review Milestones (see attached) (optional):</b>  <b>Comments:</b>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## **Appendix A (NDA and NDA Supplements only)**

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

/s/

HIREN PATEL  
04/20/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**PROPRIETARY NAME REVIEW(S)**



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: July 26, 2010

To: Thomas Laughren, MD, Director  
Division of Psychiatry Products

Through: Kristina A. Toliver, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Lori Cantin, RPh, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name(s): Kapvay (Clonidine Hydrochloride) Extended-release Tablets,  
0.1 mg and 0.2 mg

Application Type/Number: NDA 022331

Sponsor: Shionogi Pharma, Inc.

OSE RCM #: 2010-918

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***



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## **EXECUTIVE SUMMARY**

This review evaluates the proposed proprietary name Kapvay for Clonidine Hydrochloride Extended-release Tablets. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review.

The proposed proprietary name must be re-reviewed 90 days before approval of the supplemental NDA. Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review responds to the April 27, 2010, request from Shionogi Pharma, Inc., for DMEPA's assessment of the proposed proprietary name, Kapvay, regarding promotional concerns as well as potential name confusion with other proprietary or established drug names. The Applicant also submitted an Independent Name Assessment, performed by (b) (4) with the proprietary name review request.

Container labels and package insert labeling for this product have been submitted, and will be reviewed under separate cover (OSE review #2010-1154).

### **1.2 REGULATORY HISTORY**

The Applicant, Shionogi Pharma, Inc., submitted the proposed proprietary name 'Kapvay' in the April 27, 2010, submission. This is the second proposed proprietary name submission for this application. The Division of Drug Marketing, Advertising and Communication objected to the Applicant's primary name, (b) (4) (see OSE review #2009-2460, dated March 3, 2010).

### **1.3 PRODUCT INFORMATION**

The applicant, Shionogi Pharma, Inc., is seeking approval to market Clonidine Hydrochloride for monotherapy for Attention Deficit Hyperactivity Disorder (ADHD), and add-on therapy for Attention Deficit Hyperactivity Disorder (ADHD) under the proprietary name Kapvay. Shionogi is also the application holder for Clonidine Hydrochloride for hypertension, approved under the name Jenloga. However, the Jenloga product will not be distributed by Shionogi, but by another company. The only differentiating product characteristic between Kapvay and Jenloga is the indication for use. A comparison of the product characteristics is provided in Table 1.

**Table 1: Product Characteristics for Kapvay and Jenloga**

	<b>Kapvay (NDA 022331)</b>	<b>Jenloga (NDA 022331)</b>
<b>Indication</b>	<u>Proposed:</u> Monotherapy for ADHD Add-on Therapy for ADHD	<u>Approved:</u> Hypertension
<b>Strength</b>	0.1 mg, 0.2 mg	0.1 mg, 0.2 mg
<b>Dose</b>	0.1 mg to 0.2 mg	0.1 mg to 0.2 mg
<b>Dosage Form</b>	Extended-Release Tablet	Extended-Release Tablet
<b>Frequency of Administration</b>	0.1 mg once daily at bedtime 0.1 mg to 0.2 mg twice daily	0.1 mg once daily at bedtime 0.1 mg to 0.2 mg twice daily
<b>How Supplied</b>	60 and 180-count bottles	60 and 180-count bottles
<b>Tablet Shape</b>	Round, Standard Convex (0.1 mg) Oval, Standard Convex (0.2 mg)	Round, Standard Convex (0.1 mg) Oval, Standard Convex (0.2 mg)
<b>Tablet Color</b>	White	White
<b>Tablet side 1</b>	‘651’ debossed on 0.1 mg tablet ‘652’ debossed on 0.2 mg tablet	‘651’ debossed on 0.1 mg tablet ‘652’ debossed on 0.2 mg tablet
<b>Tablet side 2</b>	Blank	Blank

## 2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2 and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Kapvay.

### 2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter ‘K’ when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the ISMP Medication Error Reporting Program involve pairs beginning with the same letter.<sup>1,2</sup>

To identify drug names that may look similar to Kapvay, the DMEPA safety evaluators also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (one,

<sup>1</sup> Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

<sup>2</sup> Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

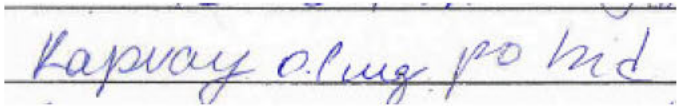
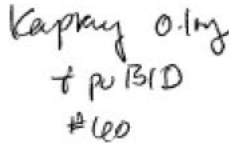
capital letter ‘K’), down strokes (two, lower case ‘p’ and ‘y’), cross strokes (none), and dotted letters (none). Additionally, several letters in Kapvay may be vulnerable to ambiguity when scripted (See Appendix B). As a result, the DMEPA safety evaluators also consider these alternate appearances when identifying drug names that may look similar to Kapvay.

When searching to identify potential names that may sound similar to Kapvay, the DMEPA safety evaluators search for names with similar number of syllables (two), stresses (KAP-vay or kap-VAY), and placement of vowel and consonant sounds. Additionally, the DMEPA safety evaluators consider that pronunciation of parts of the name can vary, such as ‘K’ may sound like ‘C’ (see Appendix B). The Applicant’s intended pronunciation (KAP-vay) was also taken into consideration, as it was included in the Proprietary Name Review request. Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

## 2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies.

**Figure 1. Kapvay Rx Study (conducted on May 6, 2010)**

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<u>Inpatient Medication Order:</u> 	Kapvay 0.1 mg Take one by mouth twice daily
<u>Outpatient Prescription:</u> 	

## 2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

For this product, the Applicant submitted a summary of an external evaluation of the proposed proprietary name, conducted by (b) (4). The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA’s database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator’s Risk

Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk associated with proposed name, the Safety Evaluator compares the findings of his/her overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

### **3 RESULTS**

#### **3.1 DATABASE AND INFORMATION SOURCES**

The DMEPA safety evaluator searches yielded a total of nine (n=9) names as having some similarity to the name Kapvay. Eight (n=8) names were thought to look like Kapvay (Kapidex, Keppra, Kepivance, Requip, Hiprex, Naprosyn, Xopenex, and Kaptiva). One remaining name, Kapvay, was thought to look and sound similar to Kapvay.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of June 4, 2010.

#### **3.2 EXPERT PANEL DISCUSSION**

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Kapvay.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

#### **3.3 FDA PRESCRIPTION ANALYSIS STUDIES**

Forty-three practitioners responded and none of the responses overlapped with existing names. Two practitioners interpreted the name correctly as 'Kapvay', with the correct interpretation occurring in the outpatient written prescription study. Misinterpretations in the written studies included 'K' being misinterpreted as 'R', and 'v' being misinterpreted as 'r' or 'u'. In the verbal studies, most responses were misspelled phonetic variations of the proposed name, Kapvay, including 'K' being misinterpreted as 'C', and 'v' being misinterpreted as 'b' or 'f'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

#### **3.4 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT**

An external proprietary name analysis was conducted by (b) (4) to evaluate the proprietary name Kapvay. (b) (4) identified and evaluated eleven (n=11) drug names thought to have some potential for look-alike or sound-alike confusion with the name Kapvay (Keppra, Captopril, Capoten, Caffeine, Capsaicin, Kapidex, Klonopin, Kadian, Keflex, Prozac, and Xanax).

Nine of the 11 names were not previously identified in the DMEPA staff searches, the Expert Panel Discussion, or FDA prescription studies. These nine names were identified as having

look-alike and/or sound-alike confusion with Kapvay (Captopril, Capoten, Caffeine, Capsaicin, Klonopin, Kadian, Keflex, Prozac, and Xanax). DMEPA included these nine names in our analysis of the proposed proprietary name.

(b) (4) concluded that it is unlikely any of the identified drug names would be confused with Kapvay due to differences in name construction and product characteristics.

### **3.5 SAFETY EVALUATOR RISK ASSESSMENT OF THE PROPOSED PROPRIETARY NAME**

Independent searches by the primary Safety Evaluator identified four (n=4) additional names (Rapinyl\*\*\*, Raptiva, Raplon, and Rapinex\*\*\*) that were thought to look similar and represent a potential source of confusion to Kapvay. Additionally, the proprietary name, Kaptiva, identified in the data base searches was determined to be, Raptiva misspelled. Therefore, Kaptiva, will not be evaluated further.

Thus, 21 names were identified for their similarity to the proposed name: eight names were identified from the database searches, nine names from the external name analysis, and four names from the Safety Evaluator's independent search. Additionally, DMEPA evaluated the Applicant's proposal to market the product, Clonidine Hydrochloride Tablets, with two different proprietary names, Jenloga and Kapvay. See Section 4.2 for further discussion.

### **3.6 COMMENTS FROM THE DIVISION OF PSYCHIATRY PRODUCTS (DPP)**

#### ***3.6.1 Initial Phase of Review***

In response to the OSE May 18, 2010, email, the Division of Psychiatry Products did not have any concerns with the proposed proprietary name, Kapvay.

#### ***3.6.2 Midpoint of Review***

On June 30, 2010, DMEPA notified DPP via email that we find the name Kapvay acceptable. Per email correspondence from DPP on July 22, 2010, they concurred with our assessment.

## **4 DISCUSSION**

Kapvay is the proposed proprietary name for Clonidine Hydrochloride Tablets, 0.1 mg and 0.2 mg, for monotherapy for Attention Deficit Hyperactivity Disorder (ADHD) and add-on therapy for Attention Deficit Hyperactivity Disorder (ADHD). This proposed name was evaluated from a promotional and safety perspective based on the product characteristics provided by the Applicant. Furthermore, input from pertinent disciplines involved with the review of this application was considered accordingly.

### **4.1 PROMOTIONAL ASSESSMENT**

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. The Division of Psychiatry Products and DMEPA concurred with the promotional assessment.

### **4.2 SAFETY ASSESSMENT**

In evaluating the proposed name, Kapvay, DMEPA assessed if the proposed proprietary name could be potentially confused with any of the 21 proprietary names identified in Section 3 above.

Additionally, DMEPA assessed whether Shionogi Pharma's proposal to use two different proprietary names for the active ingredient, Clonidine Hydrochloride Calcium Acetate could result in medication errors.

#### ***4.2.1 Clonidine Product Line Extension***

When this proposed name was first submitted, Shionogi Pharma, Inc. proposed marketing the product, Clonidine Hydrochloride Tablets, with two different proprietary names for each indication of use; Jenloga for the treatment of hypertension and Kapvay for the ADHD indications. The only differentiating product characteristic between Kapvay and Jenloga is the indication for use.

Our analysis of Shionogi Pharma's proposal to use two proprietary names for different indications of use raises concerns with the risk of concomitant therapy. Although Kapvay is indicated in patients 17 years of age and younger and Jenloga is approved for use in adults, the risk of concomitant use for these products is increased if either product is prescribed off-label for one of these populations. Concomitant use may occur in adults or pediatric patients who are diagnosed with hypertension and ADHD. For example a psychiatrist may prescribe Kapvay off-label for ADHD for an adult patient who is also taking Jenloga for hypertension. Since the prescriber population for these indications is likely to be specialized, a psychiatrist or pediatrician may not recognize that Kapvay contains the same active ingredient as Jenloga, while the reverse may also be true for cardiologists familiar with Jenloga. Additionally, patients or caregivers may not be aware that Jenloga and Kapvay contain the same active ingredient. Thus, in order to minimize the risk of concomitant administration to the greatest extent possible DMEPA concluded that Shionogi should market both indications with a single proprietary name and a single package insert.

DMEPA discussed these safety concerns with both the Division of Psychiatry Products (DPP) and the Division of Cardiovascular and Renal Products (DCRP). Subsequent to this discussion, the Agency held a teleconference with Shionogi on April 15, 2010, to discuss the Applicant's proposal for dual proprietary names. Shionogi acknowledged DMEPA's safety concern and agreed to submit combined insert labeling for both indications and to use a single name for their product.

However, in response to the April 15, 2010 teleconference, Shionogi submitted a request for reconsideration of dual proprietary names and dual package inserts instead, citing the following reasons.

1. Shionogi does not intend to market Jenloga for hypertension and plans to divest Jenloga. They intend to maintain ownership of the NDA, and divestiture of the Jenloga for the hypertension indication will occur as a licensing agreement with a distribution partner. Shionogi states that this will be difficult if there is only one proprietary name and one package insert for the product. Once divested, the label would need to reflect the Jenloga name, the new distributor's name, their location, and their labeler code. If Shionogi can not find a distribution partner, they do not intend to market the drug for hypertension.
2. Exclusivity for Jenloga will expire in advance of the exclusivity that Shionogi anticipates they will receive for Kapvay. Shionogi believes it is best for exclusivity reasons for the product indicated for ADHD to have a separate name and package insert from Jenloga.

3. The indications will cover completely separate patient populations (adults for HTN, 6-17 years of age for ADHD), and completely separate prescribers.

After considering Shionogi's request and their plan to divest Jenloga through a licensing agreement with a distribution partner, DMEPA determined that Jenloga would be considered a distributor name for Clonidine Hydrochloride rather than a dual proprietary name. The Applicant, Shionogi, will market Kapvay while Jenloga will be distributed by a partner yet to be determined. Since the regulations allow for the use of distributor names without prior approval from the Agency we find this proposal acceptable. .

#### ***4.2.2 Kapvay Risk Assessment Outside the Product Line***

DMEPA evaluated twenty-one (n=21) names for their potential similarity to the proposed name, Kapvay. Seventeen names were eliminated from further analysis for the following reasons. Eleven of the 17 names lacked convincing orthographic and/or phonetic similarity to the proposed proprietary name. Of the remaining six names, one name, Kapvay, is the subject of this review, one name was changed to a different name due to safety concerns, two names are proposed proprietary names that have not been marketed, and two names are for discontinued or withdrawn products with no generics available (see Appendices D through G).,

Failure mode and effect analysis (FMEA) was then applied to determine if the proposed proprietary name could potentially be confused with the remaining four (n=4) names and lead to medication errors. This analysis determined that name similarity between Kapvay and the four proprietary names was unlikely to result in medication errors for the reasons presented in Appendices H.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

The Proprietary Name Risk Assessment findings indicate that the proposed name, Kapvay, is not vulnerable to name confusion that could lead to medication errors nor is it promotional.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be re-evaluated. If you have further questions or need clarifications, please contact Sandra Griffith, OSE Project Manager, at 301-796-2445.



## **5.1 COMMENTS TO THE APPLICANT**

We have completed our review of the proposed proprietary name, Kapvay, and have concluded that it is acceptable.

The proposed proprietary name, Kapvay, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your April 27, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

## 6 REFERENCES

### 1. *OSE Reviews*

Cantin, L., OSE Review #2009-2460, Proprietary Name Review for (b) (4) dated March 3, 2010.

### 2. *Micromedex Integrated Index* (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

### 3. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

### 4. *Drug Facts and Comparisons, online version, St. Louis, MO* (<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

### 5. *FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]*

DARRTS is a government database used to organize Applicant and Sponsor submission as well as to store and organize assignments, reviews, and communications from the review divisions.

### 6. *Division of Medication Errors Prevention and Analysis proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

### 7. *Drugs@FDA* (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved [brand name](#), [generic drugs](#), [therapeutic biological products](#), [prescription](#) and [over-the-counter](#) human drugs and [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

### 8. *Electronic online version of the FDA Orange Book* (<http://www.fda.gov/cder/ob/default.htm>)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

### 9. *U.S. Patent and Trademark Office* (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

### 10. *Clinical Pharmacology Online* ([www.clinicalpharmacology-ip.com](http://www.clinicalpharmacology-ip.com))

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

**11. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at ([www.thomson-thomson.com](http://www.thomson-thomson.com))**

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

**12. Natural Medicines Comprehensive Databases ([www.naturaldatabase.com](http://www.naturaldatabase.com))**

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

**13. Stat!Ref ([www.statref.com](http://www.statref.com))**

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

**14. USAN Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)**

USAN Stems List contains all the recognized USAN stems.

**15. Red Book Pharmacy's Fundamental Reference**

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

**16. Lexi-Comp ([www.lexi.com](http://www.lexi.com))**

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

**17. Medical Abbreviations Book**

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

## APPENDICES

### Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>3</sup>

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>4</sup> DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.<sup>5</sup> DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look

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<sup>3</sup> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>4</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>5</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Sponsor’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

**Table 1.** Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	Considerations when searching the databases		
	<i>Potential causes of drug name similarity</i>	<i>Attributes examined to identify similar drug names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to drug name confusion in written communication</li> </ul>
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name

throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

## **1. Database and Information Sources**

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

## **2. CDER Expert Panel Discussion**

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

## **3. FDA Prescription Analysis Studies**

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

## **4. Comments from the OND review Division or Generic drugs**

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on

the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

## **5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name**

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>6</sup> When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

***“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

***“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

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<sup>6</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Sponsor. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive



reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. . (See Section 4 for limitations of the process).

**Appendix B: Letters with possible orthographic or phonetic misinterpretation for Kapvay**

Letters in Name: Kapvay	Scripted may appear as:	Spoken may be interpreted as:
Capital 'K'	B, R	C
lower case 'a'	e, or any vowel	e
lower case 'p'	g, x, y	f
Lower case 'v'	n, r, u	b, f
Lower case 'a'	e, or any vowel	
lower case 'y'	g, j, z	
Lower case 'ay'		e, é, et, , ey, ade

**Appendix C: FDA Prescription Study Responses**

Inpatient Prescription	Outpatient Prescription	Verbal Prescription
Rapvay	Kapray	Caffay
Rapvay	Kepray	Kepvay
Rapuay	Kapray	Capfade
Rapvay	Kapray	Kefey
Rapvay	Kapray	Kepfay
Rapvay	Kapvay	Capbay
Ragvay	Kapray	Capfay
Rapuay	Kapray	Capvet
Rapvay	Kespray	Café
Rapuay	Kapvay	
Rapvay	Kapray	
Rapray	Kapray	
Rapvay	Kapray	
Kapvoy	Kapray	
Rapuay	Kapray	
Rapvay	Kapray	
Rapvay	Kapray	

**Appendix D: Names Lacking Orthographic and/or Phonetic Similarity**

Name		Similarity to Kapvay
Prozac	(b) (4)	Look
Xanax	(b) (4)	Look
Keflex	(b) (4)	Look
Klonopin	(b) (4)	Look
Captopril	(b) (4)	Sound
Caffeine	(b) (4)	Sound
Capsaicin	(b) (4)	Sound
Capoten	(b) (4)	Look and Sound
Naprosyn (FDA)		Look
Kepivance (FDA)		Look
Xopenex (FDA)		Look

**Appendix E: Discontinued Proprietary Names**

Name	Similarity to Kapvay	Comments
<b>Kapidex</b> (Deslansoprazole) Capsules: 30 mg and 60 mg NDA 022287	Look	Name discontinued and changed to 'Dexilant', effective April 2010, due to confusion between Kapidex and two other marketed products, Casodex and Kadian.

**Appendix F: Proposed Names within the Agency (Name Not Marketed)**

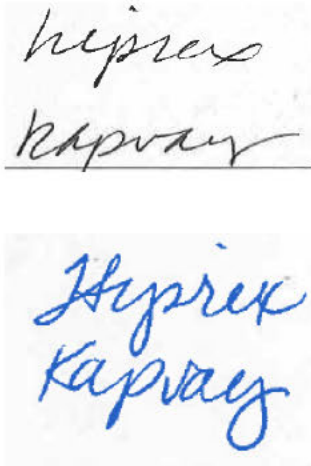
<b>Name</b>	<b>Similarity to Kapvay</b>	<b>Comments</b>
<b>Rapinyl***</b> (Fentanyl Citrate) Sublingual Immediate Release Tablets (b) (4)	Look	DMEPA consulted by DAARP on 12/7/2006 for tradename review; no record of review completion in DARRTS or the L-drive; status of review for OSE RCM#2006-979 is unknown.
<b>Rapinex***</b> (Omeprazole Powder for Suspension) NDA 021636	Look	Name found unacceptable (OSE review #04-0099); NDA approved 6/15/2004 with the proprietary name 'Zegerid'.

**Appendix G: Discontinued or Withdrawn Products with No Approved or Marketed Generics**

<b>Name</b>	<b>Similarity to Kapvay</b>	<b>Comments</b>
<b>Raptiva</b> (Efalizumab) 125 mg Powder for Injection	Look	Voluntarily withdrawn from market in April 2009 due to increased risk of Progressive Multifocal Leukoencephalopathy (PML); no generics available.
<b>Raplon</b> (Rapacuronium) Injection: 100 mg and 200 mg vials NDA 020984	Look	Discontinued per Orange Book and Drugs@FDA; no generics available

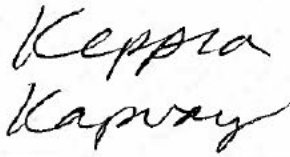
## Appendix H:

### Products with Numeric Overlap in Strength, Dose or Achievable Dose, but With Differentiating Orthographic, Phonetic, and/or Product Characteristics

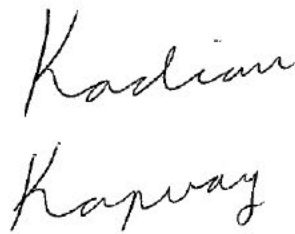
<b>Proposed name: Kapvay</b> <b>(Clonidine Hydrochloride)</b> <b>Tablets</b>	<b>Strength:</b> <b>0.1 mg and 0.2 mg</b>	<b>Usual Dose:</b> <b>0.1 mg once daily at bedtime</b> <b>0.1 mg to 0.2 mg orally twice daily</b>
<b>Failure Mode: Name confusion</b>	<b>Causes</b> <b>(could be multiple)</b>	<b>Effects</b>
<p><b>Hiprex</b>  (Methenamine Hippurate)</p> <p><u>Usual Dose:</u> 0.5 g to 1 g orally twice daily</p> <p><u>How Supplied:</u> 1 g Tablets</p> 	<p><b><u>Orthographic Similarities:</u></b></p> <p>Both names have one upstroke; both names have the downstroke 'p' in the same position; 'v' may look like 'r'; the names are the same length (6 letters)</p> <p><b><u>Product Characteristic Similarities:</u></b></p> <p>Route of administration (oral); frequency (twice daily); dosage form (tablet); numeric similarity in strength (0.1 mg and 1 g); achievable dose (0.5 g and 1 g can be achieved with 0.1 mg and 0.2 mg tablets of Kapvay); similar dosage units (mg and g)</p>	<p>Orthographic differences, along with product characteristic differences, may help to minimize the potential for medication error in the usual practice setting.</p> <p><b>Orthographic Differences:</b> The prefix 'Ka-' in Kapvay is not likely to be misinterpreted as the prefix 'Hi-' in Hiprex.</p> <p>Additionally, Kapvay contains two downstrokes (p and y), while Hiprex contains one downstroke (p). Hiprex also contains a dotted letter (i) and a crossed letter (x), which may help to differentiate the two names.</p> <p><b>Product characteristics:</b> Although doses of Hiprex are achievable with Kapvay, the number of tablets required to dispense 0.5 g or 1 g of Kapvay would cause alarm.</p> <p>The leading zero for the 0.1 mg strength or dose of Kapvay may also help to differentiate the 0.1 mg strength of Kapvay from the 1 g strength or dose of Hiprex, when present.</p>



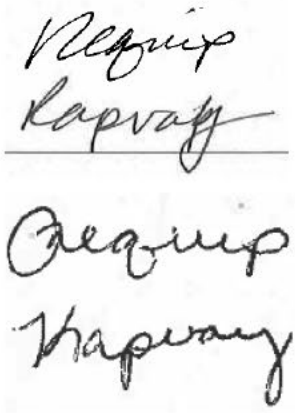
**Appendix H:****Products with Numeric Overlap in Strength, Dose or Achievable Dose, but With Differentiating Orthographic, Phonetic, and/or Product Characteristics**

<b>Proposed name: Kapvay</b> (Clonidine Hydrochloride) Tablets	<b>Strength:</b> 0.1 mg and 0.2 mg	<b>Usual Dose:</b> 0.1 mg once daily at bedtime 0.1 mg to 0.2 mg orally twice daily
<b>Failure Mode: Name confusion</b>	<b>Causes</b> (could be multiple)	<b>Effects</b>
<b>Keppra</b> (Levetiracetam) <u>Usual Dose:</u> Oral: 250 mg to 1500 mg orally twice daily Intravenous: 250 mg to 1500 mg intravenously twice daily <u>How Supplied:</u> 250 mg, 500 mg, 750 mg, and 1000 mg Tablets 100 mg/mL Oral Solution 500 mg/5 mL Injection 	<b><u>Orthographic similarities:</u></b> Both names contain 6 letters; 'Kap-' and 'Kep-' look alike when scripted; <b><u>Phonetic Similarities:</u></b> The prefixes "Kap-" and "Kep-" sound similar; both names have two syllables; <b><u>Product Characteristic Similarities:</u></b> Route of administration (oral); frequency (twice daily); dosage form (tablet); numeric similarity in strength (0.1 mg and 1 g); achievable dose (all doses of Keppra can be achieved with 0.1 mg and 0.2 mg tablets of Kapvay); same dosage units (mg and mg)	Orthographic differences, along with product characteristic differences, may help to minimize the potential for medication error in the usual practice setting. <b>Orthographic Differences:</b> The second consecutive 'p' in Keppra may help to differentiate this name from Kapvay; Kapvay ends in a downstroke (y), while Keppra does not. <b>Product Characteristic Differences:</b> Although all doses of Keppra are achievable with Kapvay, the number of tablets required to dispense 250 mg to 1500 mg of Kapvay would cause alarm. The leading zero for the 0.1 mg strength or dose of Kapvay may also help to differentiate the 0.1 mg strength of Kapvay from the 1000 mg (or 1 g) strength or dose of Keppra.

**Appendix H:****Products with Numeric Overlap in Strength, Dose or Achievable Dose, but With Differentiating Orthographic, Phonetic, and/or Product Characteristics**

<b>Proposed name: Kapvay</b> (Clonidine Hydrochloride) Tablets	<b>Strength:</b> 0.1 mg and 0.2 mg	<b>Usual Dose:</b> 0.1 mg once daily at bedtime 0.1 mg to 0.2 mg orally twice daily
<b>Failure Mode: Name confusion</b>	<b>Causes</b> (could be multiple)	<b>Effects</b>
<b>Kadian</b> (Morphine Sulfate) Capsule, Extended-Release <u>Usual Dose:</u> Individualized, titrated dosing; administer total daily dose divided every 12 hours or every 24 hours <u>How Supplied:</u> 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg 	<u><b>Orthographic similarities:</b></u> Both names contain 6 letters; both names begin with 'Ka-' <u><b>Product Characteristic Similarities:</b></u> Route of administration (oral); similar frequency (twice daily and every 12 or 24 hours; dosage form (tablet and capsule); numeric similarity in strength (0.1 mg and 10 mg, 100 mg, and 0.2 mg and 20 mg, 200 mg); achievable dose (all doses of Kadian can be achieved with 0.1 mg and 0.2 mg tablets of Kapvay); same dosage units (mg and mg)	Orthographic and phonetic differences, along with product characteristic differences, may help to minimize the potential for medication error in the usual practice setting. <b>Orthographic Differences:</b> Kapvay has two downstrokes (p and y), while Kadian has no downstrokes; Kapvay has one upstroke (K), while Kadian has two upstrokes (K and d) <b>Phonetic Differences:</b> The suffixes "-vay" and "-ian" do not sound alike <b>Product Characteristic Differences:</b> Although all doses of Kadian are achievable with Kapvay, the number of tablets required to dispense 10 mg to 200 mg of Kapvay would cause alarm. The leading zero for the 0.1 mg and 0.2 mg strength or dose of Kapvay may also help to differentiate a prescription for Kapvay from the a prescription for 10 mg, 20 mg, 100 mg, or 200 mg of Kadian.

**Appendix H:****Products with Numeric Overlap in Strength, Dose or Achievable Dose, but With Differentiating Orthographic, Phonetic, and/or Product Characteristics**

<b>Proposed name: Kapvay</b> (Clonidine Hydrochloride) Tablets	<b>Strength:</b> 0.1 mg and 0.2 mg	<b>Usual Dose:</b> 0.1 mg once daily at bedtime 0.1 mg to 0.2 mg orally twice daily
<b>Failure Mode: Name confusion</b>	<b>Causes</b> (could be multiple)	<b>Effects</b>
<b>Requip</b> (Ropinirole) <u>Usual Dose:</u> Oral: 0.25 mg to 8 mg three times a day; 0.25 mg to 4 mg once daily at bedtime <u>How Supplied:</u> 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg Tablets 	<b><u>Orthographic similarities:</u></b> 'K' may look like 'R' when scripted; both names contain one upstroke and two downstrokes in the same positions <b><u>Product Characteristic Similarities:</u></b> Route of administration (oral); similar frequency (twice daily and once daily or three times a day); dosage form (tablet); numeric similarity in strength (0.1 mg and 1 mg, 0.2 mg and 2 mg); achievable dose (most doses of Requip can be achieved with 0.1 mg and 0.2 mg tablets of Kapvay); same dosage units (mg and mg)	Orthographic and phonetic differences may help to minimize the potential for medication error in the usual practice setting. <b>Orthographic Differences:</b> Although both names contain downstroke letters in the same positions (3 <sup>rd</sup> and 6 <sup>th</sup> ), the loops are on different sides for the downstroke in the 3 <sup>rd</sup> position ('p' compared to 'q'). Additionally, Kapvay ends in a 'y' which does not have a loop following the downstroke, while Requip has a 'p' that provides a loop following the downstroke. These orthographic differences help to differentiate this name pair.



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

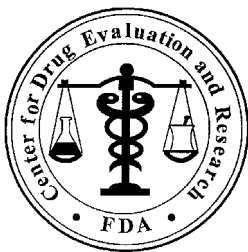
/s/

LORI G CANTIN  
07/28/2010

KRISTINA C ARNWINE  
07/28/2010

DENISE P TOYER  
07/28/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST  
07/28/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: March 3, 2010

To: Thomas Laughren, MD, Director  
Division of Psychiatry Products

Through: Kristina Arnwine, PharmD, Team Leader  
Division of Medication Error Prevention and Analysis  
(DMEPA)

From: Lori Cantin, RPh, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis  
(DMEPA)

Subject: Proprietary Name Review

Drug Name(s): (b) (4) (Clonidine Hydrochloride) Tablets, 0.1 mg

Application Type/Number: NDA 022331/S-001 and S-002

Applicant: Shiongi Pharma, Inc.

OSE RCM #: 2009-2460

## 1 INTRODUCTION

This memorandum is in response to a request from Sciele Pharma, Inc. (now Shiongi Pharma, Inc.), for a review of the proposed proprietary name, (b) (4)

### 1.1 PRODUCT DESCRIPTION

(b) (4) is the proposed proprietary name for Clonidine Hydrochloride 0.1 mg Tablets, which is currently approved under NDA 022331, and is to be indicated for the treatment of attention deficit/hyperactivity disorder (ADHD). The usual dose is 0.2 mg to 0.4 mg per day given in two divided doses.

### 1.2 REGULATORY HISTORY

September 29, 2009: NDA 022331 for Clonidine Hydrochloride 0.1 mg tablets was approved with the proprietary name, Jenloga.

September 30, 2009: Supplement 001, which provides for mono-therapy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), was received. OND PDUFA goal date: July 30, 2010.

September 30, 2009: Supplement 002, which provides for add-on therapy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), was received. OND PDUFA goal date: July 30, 2010.

November 2, 2009: Supplement 003, which provides for a 0.2 mg strength tablet, was received. OND PDUFA goal date: March 2, 2010.

November 24, 2009: Correspondence notifying FDA of the transfer of ownership of NDA 022331 from Addrenex Pharmaceuticals to Sciele Pharma, Inc., effective November 20, 2009, was received.

December 10, 2009: An amendment to Supplements 001 and 002, which requested a review of a new proprietary name for this product for the ADHD indications, was received.

January 19, 2010: Correspondence notifying FDA of a change in company name to from Sciele Pharma, Inc. to Shiongi Pharma, Inc. was received.

## 2 DISCUSSION

During the initial steps on the trade name review process, the Division of Drug Marketing, Advertising, and Communications (DDMAC) did not recommend the use of the proposed trade name, (b) (4), because it overstates the efficacy of the product. DDMAC provided the following statement:

DDMAC objects to the proposed trade name (b) (4) because it overstates and guarantees the efficacy of the drug product. (b) (4) can be broken down into two parts, (b) (4) and (b) (4). The pronunciation of these two parts sounds like (b) (4). The word (b) (4) can be defined (b) (4)S (b) (4) (<http://www.merriam-webster.com/dictionary/> accessed 12/29/09). The proposed indication for this drug

is for the treatment of ADHD, which is characterized by inattention, hyperactivity, and impulsiveness. Therefore, the proposed trade name is misleading because it overstates and guarantees the efficacy of the drug by suggesting that the drug will cause patients to be more (b) (4). In the absence of substantial clinical evidence to support this implication, we object to the proposed trade name.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed tradename or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

The Applicant submitted an external name study conducted by (b) (4) which found the proposed name (b) (4) acceptable. However, (b) (4) did not evaluate the name from a promotional perspective. Thus, this difference in evaluation accounts for the difference in our conclusion with the external name analysis submitted in support of the name.

### **3 CONCLUSIONS AND RECOMMENDATIONS**

In an e-mail correspondence dated January 11, 2010, we were notified that the Division of Psychiatry Products (DPP) concurs with DDMAC's assessment. Therefore, the Division of Medication Error Prevention and Analysis will not proceed with the safety review of the proposed proprietary name, (b) (4), since DPP supports DDMAC's objection to the name based on promotional concerns. DMEPA will notify the Applicant of FDA's decision to object to the name based on promotional concerns.

If you have any questions for DDMAC, please contact Karen Rulli at 301-796-3816. If you have any further questions or need clarification, please contact Sandra Griffith, OSE Project Manager, at 301-796-2445.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

/s/

LORI G CANTIN  
03/03/2010

KRISTINA C ARNWINE  
03/04/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22331Orig1s001**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022331

SUPPL # 001 & 002

HFD # 130

Trade Name Kapvay

Generic Name clonidine hydrochloride extended-release

Applicant Name Shionogi Pharma Inc.

Approval Date, If Known 09/28/10

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒

NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒

NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).



NDA# 022331 017503

NDA# 017407 020615

NDA# 018891

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

- 1) Study 1 (Clon-301) - A phase III, dose response evaluation of the efficacy and safety of Kapvay (clonidine HCl) extended-release vs. placebo in the treatment of children and adolescents with ADHD
- 2) Study 2 (Clon-302) - A phase III evaluation of the efficacy and safety of Kapvay (clonidine HCl) as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with ADHD

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES ☐

NO ☒

Investigation #2

YES ☐

NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- 1) Study 1 (Clon-301) - A phase III, dose response evaluation of the efficacy and safety of Kapvay (clonidine HCl) extended-release vs. placebo in the treatment of children and adolescents with ADHD
- 2) Study 2 (Clon-302) - A phase III evaluation of the efficacy and safety of Kapvay (clonidine HCl) as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with ADHD

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 76144	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND # 76144	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☒

If yes, explain:

=====

Name of person completing form: Hiren D. Patel  
Title: Regulatory Project Manager  
Date: 09/22/10

Name of Office/Division Director signing form: Thomas Laughren, M.D.  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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/s/  
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HIREN PATEL

09/28/2010

THOMAS P LAUGHREN

09/28/2010

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022331 BLA #	NDA Supplement # 001 & 002 BLA STN #	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: Kapvay Established/Proper Name: clonidine hydrochloride Dosage Form: extended-release		Applicant: Shionogi Pharma Inc. Agent for Applicant (if applicable):
RPM: Hiren Patel		Division: Psychiatry
<p><b><u>NDA:</u></b>            NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)            Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b>            Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>July 30, 2010</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None    CR 07/28/10
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.



❖ Application Characteristics <sup>2</sup>		
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Fast Track  <input type="checkbox"/> Rolling Review  <input type="checkbox"/> Orphan drug designation         </div> <div> <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Direct-to-OTC         </div> </div> <div style="display: flex; justify-content: space-between;"> <div> <p>NDAs: Subpart H</p> <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)  <p>Subpart I</p> <input type="checkbox"/> Approval based on animal studies         </div> <div> <p>BLAs: Subpart E</p> <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)  <p>Subpart H</p> <input type="checkbox"/> Approval based on animal studies         </div> </div> <div> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </div> <p>Comments:</p>		
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No	
❖ Public communications ( <i>approvals only</i> )		
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other	

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*



<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p align="center"><b>CONTENTS OF ACTION PACKAGE</b></p>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	<p>Yes</p>
<p align="center"><b>Officer/Employee List</b></p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p align="center"><b>Action Letters</b></p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) July 28, 2010</p>
<p align="center"><b>Labeling</b></p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	<p>September 07, 2010</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>September 21, 2009</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 7/8/10

❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	September 07, 2010
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	September 21, 2009
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	August 05, 2010
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	03/04/10, 07/28/10
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	04/20/10; 09/28/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>May 19, 2010</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	05/26/10, 05/18/10, 04/28/10, 04/12/10, 03/08/10, 12/10/09, 12/07/09

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 7/8/10



❖ Internal memoranda, telecons, etc.	10/23/09
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg    March 9, 2009
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	January 16, 2007
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    July 28, 2010
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    July 20, 2010
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	07/16/10
• Clinical review(s) ( <i>indicate date for each review</i> )	07/16/10
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested    05/18/10

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 7/8/10

<b>Clinical Microbiology</b>		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
<b>Biostatistics</b>		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 06/21/10	
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 06/21/10	
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 06/21/10	
<b>Clinical Pharmacology</b>		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 07/14/10	
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 07/14/10	
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None	
<b>Nonclinical</b>		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 07/28/10	
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 07/02/10	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc	
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page	
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested	
<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 09/17/10; 07/15/10	
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input checked="" type="checkbox"/> None	
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed	
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None Memo 07/23/10	

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	07/15/10
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.



## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HIREN PATEL  
09/28/2010

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022331 BLA #	NDA Supplement # 001 & 002 BLA STN #	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: Established/Proper Name: clonidine hydrochloride Dosage Form: extended-release		Applicant: Shionogi Pharma Inc. Agent for Applicant (if applicable):
RPM: Hiren Patel		Division: Psychiatry
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><u>NDA:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </div> <div style="width: 50%;"> <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <div style="margin-left: 20px;"> <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> Other (explain)                 </div> <p style="color: red;"><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <div style="margin-left: 20px;"> <input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:                 </div> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>July 30, 2010</u></li> </ul>		<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics <sup>2</sup>		
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Fast Track  <input type="checkbox"/> Rolling Review  <input type="checkbox"/> Orphan drug designation         </div> <div> <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Direct-to-OTC         </div> </div> <div style="display: flex; justify-content: space-between;"> <div> <p>NDAs: Subpart H</p> <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)  <p>Subpart I</p> <input type="checkbox"/> Approval based on animal studies         </div> <div> <p>BLAs: Subpart E</p> <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)  <p>Subpart H</p> <input type="checkbox"/> Approval based on animal studies         </div> </div> <div> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </div> <p>Comments:</p>		
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No	
❖ Public communications ( <i>approvals only</i> )		
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other	

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.



❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>CONTENTS OF ACTION PACKAGE</b>	
❖ Copy of this Action Package Checklist <sup>3</sup>	Yes
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) July 28, 2010
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	July 28, 2010
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	September 21, 2009
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 7/8/10



❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	July 28, 2010
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	September 21, 2009
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	03/04/10, 07/28/10
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	04/20/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP           <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input checked="" type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>May 19, 2010</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	05/26/10, 05/18/10, 04/28/10, 04/12/10, 03/08/10, 12/10/09, 12/07/09

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 7/8/10



❖ Internal memoranda, telecons, etc.	10/23/09
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg    March 9, 2009
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	January 16, 2007
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    July 28, 2010
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    July 20, 2010
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	07/16/10
• Clinical review(s) ( <i>indicate date for each review</i> )	07/16/10
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested    05/18/10

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 7/8/10

<b>Clinical Microbiology</b>		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None	
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None	
<b>Biostatistics</b>		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 06/21/10	
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 06/21/10	
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 06/21/10	
<b>Clinical Pharmacology</b>		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 07/14/10	
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 07/14/10	
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None	
<b>Nonclinical</b>		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 07/02/10	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc	
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page	
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested	
<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None	
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 07/15/10	
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input checked="" type="checkbox"/> None	
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed	
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None Memo 07/23/10	

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	07/15/10
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.



## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

/s/

HIREN PATEL  
07/29/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022331/S-001/S-002

Shionogi Pharma, Inc.  
Attention: Allison Lowry  
Director, Regulatory Affairs  
Five Concourse Pkwy  
Suite 1800  
Atlanta, GA 30328

Dear Ms. Lowry:

We acknowledge receipt on August 5, 2010 of your August 5, 2010 resubmission to your supplemental new drug applications for Kapvay (clonidine hydrochloride) extended-release tablets.

We consider this a complete, class 1 response to our July 28, 2010 action letter. Therefore, the user fee goal date is October 5, 2010.

If you have any questions, call Hiren D. Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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

/s/

MITCHELL V Mathis  
08/09/2010  
For Dr. Laughren

## Patel, Hiren

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**From:** David, Paul A  
**Sent:** Friday, July 23, 2010 11:24 AM  
**To:** Laughren, Thomas P; Mathis, Mitchell  
**Cc:** Grewal, Renmeet; Patel, Hiren  
**Subject:** FW: Extended-Release Definition

**Attachments:** Some comments on Yana.doc



Some comments on  
Yana.doc (37 ...  
FYI.

Paul

-----Original Message-----

**From:** Mille, Yana R [mailto:Yana.Mille@fda.hhs.gov]  
**Sent:** Friday, July 23, 2010 11:19 AM  
**To:** Lostritto, Richard T; David, Paul A; Menon-Andersen, Divya; Baweja, Raman K; Sood, Ramesh  
**Subject:** FW: Extended-Release Definition

Hi,

I thought I would take a moment and pass along the USP response to my question about the definition of "extended-release." (see the attachment - above, I highlighted the USP response in red.) The short and sweet is that the USP response supports our taking the action we decided upon yesterday.

Yana

-----Original Message-----

**From:** Andrzej Wilk [mailto:AW@usp.org]  
**Sent:** Friday, July 23, 2010 9:00 AM  
**To:** Mille, Yana R  
**Cc:** Shawn Becker  
**Subject:** Re: Extended-Release Definition

Yana,

I have a follow-up responses. Both Tom and Stephanie basically agreed with Tom Foster. Bill added:

>>>>>>QUOTE

I don't disagree with Tom's comments on Yana's email. After all, it's his Committee in charge. I only regret that present definitions are not as easy to understand as the original way back when.

Maybe we should get to the point where we can get rid of release-rate and, instead, declare a time limit on the drug product whether or not it results from a manipulated formulation or the natural time of action of the API.

Bill (Heller)



Some comments on Yana's note(see below)

Thomas S. Foster, Pharm.D.  
Professor of Pharmacy, Anesthesiology and Public Health  
University of Kentucky Medical Center

On Jul 22, 2010, at 9:24 AM, "Andrzej Wilk" <AW@usp.org> wrote:

Dear All,  
Please see below a question from Yana. I would appreciate your comments. As there is time constraint involved, I think this smaller group will expedite the discussion. The text of Yana's message is "quoted" instead of an attachment for the sake of Dr. Heller's e-mail software.  
I hope you can work with it.  
Best regards,

Andrzej Wilk

>>>> "Mille, Yana R" <Yana.Mille@fda.hhs.gov> 7/22/2010 9:12 AM >>>  
Andrzej,

An urgent issue here at FDA - When can a product be called 'extended-release?'

First some background:

A couple of decades ago, there was a requirement in USP that the dosing interval be reduced at least 2-fold for a product to be called extended release. Then, in the 1996 and 1997 HQ columns to the PF (I think the 1996 PF was the Jan-Feb vol. but don't recall offhand which vol it was for 1997) the definition was revised to drop the 2-fold requirement. However, it looks like there is still a requirement for a 'reduction in dosing frequency.'

The current <1151> definition says:

"Extended-release tablets are formulated in such manner as to make the contained medicament available over an extended period of time following ingestion. Expressions such as "prolonged-action," "repeat-action," and "sustained-release" have also been used to describe such dosage forms. However, the term "extended-release" is used for Pharmacopeial purposes, and requirements for Drug release typically are specified in the individual monographs."

The proposed <1151> definition says:

"EXTENDED-RELEASE: Descriptive term for a dosage form that is deliberately modified to protract the release rate of the API compared to that observed for an immediate-release dosage form. The term is synonymous with prolonged- or sustained-release. Many extended-release dosage forms have a pattern of release that begins with a "burst effect" that mimics an immediate release followed by a slower release of the remaining API in the dosage form."

> Foster-- the dosage form also could be zero order or pseudo zero order with no burst and still be ER

Now the question:

If a product is modified in such a way so that the release of the drug is deliberately modified to protract the release rate BUT the dosing interval is the same as an immediate-release dosage form, is it possible to still call the product an extended-release dosage form?

FOSTER- I BELIEVE YES. SUCH AN EXAMPLE COULD BE DRUGS THAT YOU WANT TO CONTROL THE RATE OF DRUG METABOLISM SUCH AS NICOTINIC ACID.

Let's take for example a drug substance with a long half-life that is normally dosed twice a day as an immediate release dosage form. Now, if the drug substance is put in a GITS tablet or its release is modified in some other way to control the release so that it releases slowly over a longer period of time BUT it is still dosed twice a day, can it be called extended-release?

FOSTER, YES I THINK THIS COULD BE CALLED ER BASED IF THERE IS AN ISSUE OF FAST SYSTEMIC AVAILABILITY CAUSING UNTOWARD SIDE EFFECTS

My thoughts: If there is a clinically relevant reason for creating a product that releases slowly and if the coating or whatever the release controlling mechanism is were to be removed so that the product would dose dump and NOT have the same clinical benefit, then YES, I think it deserves the name extended release. I believe the proposed <1151> definition provides enough leeway for this interpretation. The existing <1151> might also provide this leeway but it would be a tougher call in my mind.

FOSTER- YANA, I AGREE

I would appreciate the Committee's thoughts on this topic and, unfortunately I NEED A RESPONSE BY NOON TOMORROW, Friday, 7/23/10. I understand that we are essentially 'between' committees. It seems to me that this would be a tough request for a new Committee that has no background with nomenclature issues. Therefore, if it is not possible to get the input of the exiting committee, I would hope that at least the following individuals could weigh in on the topic: Tom Reinders (NSL chair), Tom Foster (I believe he was involved in the definition change in 1996/7), and David Long (past chair of the Dosage Form expert committee).

Also, I believe this same topic was discussed many years ago (1993 - 2000 time frame) so there might be something in some old minutes on this topic. I looked through the 4/8/2010 DRAFT document "Major Decisions, Rules and Procedures of the Nomenclature Expert Committee" and didn't find anything in there but I have some memory of this topic coming up years ago.

My thanks in advance to everyone for assisting on such short notice.

Yana

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

HIREN PATEL  
07/27/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

NDA 022331 S-001 and S-002

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Shionogi Pharma, Inc.  
5 Concourse Parkway, Suite 1800  
Atlanta Georgia 30328

ATTENTION: Allison Lowry  
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Supplemental New Drug Applications (sNDA) dated September 29, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clonidine Hydrochloride Tablets 0.1 mg and 0.2 mg.

We also refer to your April 27, 2010 correspondence, received April 27, 2010, requesting review of your proposed proprietary name, Kapvay. We have completed our review of the proposed proprietary name, Kapvay and have concluded that it is acceptable for this product.

If **any** of the proposed product characteristics as stated in your April 27, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2446. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hiren Patel at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*  
*Carol Holquist 7-26-2010*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

CAROL A HOLQUIST  
07/26/2010

## Grewal, Renmeet

---

**From:** Grewal, Renmeet  
**Sent:** Thursday, July 22, 2010 9:29 AM  
**To:** 'Alowry@shionogipharma.com'  
**Cc:** Patel, Hiren; Grewal, Renmeet  
**Subject:** NDA 22331 container label comments

Good Morning Allison,

Please find our comments regarding the container labels for your NDA 22331. Please let us know as soon as possible if you have any questions. I am covering for Hiren Patel for today so if you have any questions please send me an email and cc him as well.

- The established name appears to be less than ½ the size of the proprietary name. Additionally, the (b) (4) color used for the established name is difficult to see against the white background of the container label. Ensure the established name is at least ½ the size of the proprietary name, and that the established name has a prominence commensurate with the prominence with which the proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features as per 21 CFR 201.10(g)(2).
- The 0.1 mg strength and 0.2 mg strength are presented in a blue and a green color block, respectively. (b) (4)  
(b) (4)
- Decrease the prominence of the graphic on the principal display panel to ensure the product strength and proprietary and established names are the most prominent information. Additionally, the font in the "Rx only" statement should be debolded.
- Include instructions that state the product "must be swallowed whole and never crushed, cut, or chewed". The manufacturer and distributor information can be modified if needed to make space for this statement.
- On the container labels for Kapvay 0.1 mg and 0.2 mg tablets, we recommend revising the statement, (b) (4) (b) (4) to "Do not substitute Kapvay for other clonidine products."

Regards,  
Renmeet

Renmeet Grewal, Pharm.D., RAC, CDR USPHS  
Team Leader, Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: renmeet.grewal@fda.hhs.gov  
Fax: (301) 796-9838

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

RENMEET K GREWAL  
07/22/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>		
TO:  <b>CDER-DDMAC-RPM</b>			FROM: (Name/Title, Office/Division/Phone number of requestor) HFD-130/ Division of Psychiatry Products Hiren D. Patel, Pharm.D., M.S.		
REQUEST DATE 06/02/10	IND NO.	NDA/BLA NO. NDA 022331/S-001/S-002	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)  Labeling		
NAME OF DRUG  Clonidine HCl Tablets		PRIORITY CONSIDERATION PDUFA Goal Date: July 30, 2010	CLASSIFICATION OF DRUG ADHD	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) <b>June 16, 2010</b>	
NAME OF FIRM: Shionogi Pharma Inc.			PDUFA Date: July 30, 2010		
<b>TYPE OF LABEL TO REVIEW</b>					
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION	
<b>EDR link to submission:</b> The EDR link is <a href="#">\\Fds\wa150\nonectd\N22331\S_001\2009-09-29</a> Please note this was a mixed submission.  The path to the substantially complete label is <a href="http://eroom.fda.gov/eRoom/CDER/CDER-NPC/0_9f206">http://eroom.fda.gov/eRoom/CDER/CDER-NPC/0_9f206</a> .					
<b>Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.</b>					
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  DPP received two efficacy supplements that are integrally tied from Shionogi Pharma Inc. for the treatment of ADHD as monotherapy or as adjunctive therapy to stimulant medications. DPP has also reviewed Shionogi Pharma's draft label and has provided comments in track changes. DPP is requesting that DDMAC review this substantially completed label.  The clinical reviewer and clinical team leader is Maju Mathews and Jing Zhang, respectively.  Please note that DPP will also be receiving input from the SEALD Team.  Mid-Cycle Meeting: March 1, 2010 Labeling Meetings: June 1, 2010 ; June 21, 2010 Wrap-Up Meeting: May 26, 2010					
SIGNATURE OF REQUESTER					



Hiren D. Patel	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/  
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HIREN PATEL  
06/08/2010

THOMAS P LAUGHREN  
06/08/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, Maryland 20993

NDA 022331/S-001 and S-002

**MEETING MINUTES**

Sciele Pharma Inc.  
5 Concourse Parkway, Suite 1800,  
Atlanta, Georgia 30328

ATTENTION: Allison Lowry  
Senior Manager, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 29, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clonidine Hydrochloride Tablets, 0.1 mg.

We also refer to the teleconference between representatives of your firm and the FDA on April 15, 2010. The purpose of the meeting was to convey DDMAC's promotional concerns regarding the proposed proprietary name (b) (4), and DMEPA's safety concerns regarding dual proprietary names for this product.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any other questions about the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Hiren Patel at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and  
Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** April 15, 2010  
**TIME:** 09:00AM – 10:00 AM EST  
**LOCATION:** Teleconference, WO Bldg 22, RM 4201  
**APPLICATION:** NDA 22331  
**PRODUCT NAME:** (b) (4) (Clonidine Hydrochloride) Tablets, 0.1mg  
**SPONSOR:** Shionogi Pharma  
**TYPE OF MEETING:** Teleconference (FDA requested)  
**MEETING CHAIR:** Carol Holquist, RPh, Director, DMEPA  
**MEETING RECORDER:** Sandra J. Griffith, OSE Safety Regulatory Project Manager

### FDA ATTENDEES:

#### Office of Surveillance and Epidemiology

Sandra Griffith, Safety Regulatory Project Manager OSE  
Nina Ton, Safety Regulatory Project Manager OSE  
Carol Holquist, RPh, Director DMEPA  
Kristina Toliver, PharmD, Team Leader DMEPA  
Lori Cantin, PharmD, Safety Evaluator DMEPA

#### Office of New Drugs

Renmeet Grewal, Project Manager DPP  
Thomas Laughren, Division Director DPP  
Jing Zhang, Medical Officer DPP  
Nallaperum Chidambaram, Chemist DPP  
Maju Matthews, Medical Officer Reviewer DPP

#### Office of New Drug Quality Assessment

Lorenzo Rocca, ONDQA Reviewer DPE

#### Office of Medical Policy

Cynthia Collins, Regulatory Review Officer DDMAC

### EXTERNAL CONSTITUENT ATTENDEES:

Shionogi Sciele Pharma Inc. Attendees as of this e-mail:  
Marty Solberg, EVP Regulatory Affairs and Quality Assurance  
Allison Lowry, Director, Regulatory Affairs  
Kim Hight, Senior Associate, Regulatory Affairs Labeling  
(b) (6), Consultant (also represents Shionogi).

## MEETING OBJECTIVES:

This meeting was requested to discuss promotional issues with the sponsor's proposed proprietary name, (b) (4) and safety concerns related to the sponsor's proposal for dual proprietary names for this Clonidine product.

## DISCUSSION POINTS:

DDMAC maintained the position that the proposed proprietary name (b) (4) suggests the phrase (b) (4) which misleadingly implies that treatment with (b) (4) is guaranteed to cause ADHD patients to be more (b) (4). Without substantial evidence to support such an absolute treatment response, the proposed proprietary name misleadingly overstates the efficacy of the drug.

DMEPA communicated their safety concerns relating to the use of dual proprietary names for this product

- The rationale submitted February 15, 2010, to support the sponsor's dual proprietary name proposal was acknowledged. In this submission Shionogi stated that each indication should have a distinct and distinguishing proprietary name since each indication involves different patient populations, age groups, clinical research, and specialty prescribing physicians.. However, it was noted that there is no data provided in this submission to support the safe use of this product if it were to be marketed with dual proprietary names.
- DMEPA expressed concern that there is a potential for risk of concomitant administration of Jenloga and (b) (4), particularly with off-label use. It was acknowledged that although differing indications and patient populations may help to minimize the possibility that a patient may be prescribed concomitant therapy with Jenloga and (b) (4) there would be an increased risk of concomitant administration if this product were to have dual proprietary names vs. a single proprietary name.

Currently, oral Clonidine is marketed under the proprietary name, Catapres, and there are multiple generic clonidine products on the market as well. DMEPA noted that there is a potential that the risk of concomitant use may increase with the addition of two more proprietary names for Clonidine to the marketplace that do not have the same name recognition among healthcare providers that Catapres currently has. Additional concerns regarding the potential for concomitant use that may lead to an increased risk of adverse events in the pediatric population were also raised.

- DMEPA noted that postmarketing experience with other drug products marketed with dual proprietary names (e.g., Wellbutrin and Zyban) has shown that differing indications for products marketed with dual proprietary names has not prevented medication errors in which patients have inadvertently received two products containing the same ingredient.
- DMEPA does not believe that the labeling for this product, if it were to be marketed with dual proprietary names, will adequately mitigate the risk for concomitant administration with this product.

In summary, DMEPA believes that it would be prudent to market this product for both indications with a single proprietary name in order to minimize the risk of concomitant administration to the greatest extent possible.

Shionogi questioned whether one package insert label or two package insert labels would be advised if they decided to pursue a single proprietary name for their product, and questioned the feasibility of combining the two different indications into one package insert label. FDA informed Shionogi that one package insert for both indications is recommended. Examples of other products with labeling that incorporate more than one indication were provided (e.g., Inderal, Thorazine, and Valium).

Shionogi inquired about the possibility of selecting an alternative single proprietary name to Jenloga for their Clonidine product. FDA replied that an alternative proprietary name would be an acceptable path forward, since Jenloga has not yet been marketed. FDA noted that a proposal for an alternative proprietary name would require the submission of a prior approval labeling supplement to NDA 022331 (b) (4)

(b) (4). FDA replied that this would also be acceptable.

FDA informed Shionogi that they should proceed with the submission of a combined label for this product as soon as possible so that FDA's review of the labeling can proceed, and stated that Shionogi's decision regarding a proprietary name should not delay the submission of the labeling.

DMEPA noted that the PDUFA review timeline for a proprietary name is 90 days, but agreed to expedite the review of a new proprietary name for this product to ensure that an acceptable name is found prior to the OND PDUFA goal date for the supplemental NDAs for the ADHD indications. DMEPA realizes that Shionogi will need to hold internal discussions to make a decision regarding a proprietary name, but given the approaching OND PDUFA goal date, DMEPA requested that Shionogi communicate their decision to FDA within 7 days and expedite the submission of a proposed proprietary name (b) (4)

#### **DECISIONS (AGREEMENTS) REACH/ACTION ITEMS:**

Shionogi agreed to:

- Submit a combined label for both indications as soon as possible
- Notify FDA of their decision regarding a proprietary name within 7 days
- Expedite the submission of a request for a proposed proprietary name (b) (4) and to submit a prior approval labeling supplement to NDA 022331 to provide for a change of proprietary name.

FDA agreed to:

Expedite the review of a request for a proposed proprietary name if Shionogi decides to select an (b) (4).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

CAROL A HOLQUIST  
05/26/2010



Matthew N. Brams, M.D.  
Bayou City Research, Ltd.  
550 Westcott, Suite #310  
Houston, TX 77007

Dear Dr. Brams:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected. Between January 12 and 20, 2010, Ms. Jocelyn C. Turner, representing the FDA, met with you to review your conduct of a clinical investigation [Protocol CLON-302 entitled "A Phase 3, Dose-Response Evaluation of the Efficacy and Safety of CLONICEL (clonidine HCL sustained release) Vs. Placebo in the Treatment of Children and Adolescents With Attention Deficit Hyperactivity Disorder (ADHD)"], of the investigational drug clonidine HCL sustained release (CLONICEL), performed for Adrenex Pharmaceuticals, Inc.

Based upon our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

1. You did not ensure that the investigation was conducted according to the investigational plan or general responsibilities of investigators [21 CFR 312.60]. For example:
  - a. The protocol specified dose escalation schedules until Week 4 of study and subsequent tapering schedules. Subject #3209, however, took 1 tablet per day for the entire 8 weeks without any upward dose titration and subsequent drug taper.
  - b. You did not list (b) (6) and (b) (6) as study sub-investigators on the Form FDA 1572. The firm's Bayou City Research (b) (6) dispensed the investigational drug and maintained drug disposition records. (b) (6) was a member of the clinical research staff under Protocol CLON-302.



Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Turner during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Bldg. 51, Rm. 5358  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

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/s/  
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TEJASHRI S PUROHIT-SHETH  
05/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): <b>Mail: OSE</b> <b>Division of Pharmacovigilance (DPV) I HFD-430</b>		<b>FROM: Division of Psychiatry Products</b> RPM – Hiren Patel, PharmD CDTL – Mitch Mathis, MD, MTL – Jing Zhang, MD, Maju Matthews, MD		
DATE May 10, 2010	IND NO.	NDA NO. 022331/S-001/S-002	TYPE OF DOCUMENT Efficacy Supplements	DATE OF DOCUMENT 9-29-09
NAME OF DRUG Clonidine Modified Release Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG ADHD	DESIRED COMPLETION DATE June 18, 2010
NAME OF FIRM: SHIONOGI PHARMA INC				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input checked="" type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
DPP is requesting that DPV perform a search of the AERS database for all reports of death associated with the concurrent use of alpha agonists (clonidine or guanfacine) and stimulants (methylphenidate, dexamethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts). We are specifically interested in cases that do not report coexisting physical disorders known or suspected to be associated with death, or deaths with known causes (e.g. suicides, homicides, accidents, overdoses, natural disease progression). In addition, please perform a literature search for additional case reports of death associated with the concurrent use of these products.				
Current labeling for methylphenidate products has a drug-drug interaction statement warning clinicians				

about SAEs that may occur with concomitant use of methylphenidate and clonidine. Current literature and practice guidelines support the concomitant use of stimulants and alpha agonists to treat ADHD, and there is no clear evidence of death from the combination. Clonidine and guanfacine are currently being studied for use with stimulants to treat ADHD and we need to know if there is any AERS evidence of death from the use of the two classes of drugs together.

Please categorize your findings on combination drug use and death as follows:

1. Clonidine and methylphenidates (methylphenidate or dextromethylphenidate)
2. Clonidine and amphetamines (mixed amphetamine salts, dextroamphetamine or lisdexamfetamine)
3. Guanfacine and methylphenidates (methylphenidate or dextromethylphenidate)
4. Guanfacine and amphetamines (mixed amphetamine salts, dextroamphetamine, or lisdexamfetamine)

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

☐ MAIL

☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

PAUL A DAVID  
05/10/2010

THOMAS P LAUGHREN  
05/10/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, Maryland 20993

NDA 022331/S-001 and S-002

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Shionogi Pharma, Inc.  
5 Concourse Parkway, Suite 1800  
Atlanta, Georgia 30328

ATTENTION: Allison Lowry, RAC  
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your Supplemental New Drug Applications (sNDA) dated September 29, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clonidine Hydrochloride Tablets, 0.1 mg.

We also refer to your March 18, 2010, correspondence, received March 18, 2010, requesting reconsideration of your proposed proprietary name (b) (4). We have completed our re-review of the proposed proprietary name, (b) (4) and continue to conclude that it is unacceptable for promotional reasons.

We maintain the position that the proposed proprietary name (b) (4) suggests the phrase (b) (4) (b) (4), which misleadingly implies that treatment with (b) (4) is guaranteed to cause patients to be more (b) (4). We are not aware of substantial evidence to support such an absolute effect. Without substantial evidence to support such a treatment response, the proposed trade name misleadingly overstates the efficacy of the drug.

As stated previously, please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Hiren Patel at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

CAROL A HOLQUIST  
04/28/2010





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

NDA 022331/S-001 and S002

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Shionogi Pharma, Inc.  
Five Concourse Parkway  
Suite 1800  
Atlanta, Georgia 30328

ATTENTION: Allison Lowry, RAC  
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your supplemental New Drug Applications (sNDA) dated September 29, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clonidine Hydrochloride Tablets, 0.1 mg.

We acknowledge receipt of your March 24, 2010, correspondence, on March 24, 2010, notifying us that you are withdrawing your March 18, 2010 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of March 24, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Hiren Patel at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

CAROL A HOLQUIST  
04/12/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, Maryland 20993

NDA 022331/S-001 and S-002

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Sciele Pharma Inc.  
5 Concourse Parkway, Suite 1800  
Atlanta, Georgia 30328

ATTENTION: Allison Lowry  
Senior Manager, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your Supplemental New Drug Applications (sNDA) dated September 29, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clonidine Hydrochloride Tablets 0.1 mg.

We also refer to your December 10, 2009, correspondence, received December 10, 2009, requesting review of your proposed proprietary name (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is unacceptable for the following promotional reasons.

The proposed proprietary name (b) (4) overstates and guarantees the efficacy of the drug product. (b) (4) can be broken down into two parts, (b) (4) and (b) (4). The pronunciation of these two parts sounds like, (b) (4). The word (b) (4) can be defined as (b) (4) (http://www.merriam-webster.com/dictionary/ (b) (4) accessed 12/29/09). The proposed indication for this drug is for the treatment of ADHD which is characterized by inattention, hyperactivity, and impulsiveness. Therefore, the proposed proprietary name is misleading because it overstates and guarantees the efficacy of the drug by suggesting that the drug will cause patients to be more (b) (4). In the absence of substantial clinical evidence to support this implication, we object to the proposed proprietary name.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We note that you have proposed an alternate proprietary name in your submission dated December 10, 2009. In order to initiate the review of the alternate proprietary name, Kapvay, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Hiren Patel at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

CAROL A HOLQUIST  
03/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): OSE Attention: Sandra Griffith			FROM: HFD-130/ Division of Psychiatry Products	
DATE 01/28/10	IND NO.	NDA NO. NDA 022331/S-001/S-002	TYPE OF DOCUMENT Patient Labeling (Medication Guide)	DATE OF DOCUMENT Letter Date: January 28, 2010
NAME OF DRUG  Clonidine HCl Tablets		PRIORITY CONSIDERATION PDUFA GOAL Date: July 30, 2010	CLASSIFICATION OF DRUG ADHD	DESIRED COMPLETION DATE <b>Labeling Meetings:</b> <b>May 14, 2010 at 4:00PM;</b> <b>June 1, 2010 at 1:00PM;</b> <b>June 21, 2010 at 2:00PM</b>
NAME OF FIRM: Shionogi Pharma Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: DPP received two efficacy supplements that are integrally tied from Shionogi Pharma Inc for the following two indications: 1) <u>Monotherapy</u> : TRADENAME® (modified release clonidine hydrochloride) is indicated in the treatment of attention deficit/hyperactivity disorder (ADHD). 2) <u>Add-on Therapy</u> : TRADENAME® (modified release clonidine hydrochloride) is also indicated as add-on therapy to stimulant medication in the treatment of ADHD. The sponsor also submitted revised labeling that includes a Medication Guide on January 18, 2010. DPP is requesting that OSE review patient labeling. The path to the EDR location is <a href="#">\CDSESUB1\EVSPROD\NDA022331\022331.enx</a> . Thanks, Hiren				
SIGNATURE OF REQUESTER Hiren Patel Pharm.D. Regulatory Project Manager 301-796-2087			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	

hiren.patel@fda.hhs.gov	
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SCIELE PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SCIELE PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/  
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HIREN PATEL  
01/28/2010

THOMAS P LAUGHREN  
01/28/2010





NDA 022331/S-001, S-002

**FILING COMMUNICATION**

Sciele Pharma, Inc  
Attention: Allison Lowry  
Senior Manager, Regulatory Affairs  
5 Concourse Parkway, Suite 1800  
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your September 29, 2009 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clonigel (Clonidine HCl) 0.1 mg modified release tablets.

We also acknowledge receipt of your submissions dated November 3, 2009 and November 5, 2009.

We have completed our filing review and have determined that your supplemental applications are sufficiently complete to permit a substantive review. Therefore, these supplemental applications are considered filed 60 days after the date we received your supplemental applications in accordance with 21 CFR 314.101(a). The review classification for these supplemental applications is Standard. Therefore, the user fee goal dates for both supplements are July 30, 2010.

At this time, we have the following requests that require your response:

1. For CLON-301 study, Table 14.1.1 Subject Disposition shows that the numbers of subjects who completed treatment phase are 48 and 41 on Clonigel 0.4mg and Placebo, respectively. However, the numbers of completers based on a variable COMPLT (completers population flag) from your submitted analysis data set, (adsl.sas7bdat), do not match those from Table 14.1.1. Please clarify this potential discrepancy issue.
2. Additionally, we note that a maintenance study was not conducted in the patient population for which efficacy claims are sought. Please provide the status of any ongoing or anticipated maintenance study(ies).

If any of the above requests is already addressed in your submission, please indicate its location.

Please note that our filing review is only a preliminary evaluation of the supplemental applications and is not indicative of deficiencies that may be identified during our review.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted pediatric studies with this application for pediatric patients 6 to 17. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Hiren D. Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SCIELE PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SCIELE PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

THOMAS P LAUGHREN  
12/10/2009



NDA 022331/S-001/S-002

**PRIOR APPROVAL SUPPLEMENT**

Sciele Pharma, Inc  
Attention: Allison Lowry  
Senior Manager, Regulatory Affairs  
5 Concourse Parkway, Suite 1800  
Atlanta, GA 30328

Dear Ms. Lowry:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Clonixel (Clonidine HCl) Tablets; 0.1 mg

NDA Number: 022331

Supplement numbers: 001 and 002

Review Priority Classification: Standard (S)

Date of supplement 001: September 29, 2009

Date of receipt supplement 001: September 30, 2009

Date of supplement 002: September 29, 2009

Date of receipt supplement 002: November 9, 2009

These supplemental applications propose the following new indications:

- 1) Monotherapy: CLONICEL<sup>®</sup> (modified release clonidine hydrochloride) is indicated in the treatment of attention deficit/hyperactivity disorder (ADHD).
- 2) Add-on Therapy: CLONICEL<sup>®</sup> (modified release clonidine hydrochloride) is also indicated as add-on therapy to stimulant medication in the treatment of ADHD.

These applications have been filed as of November 29, 2009 in accordance with 21 CFR 314.101(a). The user fee goal date will be a 10 month goal date for standard efficacy supplement.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have questions, contact me at [hiren.patel@fda.hhs.gov](mailto:hiren.patel@fda.hhs.gov) or (301) 796-2087.

Sincerely,

*{See appended electronic signature page}*

LT Hiren D. Patel, Pharm.D.  
Regulatory Health Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SCIELE PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SCIELE PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

HIREN PATEL  
12/07/2009

## DSI CONSULT: Request for Clinical Inspections

**Date:** November 17, 2009

**To:** Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
Anthony Orenca, M.D., Medical Officer  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Thomas Laughren, M.D., Division Director  
Division of Psychiatry Products/HFD-130

**From:** Hiren D. Patel, Pharm.D., Regulatory Health Project Manager  
Division of Psychiatry Products/HFD-130

**Subject:** Request for Clinical Site Inspections

### **I. General Information**

Application#: Supplements # NDA-022331/S-001 and S-002  
Applicant/ Applicant contact information (to include phone/email):  
Addrenex Pharmaceuticals Inc.  
Attention: Moise A. Khayrallah, Ph.D.  
[mk@addrenex.com](mailto:mk@addrenex.com)  
(919) 941-0800 Ext. 202

Drug Proprietary Name: Clonixel [clonidine HCL] modified-release tablets  
NME or Original BLA (Yes/No): No  
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes  
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):

Monotherapy: CLONICEL<sup>®</sup> (modified release clonidine hydrochloride) is indicated in the treatment of attention deficit/hyperactivity disorder (ADHD).

Add-on Therapy: CLONICEL<sup>®</sup> (modified release clonidine hydrochloride) is also indicated as add-on therapy to stimulant medication in the treatment of ADHD.

PDUFA: July 30, 2010

Action Goal Date: May 31, 2010

Inspection Summary Goal Date: April 30, 2010

## **II. Background Information**

This is an efficacy supplemental NDAs for clonidine modified release tablets. The proposed indications are to treat ADHD when used as monotherapy and to treat ADHD when used as adjunctive therapy with stimulant medications.

This submission includes 2 clinical studies in children and adolescents (6 to 17 years) with ADHD.

CLON-301: Multicenter, 5-week (Total 8 weeks, including taper down period), parallel-group, randomized, double-blind, placebo-controlled study of the efficacy and safety of two dosing regimens (0.2 mg/day and 0.4 mg/day) of CLONICEL for the treatment of ADHD. Study subjects were children between the ages of 6 and 17 years who met DSM-IV criteria for ADHD. Dosing for CLON started at 0.1 mg/day and a proper titration schedule was used to escalate patients to their respective fixed dose. Subjects were maintained at their dose level for minimum period of 2-weeks before gradual taper down to 0.1 mg/day at the last week. The primary efficacy endpoint was the comparison between treatment groups on change scores from Baseline to the Week 5 measure (or discontinuation measure if earlier than Week 5) of the ADHDRS-IV scale. A total of 236 male and female patients were randomly assigned to the three treatment groups: CLONICEL (CLON) 0.2 mg/day (N=78), CLON 0.4 mg/day (N=80), or placebo (N=78).

CLON-302: Multicenter, 5-week (Total 8 weeks, including taper down period), parallel group, randomized, double-blind, placebo-controlled study of CLONICEL flexible dose as add-on to a psychostimulant (CLON+STM) or a psychostimulant and placebo (PBO+STM). Patients should have been on a stable regimen of approved stimulant medication of either methylphenidate or amphetamine for a minimum of 4-weeks and could potentially benefit from alpha-adrenergic agonist as evidenced by a lack of adequate response to this stable regimen of stimulant medication. The CLON dose was initiated at 0.1 mg/day and titrated to 0.4 mg/day (0.2mg q12 hr) over a 3-week period. The dose was maintained at this level for 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. Efficacy assessments were same as those in Study CLON-301. A total of 198 male and female patients were randomly assigned to one of two groups: CLON+STM (N=102) or PBO+STM (N=98).

Both were positive studies. There were no deaths in the program. The major AE's observed were somnolence, fatigue, irritability and insomnia. There was also a mild decrease in blood pressure.



### **III. Protocol/Site Identification**

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol #</b>	<b>Number of Subjects</b>	<b>Indication</b>
Site # 06 R/D Clinical Research 461 This Way Lake Jackson, TX 77566 P: 979-297-3535 F: 979-297-1497 <span style="background-color: #cccccc; display: inline-block; width: 150px; height: 1.2em; vertical-align: middle;">(b) (6)</span>	CLON-301	0.2mg arm 15 subjects, 0.4mg arm 16 subjects, Placebo 13 subjects	<u>Monotherapy</u> : CLONICEL <sup>®</sup> (modified release clonidine hydrochloride) is indicated in the treatment of attention deficit/hyperactivity disorder (ADHD).
Site #09 CNS Healthcare of Jacksonville 6867 Southpointe Drive North, Suite 101 Jacksonville, FL 32216 P: 904-281-5757 F: 904-281-5758 <a href="mailto:Mjoyce@cnshealthcare.com">Mjoyce@cnshealthcare.com</a>	CLON-301	0.2mg arm 9 subjects, 0.4mg arm 8 subjects, Placebo 9 subjects	<u>Monotherapy</u> : CLONICEL <sup>®</sup> (modified release clonidine hydrochloride) is indicated in the treatment of attention deficit/hyperactivity disorder (ADHD).
Site #30 Florida Clinical Research Center 3914 State Rd. 64 East Bradenton, FL 34208 P: 941-747-7900 F: 941-747-7992 <a href="mailto:acutler@flcrc.com">acutler@flcrc.com</a>	CLON-302	treatment arm 7 subjects, Placebo 8 subjects	<u>Add-on Therapy</u> : CLONICEL <sup>®</sup> (modified release clonidine hydrochloride) is also indicated as add-on therapy to stimulant medication in the treatment of ADHD.
Site #32 Bayou City Research 550 Westcott, Suite 310 Houston, TX 77007 P; 832-251-7000 F: 832-251-7011 <span style="background-color: #cccccc; display: inline-block; width: 100px; height: 1.2em; vertical-align: middle;">(b) (6)</span>	CLON-302	treatment arm 11 subjects, Placebo 11 subjects	<u>Add-on Therapy</u> : CLONICEL <sup>®</sup> (modified release clonidine hydrochloride) is also indicated as add-on therapy to stimulant medication in the treatment of ADHD.

### **IV. Site Selection/Rationale**

These sites enrolled a relatively large number of subjects and also had relatively large treatment effects. The sponsor will be using data from 1 positive monotherapy study and 1 positive adjunctive therapy study to support dual indications.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- ☒ Enrollment of large numbers of study subjects
- ☒ High treatment responders (specify):
- ☒ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ☐ Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- ☐ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☐ Domestic and foreign data show conflicting results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ☐ Other (specify)

Should you require any additional information, please contact *Hiren D. Patel, Pharm.D.* at 301-796-2087 or *Maju Mathews, M.D.* at 301-796-4962.

Concurrence:

Maju Mathews, M.D., Medical Reviewer, DPP  
Jing Zhang, M.D., Medical Team Leader, DPP  
Thomas Laughren, M.D., Division Director, DPP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	ADDRENEX PHARMACEUTICA LS INC	JENLOGA
NDA-22331	SUPPL-2	ADDRENEX PHARMACEUTICA LS INC	JENLOGA

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/s/

HIREN PATEL  
11/17/2009

THOMAS P LAUGHREN  
11/17/2009

## MEMORANDUM OF TELECON

DATE: 10/21/2009

APPLICATION NUMBER: NDA 022331 - Supplement 001 (new indication) and S-002 (new indication)

BETWEEN:

Name: Moise Khayrallah, Paul Ketteridge, Allison Lowry  
Phone: (b) (6)  
Representing: Addrenex Pharmaceuticals, Inc

AND

Paul David, CPMS  
Hiren D. Patel, Pharm.D.  
Michael Jones

Chief Regulatory Project Management Staff  
Regulatory Project Manager  
User Fee Staff

SUBJECT: NOTIFICATION OF USER FEE DETERMINATION

- NDA 022331 for modified release clonidine tablets was approved on September 29, 2009, for the treatment of hypertension.
- An Efficacy Supplement for the treatment of attention-deficit hyperactivity disorder (ADHD) was received September 30, 2009.
- The Agency determined that the supplement contained two changes to the approved NDA. These changes constituted 2 efficacy claims. One claim was for use as Monotherapy for ADHD and another claim was for use as Add-on (Adjunctive) Therapy. Therefore, the sponsor was notified that the original efficacy supplement would be unbundled and a separate supplement would be created for the additional efficacy claim. For administrative purposes, S-001 has been designated the monotherapy efficacy supplement, and S-002 has been designated the Add-on (Adjunctive) efficacy supplement.
- The sponsor was also informed that an additional user fee would be required to comply with existing statutes. The terms that were conveyed included payment in accordance with fiscal year 2009 fees if the additional efficacy claim was pursued in parallel to the submission of the original supplement.
- The sponsor indicated that they may not pursue the additional claim in parallel to the original supplement because they did not want to pay the additional fee and that if they did not pursue add-on therapy a revised label for only the Monotherapy claim would be submitted. The add-on study would only be used as adjunctive evidence to support the monotherapy claim.
- The sponsor also acknowledged that an additional user fee in accordance with the respective fiscal year would be required when the additional claim was pursued.
- The sponsor wished to discuss their options internally prior to making a decision. However, and as stated above, they were inclined to only pursue the monotherapy

claim at this point. If this occurs, they will submit revised labeling to denote this one claim.

- The sponsor will contact Dr. Patel to inform him of their intentions within the next couple of days.

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Hiren D. Patel, Pharm.D.  
Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	ADDRENEX PHARMACEUTICA LS INC	JENLOGA
NDA-22331	SUPPL-2	ADDRENEX PHARMACEUTICA LS INC	JENLOGA

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

/s/

HIREN PATEL  
10/23/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 76, 144

Addrenex Pharmaceuticals, Inc.  
Attention: Moise A. Khayrallah, Ph.D.,  
President and CEO  
4825 Creekstone Drive, Suite 100  
Durham, NC 27703

Dear Dr. Khayrallah:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for clonidine sustained release tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 9, 2009. This meeting was a pre-NDA meeting to give you guidance on submitting your NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please email Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager at [Renmeet.grewal@fda.hhs.gov](mailto:Renmeet.grewal@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Division Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** March 9, 2009  
**TIME:** 3:00pm  
**LOCATION:** FDA White Oak, Silver Spring, MD  
**APPLICATION:** 76,144  
**DRUG NAME:** clonidine sustained release tablets  
**TYPE OF MEETING:** pre-NDA meeting

### FDA ATTENDEES:

Thomas Laughren, M.D., Division Director, Division of Psychiatry Products (DPP)  
Mitchell Mathis, M.D., Deputy Director, DPP  
Ni Aye Khin, M.D., Clinical Team Leader, DPP  
Glenn Mannheim, M.D., Clinical Reviewer, DPP  
Raman Baweja, Ph.D., Clinical Pharmacology Team Leader, OCP  
Kofi Kumi, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)  
Linda Fossom, Ph.D., Pharmacology/Toxicology Team Leader, DPP  
Ikram Elayan, Ph.D., Pharmacology/Toxicology Reviewer, DPP  
Thomas Oliver, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment  
Yeh-Fong Chen, Ph.D., Statistics Reviewer, OBI  
Renmeet Grewal, Pharm. D., Team Leader, Project Management Staff, DPP  
Juliette Toure, Pharm.D., Regulatory Project Manager, DPP

### EXTERNAL CONSTITUENT ATTENDEES:

Moise Khayrallah, Ph.D.	President and CEO
Paul Ketteridge, R.Ph.	Regulatory Affairs Consultant
David Ward, M.D.	Medical Monitor
(b) (4)	Scientific Consultant
	Pharmacology/toxicology Consultant
Larry Dillaha, M.D.	Medical Advisor

### BACKGROUND:

Clonidine is a centrally acting alpha<sub>2</sub> adrenergic agonist that was originally approved for the treatment of hypertension. Clonidine is available in the US in 3 formulations:

- Oral dose immediate release tablet (Catapres brand and generics) supplied in 3 doses: 0.1, 0.2, and 0.3 mg
- Transdermal system formulation (Catapres-TTS) supplied in 3 patch sizes: 3.5, 7.0, and 10.5 cm<sup>2</sup> delivering 0.1, 0.2, and 0.3 mg per day of clonidine, respectively
- Epidural injection (Duraclon) supplied in 100 and 500 mcg/mL solutions in 10 mL vials

Under this IND (76,144), the sponsor's development program of CLONICEL is intended to market a sustained release oral formulation of clonidine for monotherapy and adjunctive therapy to stimulant treatment in pediatric patients (6-17 yrs) with ADHD.



The purpose of the requested Type B pre-NDA meeting is to present the adequacy of data from three clinical trials, and to discuss the content, and format of a potential NDA for this compound in ADHD.

In support of this application, they will be referencing a single-dose PK and food effect study with the 0.1 mg CLONICEL tablet and a PK/PD study in adults under NDA 22-331 (CloniBID) submitted on February 15, 2008 to the Division of Cardio-Renal Products. Preclinical study protocol PRO 0978-08382, a Ten-Week Oral Toxicity Study of Clonidine HCl in Juvenile Rats was submitted to the IND (#027) on September 16, 2008.

The clinical development program consists of three clinical studies: two placebo-controlled efficacy and safety studies (CLON-301 and CLON-302); and one open-label safety study (CLON-303). The sponsor reports that these studies have been completed or are in the process of being completed:

- Study CLON-301: This was an 8-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of two dosing regimens of CLONICEL in 236 children and adolescents (6 to 17 years) with ADHD. Subjects were randomized to either 0.2 mg/day (N=78), 0.4 mg/day (N=80), or placebo (N=78). Primary efficacy endpoint was change from baseline in ADHDRS- IV scale total score at week 5, using an LOCF analysis.
- Study CLON-302: This was an 8-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of a flexible (0.1-0.4 mg/day) dose of CLONICEL in 198 children and adolescents (6-17 yrs) with ADHD. Subjects were randomized to one of two groups: CLONICEL as add-on to a psychostimulant (CLON+STM) or a psycho-stimulant and placebo (PBO+STM). Primary efficacy endpoint was change from baseline in ADHDRS- IV scale total score at week 5, using an LOCF analysis.
- Study CLON-303: This was an 12-month, open-label safety in 276 children and adolescents (6-17 yrs, mean age 10.1 yrs) with ADHD, using a flexible dosing regimen of CLONICEL (0.1-0.4 mg/day) either as monotherapy or in combination with a stimulant. Exposure to date consists of:
  - 174 subjects have  $3 \leq 6$  months
  - 114 subjects have  $6 \leq 9$  months
  - 31 subjects have  $9 \leq 12$  months
  - 4 subjects have  $\geq 12$  monthsExposure at the end of the study is estimated to be 185 subjects for  $\geq 6$  months and 115 subjects for  $\geq 12$  months.

**Questions:****Pre-clinical**

**Question 1:** At the pre-IND meeting, the Division agreed that the sponsor could reference pharmacology and toxicology data that are publicly available for approved clonidine formulations, including the Agency's previous findings, in an eventual NDA, but that the Sponsor also would need to provide a juvenile rat toxicology study. The sponsor submitted a draft protocol for such a study to the Division for review as Serial Number 0027 [16 September 2008] of IND 76,144. The Division reviewed the protocol and recommended a number of changes. Based on the Division's recommendations, the Sponsor has decided to conduct not one, but two, toxicology studies in juvenile rats—one to evaluate systemic toxicity and potential effects on learning, memory, locomotor activity, and bone growth, and another to evaluate potential effects on reproductive function. The studies will begin in March 2009 (see Section 3 and Appendix 1 of the meeting package). Will the proposed toxicology studies in juvenile rats, together with the pharmacology and toxicology data that are publicly available for approved clonidine formulations, including the Agency's previous findings, be sufficient to support the planned NDA?

**Preliminary Comments:** On face, yes, with the following qualifications regarding your proposed juvenile animal study/studies. Based on the brief description provided in the background package, the protocols for your (2) proposed toxicity studies of clonidine in juvenile rats, as revised in response to our comments (communicated to you on 11/12/08), appear generally acceptable. However, it is not clear that you plan to evaluate the potential for long-term effects, as well as the acute effects, on learning and memory. In our comments we stated that: "Specific tests to evaluate the effect of treatment on learning and memory should be conducted during the treatment period (to capture the acute effects of the drug) and also during the recovery period (for potential long-term effects)." Evaluation of long-term effects (after drug cessation) could be accomplished by testing the rats in your "reproductive function" study at approximately 2-4 weeks after drug has been discontinued, before reproductive function is assessed.

Additionally, in order to support safe use of clonidine as adjunctive therapy with stimulants in pediatric patients and to provide additional safety information for labeling, you will need to conduct a juvenile animal study where clonidine is administered in combination with a stimulant (e.g., d-amphetamine or methylphenidate); each drug (i.e., clonidine and the selected stimulant) should be administered separately and in combination, assessing the same parameters as for the clonidine monotherapy juvenile animal study/studies. We encourage the sponsor to submit a draft protocol to the Division for our comments on whether the standard outcomes of this study have been adequately addressed. This combination study may be conducted as a post-marketing commitment.

**Discussion at Meeting:** The Sponsor confirmed that they are planning to conduct neurological/behavioral assessments after clonidine has been discontinued, as well as toward the end of the dosing phase. They plan to test after drug has been discontinued for 10 weeks to allow enough time for any drug-related changes to resolve. We noted that a

washout period of 2-4 weeks duration, based on pharmacokinetics, is usually acceptable to ensure the clearance of the drug in order to test for effects that might persist after treatment discontinuation. The Sponsor will consider incorporating this suggestion into their protocol; we agreed to provide comments on their revised protocol.

Discussion regarding the need for a juvenile animal combination study is provided under Question 2, below.

**Question 2:** It is anticipated that data reports for the two toxicology studies in juvenile rats will be available after the NDA is submitted. Is this acceptable to the Division?

**Preliminary Comments:** No; the juvenile rat study/studies evaluating clonidine alone should be submitted with the NDA. However, the combination study (of clonidine in combination with a stimulant, as described above) may be conducted as a post-marketing commitment.

**Discussion at Meeting:** Regarding the need for the report for the clonidine juvenile rat study/studies at the time of NDA submission, the Sponsor was concerned that this would delay their NDA submission. We explained that the study report is required at NDA submission and that this was communicated to them at our earlier meeting (1/16/2006). We offered to allow them to submit an audited draft report for NDA filing, with a commitment to submit a final report early in the review cycle, however, they did not think this would save them much time. They suggested providing an interim report of the data from the dosing phase at NDA submission, with the full report, including the drug-discontinuation phase, to be submitted at a pre-arranged date during the review cycle; however, we explained that this would not be acceptable, because the data from the drug-discontinuation phase is necessary for us to make a decision on the NDA. They suggested that if they did not submit the full study report at the pre-arranged date during the review cycle, we could stop the review clock. We explained that stopping a review clock is very inefficient from the Agency's perspective; because of our heavy work load, especially due to additional responsibilities mandated in PDUFA IV, we have been encouraged to refuse to file NDA submissions that are deficient. We suggested that the change we recommended in their study design (see Discussion of Question 1, above) might allow them to submit their NDA earlier.

Regarding the need for a combination study of clonidine with a stimulant, the Sponsor felt that this requirement was unusual and asked if we had specific concerns about clonidine. We agreed that combination studies in juvenile animals are not often required, but we explained that for a claim for adjunctive therapy for ADHD in children, we feel they are necessary, because stimulants, as a class (specifically d-amphetamine and methylphenidate), are so widely used for ADHD and we do not get adequate long-term clinical safety data for the combination(s) in children. We recommended that they seek advice from the Division on the design of their combination study after they have the results of the clonidine ("monotherapy") study/studies and we have reviewed those results under their NDA.

## **Clinical**

**Question 3:** At the pre-IND meeting, the Division noted that if two positive studies were completed for CLONICEL, one as monotherapy and one as add-on therapy to stimulant medications, then these two studies could support claims for both monotherapy and for add-on therapy. Does the Division agree that data from Studies CLON-301 and CLON-302 (see Section 5 and Appendix 2 of the meeting package), if confirmed in the final analysis, are adequate and sufficient to support intended claims for both monotherapy and add-on therapy?

**Preliminary Comments:**

On face, these studies are adequately designed to support the proposed indications for pediatric ADHD; however, whether or not the data will support these claims can be determined only after review of the planned NDA

**Discussion at Meeting:**

No further discussion.

**Question 4:** In addition to controlled data, the Division requested open-label safety experience under conditions of usual use which may include use in combination with stimulants. Study CLON-303 (see Section 5 and Appendix 2) was designed to address this request. Enrollment data and projections for continued enrollment in this study are provided in the summary below. Does the plan outlined for collection of open-label safety information satisfy the Division's request?

**Preliminary Comments:**

Yes.

**Discussion at Meeting:**

No further discussion.

**Question 5:** At the pre-IND meeting, the Division accepted that the proposed pharmacology/biopharmaceutics studies that would be completed by the sponsor for the adult hypertension indication for CLONICEL would fulfill the Division's requirements for the pediatric indication. These studies have since been completed and an NDA filed for the hypertension indication in adults (see Section 4 and Appendix 3). The sponsor plans to reference these studies in the proposed ADHD NDA. Is this acceptable to the Division?

**Preliminary Comments:**

Yes. You can reference the clinical pharmacology and biopharmaceutics studies from the adult hypertensive program. See response to Question 6 also.

**Discussion at Meeting:**

No further discussion.

**Question 6:** Plasma samples for assay of clonidine concentrations were collected from approximately 270 patients in both Studies CLON-301 and CLON-302. The sponsor plans to summarize PK data from these samples and present them in a separate PK report filed as a supplement to the NDA. Is this acceptable to the Division?

**Preliminary Comments:**

No. The full pharmacokinetic (PK) report obtained from studies in the intended pediatric patients must be included when the application is submitted. Since PK information in the intended pediatric patients is needed for labeling purposes, the absence of PK data in the intended pediatric patients will be an issue in determining whether the application can be filed.

Further, since the NDA will also include Clonicef as add-on to psychostimulant, the sponsor should provide drug-drug interaction information between psychostimulants and Clonicef. It is possible that this information can be obtained from the PK data obtained from the two clinical studies mentioned above.

**Discussion at Meeting:**

The sponsor indicated they will include the PK report in the NDA at the time of its submission. The sponsor also indicated that they will provide information on the drug-drug interaction between psychostimulants and Clonicef in the NDA.

**CTD Content and Format**

**Question 7:** CLON-301 was a fixed-dose, forced titration monotherapy study, whereas CLON-302 utilized a flexible dosing design as add-on therapy to existing ADHD stimulant medications. In addition, CLON-303 is an open-label safety study. Because of the different study designs of these Phase 3 trials, the Sponsor does not intend to summarize the data in the clinical summaries in an integrated format; rather summary data will be presented separately and contiguously for the different studies. Is this approach acceptable to the Division?

**Preliminary Comments:**

Yes.

**Discussion at Meeting:**

No further discussion.

**Question 8:** The Sponsor plans to include the interim results of the open-label safety study CLON-303 in the CTD summary of clinical safety (Module 2, section 2.7.4). An interim CSR is not planned to be submitted with the NDA; however, the statistical tables and listings supporting the clinical summary for CLON-303 will be provided in Module 5, Section 5.3.5.2 Uncontrolled Clinical Studies. (A clear explanation of where the summary and statistical data are located will be provided in Module 2 and Module 5). An update will be presented for the 120-day safety update and a final CSR (including efficacy and safety data) will be submitted as a supplement to the NDA when the CLON-303 study is completed. Is this acceptable to the Division?

**Preliminary Comments:**

No. A Clinical Study Report (CSR) for CLON-303 should be submitted at the time of the filing of the NDA. Additional safety information from this study may be provided at the 4 month safety update. As we have indicated to you before, regarding safety experience, the extensive literature on clonidine in ADHD, both as monotherapy and in combination with stimulants, would need to be supplemented; and the ICH criteria for chronic exposure would need to be satisfied at the time the NDA is submitted.

**Discussion at Meeting:**

The sponsor stated that they anticipate an enrollment of approximately 300 subjects in the CLON-303, open-label study with chronic exposure data of at least 200 subjects exposed to clonidine up to 6 months, and 120 subjects up to one year. They acknowledged that the extensive literature on clonidine in ADHD, both as monotherapy and in combination with stimulants, would be supplemented for the NDA submission. We stated that, on face, their plan seems reasonable; however, whether or not the data will adequately support safety requirement can be determined only after review of the submitted NDA.

**Question 9:** The Guidance for Industry, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* specifies that Module 2, sections 2.7.3 and 2.7.4 should contain summarized information derived from the full NDA integrated summaries of efficacy and safety (ISE and ISS) provided in Module 5, section 5.3.5.3 (i.e., the highlights of the appropriate sections of each document as outlined in ICH M4E). Due to the small number of studies and the nature of the ADHD clinical program for CLONICEL, the Sponsor believes that sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, will be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, and still accommodate the suggested size limitations for Module 2. Therefore, the Sponsor proposes that only sections 2.7.3 and 2.7.4 will be provided in the CTD/NDA, and a separate ISS and ISE will not be provided in section 5.3.5.3. Is this acceptable to the Division?

**Preliminary Comments:**

Yes.

**Discussion at Meeting:**

No further discussion.

**Additional Comments****Clinical Comments on CLON-301, 302 and 303:**

1. Seemingly related adverse event terms should be combined as single terms in your calculation of AE incidence rates: for example, somnolence and sedation under somnolence; fatigue and lethargy under fatigue, etc.
2. Provide information identifying the impact of somnolence/sedation and fatigue/ lethargy on subjects day to day functioning, if such data are available.

3. For the following AE terms, identify what investigator terms were subsumed under each preferred term:
  - a. emotional disorders
  - b. affect lability
  - c. aggression
  - d. irritability
  - e. nightmares
4. In addition to the most common and drug-related AE table (defined as the incidence rate of  $\geq 5\%$  and twice the rate of placebo), you should also provide Treatment Emergent Adverse Event Tables (TEAE) that occurred at an incidence rate of  $\geq 2\%$ .
5. For studies 302 and 303, please perform sub-group analyses of safety data (e.g. adverse events, vital signs) based on concomitant stimulant class (e.g. amphetamine, methylphenidate and others).
6. Please provide a suicidality analysis including information about any suicide attempts or ideation. Possibly suicide related adverse events should be classified using the C-CASA (Columbia Classification Algorithm for Suicide Assessment).

**Statistical Comments on CLON-301 and 302:**

Please include the following items in your future NDA submission for both of these studies:

1. Perform some sensitivity analyses to assess the robustness of the efficacy findings in addition to the analysis based on the observed data. In particular, for Study CLON-301 the sensitivity analyses should include the analysis by grouping patients per their treated doses.
2. Perform the subgroup analyses by demographic variables (such as gender, age and race), as well as by region if applicable.
3. All raw and derived variables, including patients' weekly prescribed dose data, in .xpt format.
4. The original study protocols, all amendments, SAPs, and related meetings, as well the submission dates and IND/serial numbers.
5. SAS programs for all efficacy analyses (whether primary or sensitivity) on the primary endpoint.

**Discussion at Meeting:**

We clarified with the sponsor regarding item #1 stated under additional clinical and statistical comments above. No further discussion at the meeting.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 76144

ADDRENEX  
PHARMACEUTICALS  
INC

CLONICEL TABLETS

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

/s/

THOMAS P LAUGHREN  
03/20/2009





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

PIND 76,144

Addrenex Pharmaceuticals, Inc.  
Attention: Paul Ketteridge, PD Regulatory Consulting, LLC  
113 Glenspring Way  
Morrisville, NC 27560

Dear Mr. Ketteridge:

Please refer to your Pre-Investigational New Drug Application (PIND) file for CLONICEL.

We also refer to the meeting between representatives of your firm and the FDA on January 16, 2007. The purpose of the meeting was to discuss and obtain agreement with the Psychiatry Division on: (1) the appropriateness of the 505(b)(2) application path for CLONICEL, and (2) the investigational plan for this development program.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LT Felecia Curtis, Regulatory Project Manager, at (301) 796-0877.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** January 16, 2006  
**TIME:** 1:00-2:00  
**LOCATION:** WO 1415  
**APPLICATION:** PIND 76,144  
**DRUG NAME:** CLONICEL® (sustained release clonidine hydrochloride)  
**TYPE OF MEETING:** Pre-IND, Type B meeting

**MEETING CHAIR:** Thomas Laughren, M.D./Division Director, DPP

**MEETING RECORDER:** Felecia Curtis/Regulatory Management Officer, DPP

**FDA ATTENDEES:** (Title and Office/Division)

Thomas Laughren, M.D./Division Director, DPP  
Mitch Mathis, M.D./Deputy Director, Psychiatry, DPP  
Ni Khin, M.D./ Clinical Team Leader, DPP  
Ikram Elayan Ph.D./Pharmacology Reviewer  
Ray Baweja, Ph.D./Team Leader, Clinical Pharmacology/Biopharmaceutics Reviewer,  
Andre Jackson, Ph.D. / Clinical Pharmacology/Biopharmaceutics Reviewer  
Wayne Mitchell, Regulatory Counsel  
Felecia Curtis/Regulatory Management Officer, DPP

**EXTERNAL CONSTITUENT ATTENDEES:**

Moise A. Khayrallah, Ph.D. / President & CEO, Addrenex Pharmaceuticals, Inc.  
Rakesh Jain, M.D. / Medical Affairs Consultant  
Paul Ketteridge, R.Ph. / Regulatory Consulting, LLC

**BACKGROUND:**

Clonidine is a centrally acting alpha<sub>2</sub> adrenergic agonist that was originally approved for the treatment of hypertension. Clonidine is available in the US in 3 formulations:

- Oral dose immediate release tablet (Catapres brand and generics) supplied in 3 doses: 0.1, 0.2, and 0.3 mg
- Transdermal system formulation (Catapres-TTS) supplied in 3 patch sizes: 3.5, 7.0, and 10.5 cm<sup>2</sup> delivering 0.1, 0.2, and 0.3 mg per day of clonidine, respectively
- Epidural injection (Duraclon) supplied in 100 and 500 mcg/mL solutions in 10 mL vials

The sponsor intends to develop and market a sustained release formulation of clonidine, i.e., CLONICEL, for the treatment of ADHD. They plan to file an NDA for CLONICEL under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and to rely in part on the Agency's previous findings of safety and efficacy for the approved formulations.

The sponsor refers to a literature review of studies focusing on the use of clonidine in the treatment of ADHD (Connor et al, 1999). They cite this as evidence for clonidine's efficacy for ADHD symptoms, particularly for behavior. Two more recent studies looking at the combination of methylphenidate and clonidine have apparently shown a benefit of adding clonidine to methylphenidate in the treatment of ADHD (TACT and CAT).

The sponsor expresses a view that, based on the extensive literature supporting the efficacy of clonidine in ADHD and the large number of clonidine prescriptions written annually for this drug for the treatment of ADHD, a single adequate and well-controlled trial in ADHD should suffice. The sponsor has proposed an 8-week, parallel group, placebo-controlled, flexible dose outpatient study (clonidine in a dose range of 0.1 to 0.4 mg/day) in children and adolescents with ADHD (6-17). Patients would be titrated up to 0.4 mg/day, as needed and tolerated, over 3 weeks, and maintained on the optimal dose for 2 weeks, before beginning a 3-week taper period. Dosing would be on a bid basis. There would be a total of 150 patients (75 per group). This would be a monotherapy study. The primary efficacy assessment would be the ADHDRS-IV and the primary outcome would be change from baseline to week 5 on the ADHDRS-IV total score.

The purpose of this requested meeting is to obtain agreement with the Psychiatry Division on: (1) the appropriateness of the 505(b)(2) application path for CLONICEL, and (2) the investigational plan for this development program.

### **MEETING OBJECTIVES:**

**Question 1:** Does the Division agree that the 505(b)(2) application path is appropriate for the development and approval of CLONICEL for the treatment of ADHD in children and adolescents?

**Preliminary Comments:** *Yes. A 505(b)(2) application may be submitted for a change in dosage form and a new indication as you proposed for CLONICEL.*

*A 505(b)(2) application is submitted under section 505(b)(1) of the Act and therefore should be supported by full reports of investigations which have been made to show whether such drug is safe for use and effective in use. A 505(b)(2) NDA may refer to the agency's finding of safety for a listed drug only if an adequate clinical bridge is established to its listed drug. If an adequate clinical bridge is not established to its listed drug then the 505(b)(2) application should be supported by complete nonclinical information. This preclinical information should be from studies conducted by or for the sponsor or for which the sponsor has right to refer. The information may also be from literature of sufficient quality and detail to permit an independent assessment of safety.*

*The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/guidance.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408.*

**Discussion at Meeting:** *The sponsor asked for clarification on what is meant by a "clinical bridge." With regard to clinical data, we noted that the plan for clinical trials would largely address the need for a clinical bridge. We referred to the clinical pharmacology addendum for details on what clinical studies would be needed to bridge*

*the new formulation to a reference product (see later). See response to question #2 for the bridging data needed from a pharm/tox perspective.*

**Question 2:** Does the Division agree that the sponsor can reference pharmacology and toxicology data that is publicly available for the marketed clonidine formulations, including the Agency's previous findings, in both IND and eventual NDA applications, and that no additional preclinical pharmacology and toxicology studies are required?

***Preliminary Comments:*** *A rat juvenile animal study will be needed at the time of the NDA submission.*

***Discussion at Meeting:*** *It was suggested that the sponsor submit a protocol for a juvenile study for comment.*

**Question 3:** Does the Division agree that a single Phase III adequate and well controlled study provides sufficient evidence for marketing approval for CLONICEL?

***Preliminary Comments:*** *No. Two positive studies in ADHD would be needed. We would recommend a fixed dose laboratory classroom study as a second study. In addition, it will be necessary to have some open-label safety experience under conditions of usual use, which may include use in combination with stimulants.*

***Discussion at Meeting:*** *We discussed the role of literature reports for studies conducted by other groups, and the difficulty we have in interpreting such results without direct access to original data. The sponsor will consider the feasibility of obtaining access to original data, but understands the need for two independent sources of evidence, and will also consider conducting a second study. They indicated that the pk characteristics of their formulation of clonidine would not support a crossover study because of the extended period of time needed to clear drug after each period. Thus, they will consider a parallel group, outpatient study. We strongly encouraged a fixed dose study as the second study, and they will consider such a study. We noted that an add-on study as a second study would, if both monotherapy and add-on studies were positive, support claims for both monotherapy and adjunctive therapy. Regarding safety experience, we suggested that the extensive literature on clonidine in ADHD, both as monotherapy and in combination with stimulants, should help, but would need to be supplemented with direct experience. We indicated that ICH criteria for chronic exposure would need to be satisfied.*

**Question 4:** Is the proposed Phase III trial design adequate to demonstrate efficacy and safety of CLONICEL in the indication sought?

***Preliminary Comments:*** *The proposed study is acceptable by design as 1 of 2 required studies.*

***Discussion at Meeting:***  
*No further discussion.*

**Additional Preliminary Comments:**

## **Clinical Pharmacology/Biopharmaceutics:**

The general BA/BE guidance recommends that the following BA studies be conducted for an extended release drug product submitted as an NDA:

1. A single-dose, fasting study on all strengths of tablets and capsules and highest strength of beaded capsules
2. A single-dose, food-effect study on the highest strength
3. A steady-state study on the highest strength of the SR compared to an approved reference product.
4. Dissolution method and proposed specification for all product strengths the firm plans to market.
5. The sponsor is referred to 21CFR 320.25(F) and the general BA/BE Guidance for any additional information.

### **Discussion at Meeting:**

*You did not have specific questions for Clinical Pharmacology/Biopharmaceutics but, since you are proposing to make a controlled release formulation for a current IR formulation, the following studies will have to be done to characterize dosage form performance:*

*The general BA/BE guidance recommends that the following BA studies be conducted for an extended release drug product submitted as an NDA:*

1. *A single-dose, fasting study on all strengths of tablets and capsules and highest strength of beaded capsules*
2. *A single-dose, food-effect study on the highest strength*
3. *A steady-state study on the highest strength of the SR compared to an approved reference product.*
4. *Dissolution method and proposed specification for all product strengths the firm plans to market.*
5. *We refer you to 21CFR 320.25(f) and the general BA/BE Guidance for additional information.*
6. *You noted that you also have a Clinical program in the Cardio-Renal Division to which you had planned to submit:*
  - a. *single dose studies/waivers on all strengths*
  - b. *food effect study*
  - c. *a pk/pd study comparing your product to the currently marketed IR product*

*We note that the proposed studies done in adults for Cardio-Renal would fulfill the current Clinical Pharmacology/Biopharmaceutics Psychiatry requirements for your CR product; however, these studies would have to be completed prior to the arrival of the NDA for ADHD.*

*If the studies for the Cardio-Renal Division have not been completed by the time the NDA for ADHD arrives, then the requisite studies under items 1-3 (see above) would have to be included in the NDA for ADHD.*

*7. You also mentioned that the pharmacokinetics of Clonicef CR in children would be collected during the Clinical ADHD program.*

**Chemistry, Manufacturing and Controls:**

All organic impurities should be integrated and reported by retention time (RT) or relative retention time (RRT) and be reported in your testing results. Appropriate residual solvents (refer to ICH Q3C: Guideline for Residual Solvents) and residual heavy metals should be tested for and reported.

**Discussion at Meeting:** *No further discussion.*

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/s/

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Thomas Laughren  
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