

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-411**

**MEDICAL REVIEW(S)**

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

**DATE:** July 17, 2009

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

**SUBJECT:** Recommendation for Complete Response action for trazodone extended release (ER) tablets for the treatment of major depressive disorder

**TO:** File NDA 22-411  
[Note: This overview should be filed with the 9-18-08 original submission of this application.]

**1.0 BACKGROUND**

Trazodone extended release is an extended release tablet formulation of trazodone, a triazolopyridine derivative that is both an SSRI and a 5HT2 antagonist. Trazodone has been marketed worldwide in an immediate release formulation as an antidepressant for almost thirty years. Trazodone ER is available in strengths of 150 and 300 mg (scored tablets), and the sponsor is proposing doses in a range of 150-375 mg/day. This was a 505(b)(2) application that relied on available data from the original application for trazodone IR.

We met with the sponsor for a PreIND meeting on 11-8-06, and held a PreNDA meeting on 2-28-08. We provided comments on the pivotal phase 3 protocol on 8-10-07.

The primary review of the efficacy and safety data was done by Victor Crentsil, M.D., from the clinical group. George Kordzhakhia, Ph.D., from the biometrics group, also reviewed the efficacy data. Kofi Kumi, Ph.D. from OCP reviewed biopharmaceutics data.

The study supporting this supplement were conducted under IND 76,137, and this supplement was submitted on 9-18-08.

We decided not to take this application to the Psychopharmacological Drugs Advisory Committee (PDAC).

## **2.0 CHEMISTRY**

Although all CMC issues for this new formulation have been resolved, we have received an overall WITHHOLD recommendation from the office of compliance due to an unsatisfactory inspection of the DS site. We will send our recommended dissolution specifications separately. We also send separately our advice regarding an alcohol interaction study.

## **3.0 PHARMACOLOGY**

All pharm/tox issues for this new formulation have been resolved.

## **4.0 BIOPHARMACEUTICS**

Trazodone ER has a very substantial food effect, with an 86% increase in Cmax when taken with food. Thus, labeling will recommend dosing at bedtime, on an empty stomach. The sponsor has agreed to conduct a study to assess any potential for dose-dumping when the drug is taken with ethanol.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

The only efficacy data submitted in support of this application came from study 04ACL3-001, an 8-week, multicenter (US and Canada), double-blind, randomized, parallel-group, placebo-controlled, flexible-dose (150 to 375 mg/day) study in adult patients with major depressive disorder (MDD). We had agreed to a single study because trazodone IR was previously approved based on multiple studies in MDD. The primary endpoint was change from baseline to endpoint on the HAM-D17 total score. There were n=406 patients in the ITT analysis (204 for placebo and 202 for trazodone). Trazodone ER was statistically significantly superior to placebo on the primary endpoint (p=0.01). The difference between trazodone and placebo on change from baseline for HAM-D17 was about 2 units, a relatively modest effect. Subgroup analyses based on age, gender, and race did not suggest any differences by age or gender, but did suggest minimal benefit in non-white subgroups. However, these non-white subgroups were quite small. In summary, I agree with Drs. Crentsil and Kordzakhia that this is a positive study. The sponsor has agreed to both a maintenance study and a pediatric depression program in ages 7-17.

### **5.2 Safety Data**

Safety data for this application were derived from 9 phase 1 studies and the sole phase 3 study. There were no new findings from the review of these data that were inconsistent with the well-known safety profile for this drug. There are accumulated data from AERS and the literature

(both animal and human) suggesting that trazodone can cause modest QTc prolongation and be may associated with cardiac arrhythmias. The QTc effect appears to on the order of 4-8 msec. We consulted with DCRP on this issue, and they advised us that the signal for QTc prolongation is sufficiently clear, and consequently, they do not feel a thorough QT study is needed. Thus, labeling will have Warnings/Precautions language alerting prescribers to this risk. The safety data for this program also confirmed the well-known sedative effects of this drug. To partly minimize this effect during the day, dosing will be recommended at bedtime.

### **5.3 Clinical Sections of Labeling**

We substantially modified the labeling proposed by the sponsor, and have now reached agreement with them on final labeling.

### **6.0 WORLD LITERATURE**

Literature pertinent to QT prolongation was reviewed as part of the review of this application, and these sources did support the view that trazodone is associated with QTc prolongation.

### **7.0 FOREIGN REGULATORY ACTIONS**

Apparently a controlled release formulation of trazodone is marketed in Europe.

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

We decided not to take this application to the PDAC.

### **9.0 DSI INSPECTIONS**

Inspections were conducted at 4 US sites, and data from these sites were deemed to be acceptable.

### **10.0 LABELING AND COMPLETE RESPONSE LETTER**

We have included the final labeling that is mutually agreed upon with the sponsor in the CR letter.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

Although the sponsor has provided sufficient safety and efficacy data to support an approval action for this application, the one remaining issue to be resolved is the failed inspection at the drug substance manufacturing site. This issue must be resolved before we can take a final action.

cc:

Orig NDA 22-411

HFD-130

HFD-130/TLaughren/MMathis/GZornberg/VCrentsil/WBender

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/s/

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Thomas Laughren  
7/17/2009 10:00:52 AM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-411
Priority or Standard	Standard
Submit Date(s)	18 September 2008
Received Date(s)	18 September 2008
PDUFA Goal Date	18 July 2009
Division / Office	Division of Psychiatry Products Office of New Drugs
Reviewer Name(s)	Victor Crentsil, M.D., M.H.S
Review Completion Date	1 May 2009
Established Name	Trazodone Contramid® OAD
(Proposed) Trade Name	Oleptro™
Therapeutic Class	Serotonin Antagonist Reuptake Inhibitor
Applicant	Labopharm, Inc.
Formulation(s)	Extended-Release Caplet
Dosing Regimen	150 mg/day- Starting dose 375 mg/day- Maximum dose
Indication(s)	Unipolar Major Depressive Disorder
Intended Population(s)	Adults

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

From the clinical perspective, it is recommended that this supplemental New Drug Application (sNDA) for Trazodone Contramid<sup>®</sup> OAD be approved for the treatment of unipolar major depressive disorder, contingent on satisfactory responses to requests and issues raised by the Office of New Drug Quality Assessment as well as reviewers from the Office of Clinical Pharmacology, Biometrics, and Division of Scientific Investigations of the FDA, and agreement on labeling.

Additional information on Chemistry Manufacturing and Controls has been requested from the sponsor by reviewers from the Office of New Drug Quality Assessment and the sponsor's response was pending at the time of completion of this review.

### 1.2 Risk Benefit Assessment

With regard to the assessment of the benefit of Trazodone Contramid<sup>®</sup>, based on the results of the pivotal study (04ACL3-001), Trazodone Contramid<sup>®</sup> OAD demonstrated superior antidepressant efficacy against placebo. The efficacy data provided in this sNDA are supplemental and consistent with the existing efficacy data on trazodone hydrochloride (HCL) for major depressive disorder, referenced by the sponsor as this application uses a 505(b) (2) mechanism.

For risk assessment, this sNDA was evaluated as a supplement to the accumulated data on the risks/safety of trazodone HCL referenced by the sponsor of this sNDA. The integrated review of the safety data submitted with this sNDA (from 9 Phase I and one Phase III studies) did not reveal any reason to preclude recommendation of approval, from a clinical safety perspective. No serious adverse events (SAEs) or fatalities were reported for the Phase I studies. The Phase III study reported one death (a patient randomized to placebo) and 4 non-fatal SAEs, none of which appears to be directly linked with exposure to trazodone. There is however data from multiple sources on the propensity of trazodone to prolong QT interval and induce cardiac arrhythmia. In the literature review submitted by the sponsor as part of this sNDA, the sponsor admits that QT prolongation and syncope have been reported in the literature on trazodone. A Thorough QT study is more likely to be positive than negative; hence, a Thorough QT is not recommended at this time, especially since it would not seem to be necessary for the suggested labeling changes and it is not without risks to research subjects. In stead, it is recommended that the labeling of Trazodone Contramid<sup>®</sup> reflect its propensity to prolong QT and induce cardiac arrhythmia even at therapeutic dosages.

In addition, it is recommended that Trazodone Contramid<sup>®</sup> should be taken in the evening (due to the associated somnolence/sedation) but on an empty stomach, i.e., before supper/dinner. The rationale behind this recommendation is food increases the maximum drug concentration ( $C_{max}$ ) of Trazodone Contramid<sup>®</sup> by 86%. To avoid or minimize adverse events that may be associated with such appreciable post-prandial increase in  $C_{max}$ , administration of Trazodone Contramid<sup>®</sup> before an evening meal may be a risk-minimizing approach.

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

The sponsor has submitted a Medication Guide and it is recommended that the Medication Guide is retained and followed.

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

There is no recommendation for postmarket requirements and commitments.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Trazodone HCL is a triazolopyridine derivative and a serotonin-2 antagonist as well as a selective postsynaptic inhibitor of serotonin reuptake. The immediate-release formulation (tablet, capsule, and oral liquid) is marketed globally and the controlled-release formulation (75mg and 150mg once or twice daily) is marketed in Europe.

Trazodone Contramid<sup>®</sup> OAD is the first extended-release formulation of trazodone HCL to be introduced to the US. Trazodone Contramid<sup>®</sup> OAD, a once-a-day Trazodone HCL formulation, uses a technology developed by the sponsor to create a solid sustained release oral dosage form in which (b) (4)

Trazodone Contramid<sup>®</sup> OAD is a scored “caplet.” The Reference Listed Drug (RLD) for this application was initially Desyrel,<sup>®</sup> but after Desyrel<sup>®</sup> was discontinued in 2006, the new RLD became trazodone HCL (NDA 071196).

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Available Treatments for Major Depressive Disorder

GENERIC NAME	TRADE NAME
<b>Selective Serotonin Reuptake Inhibitors (SSRIs)<sup>1</sup></b>	
Fluoxetine	Prozac
Paroxetine	Paxil
Sertraline	Zoloft
Citalopram	Celexa
Escitalopram	Lexapro
Fluvoxamine	Luvox
<b>Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)<sup>1</sup></b>	
Venlafaxine	Effexor
Desvenlafaxine	Pristiq
Duloxetine	Cymbalta
<b>Mixed Reuptake and Neuroreceptor Antagonists<sup>1,2</sup></b>	
Imipramine	Tofranil
Amitriptyline	Elavil
Doxepine	Sinequan
Clomipramine	Anafranil
Trimipramine	Surmontil
Amoxapine	Ascendin
<b>Norepinephrine Selective Reuptake Inhibitors<sup>1,2</sup></b>	
Desipramine	Norpramin
Nortriptyline	Aventyl, Pamelor
Protriptyline	Vivactil
Maprotiline	Ludiomil
<b>Dopamine and Norepinephrine Reuptake Inhibitors<sup>1</sup></b>	
Bupropion	Wellbutrin, Zyban, Aplenzil
<b>Monoamine Oxidase Inhibitors (MAOIs)<sup>1</sup></b>	
Selegiline Transdermal system	Emsam
Phenelzine	Nardil
Tranylcypromine	Parnate
<b>Serotonin (5-HT<sub>2A</sub> and 2C) and α<sub>2</sub> Norepinephrine Blocker<sup>1</sup></b>	
Mirtazapine	Remeron

<sup>1</sup> Presumed Mechanism of Action of the listed drugs; <sup>2</sup> Some members are also classified as Tricyclic Antidepressants. Nefazodone is also a serotonin -2A receptor blocker and a weak serotonin uptake inhibitor used to treat MDD.

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

Trazodone HCL, the active ingredient of Trazodone Contramid® OAD, is approved and available in the United States. The first immediate-release formulation of trazodone HCL (Desyrel®) was introduced in the US in December, 1981 and discontinued in September, 2006; however, generic products are still marketed in the US.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Nefazodone (marketed under the tradename Serzone) is the other triazolopyridine in addition to trazodone. Serzone has been withdrawn from the US market. An important safety issue associated with nefazodone, a drug related to trazodone, is life-threatening liver failure. Other adverse events associated with nefazodone were orthostatic hypotension, light-headedness, asthenia, somnolence and dry mouth. Unlike trazodone, nefazodone exposure was not associated with priapism; however, there is at least one case report of nefazodone-induced clitoral priapism (Brodie-Meijer CC et al., 1999).

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

Trazodone immediate release (Desyrel®) was approved in 1981 for the treatment of depression with or without anxiety.

- |                   |   |
|-------------------|---|
| 8 November 2006   | Pre-IND Meeting (IND # 76, 137) between FDA and Canreg (on behalf of Labopharm, Inc.)                   |
| 28 February 2007  | IND # 76,137 for Trazodone Contramid® OAD submitted   |
| 28 March 2007     | Full Clinical Hold placed on IND# 76, 137 due to the lack of control (b) (4) of Tazodone Contramid® OAD |
| 23 May 2007       | The Full Clinical Hold was removed  |
| 10 August 2007    | FDA sent the comments on Phase III study protocol (04ACL3-002) to the sponsor                           |
| 28 February 2008  | Pre-NDA Meeting between FDA and sponsor   |
| 18 September 2008 | NDA 22-411 was submitted to FDA by sponsor  |

## **2.6 Other Relevant Background Information**

There is no additional relevant background information.

## **3 Ethics and Good Clinical Practices**

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

The quality and integrity of the submission were adequate for review.

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

The undersigned reviewer is not aware of any compliance with good clinical practices issues at the time of review of this sNDA. Below are summaries of reports submitted by Division of Scientific Investigations (DSI):

The DSI inspector's report on the inspection of Dr. Steven Glass (US Site #111, New Jersey) concluded that: "In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Dr. Dennis Munjack (US Site # 120, Southwestern Research, Inc., California) passed away in the Spring of 2008, and the clinical studies were transferred to Dr. John Murphy, the co-owner of the site. Though the investigator included one subject on a prohibited antidepressant (Prozac) and there were minor documentation issues, the DSI inspector's assessment was that, "In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication."

### **3.3 Financial Disclosures**

The sponsor certifies that no financial arrangements have been made with the listed clinical investigators whereby their compensation will be affected by the outcome of the study. The sponsor also certifies that the listed clinical investigators did not disclose any proprietary interest in Trazodone Contramid® or a significant equity in the sponsor.

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

### 4.1 Chemistry Manufacturing and Controls

Dr. Sherita McLamore is the Chemistry reviewer for this sNDA (*Please see her review for more information*). At the time of the review of this sNDA, there were a variety of Chemistry, Manufacturing, and Control (CMC) issues to be addressed by the sponsor.

In addition to a deficient drug substance DMF (b) (4) the following are some of contents of an information request letter recently sent to the sponsor:

“We request a prompt written response in order to continue our evaluation of your NDA.

1. In the dosage and administration section you indicate that the caplets should be swallowed whole and should not be chewed or crushed; however, in more than one place in the application you indicate that the caplets may be broken in half along the score line for dosing flexibility. Please explain.
2. Update the drug product specification to include an acceptance criterion for (b) (4).
3. Confirm that the method used for (b) (4) is USP or provide validation for this method.
4. Your acceptance criterion for hardness in the drug product should include an upper and a lower limit.
5. The proposed specification for (b) (4) is not acceptable as it appears not to be qualified and is above threshold of qualification (0.2%). Please lower the specification or complete non-clinical studies to qualify this impurity.
6. The proposed specification limit for “any single impurity” in the drug substance specification is NMT (b) (4). Be advised that threshold of identification is 0.1%. Accordingly, a limit of (b) (4) for any single impurity is not acceptable. Please lower your drug substance specification limit for “any single impurity” to an NMT 0.1% based on ICHQ3A.
7. The term “caplet” is not a recognized dosage form in the CDER Data Standards Manual. Please change the dosage form from Caplet to Tablet.
8. You have proposed two sets of specifications for the release and shelf life and stability for the drug product. Please be advised that the specification that you propose for shelf-life is your regulatory specification. Provide a consolidated drug product specification table with release and stability limits.

9. Provide a sample of the 150 mg and 300 mg drug product.”

## **4.2 Clinical Microbiology**

The undersigned reviewer is not aware of any clinical microbiology issues at the time of review of this sNDA.

## **4.3 Preclinical Pharmacology/Toxicology**

The undersigned reviewer is not aware of any non-clinical pharmacology/toxicology issues at the time of review of this sNDA.

## **4.4 Clinical Pharmacology**

Dr. Kofi Kumi is the clinical pharmacology reviewer for this sNDA (*Please refer to his review for additional information*).

The undersigned reviewer is not aware of any clinical pharmacology issues that may preclude approval of this sNDA at the time of review.

Below is a synopsis of the clinical pharmacology of Trazodone/Trazodone Contramid®:

### **4.4.1 Mechanism of Action**

Although the precise mechanism of action of the antidepressant effect of trazodone is not clear, it is believed to be due to 5-HT<sub>2A</sub> serotonin receptor antagonism and selective inhibition of serotonin re-uptake at the presynaptic neuronal membrane. The active metabolite of trazodone, m-chlorophenylpiperazine, is a weak partial agonist at several serotonin receptor subtypes.

### **4.4.2 Pharmacodynamics**

Trazodone seems to be a serotonin antagonist at low dosages (0.05 – 1 mg/kg) but a serotonin agonist at high dosages (6-8 mg/kg). Though in animals there is evidence to suggest that trazodone may enhance norepinephrine release, it may block the pressor response to norepinephrine, thus its potential to cause hypotension. The sedative effect of trazodone may be due to its alpha adrenergic blocking action as well as its modest histamine blockade. Trazodone is reported to however have no effect on stage 4 of the sleep cycle but may decrease rapid eye movement sleep. Trazodone has

an anticholinergic property albeit lower than that of tricyclic antidepressants. Trazodone has a weak muscle relaxant activity. Trazodone is also believed to have an anxiolytic effect of unknown mechanism; though, it may have a reductive effect on GABAergic tone. Furthermore, it has also been shown to have an analgesic property.

Long-term therapy with trazodone may reportedly result in a reduction of post-synaptic serotonin<sub>2</sub> and  $\beta$ -adrenergic binding sites in the animal brain. It is believed that this postsynaptic receptor modification is associated with functional increase in serotonin activity, which may be responsible for its antidepressant activity associated with prolonged treatment with trazodone.

Trazodone may antagonize  $\alpha_2$ -adrenergic receptors to result in tissue relaxation as well as enhancing arterial blood flow into penile vasculature and corporal smooth muscle leading to an erection.

Trazodone has no effect on the reuptake of norepinephrine or dopamine or monoamine oxidase systems. It has no anticonvulsant activity, no direct quinidine-like activity on the cardiovascular system, and does not appear to affect the respiratory system.

#### 4.4.3 Pharmacokinetics

The pharmacokinetics of the immediate-release trazodone is provided in the approved registration dossier of Desyrel.<sup>®</sup> In summary, trazodone has an estimated bioavailability of 65%. Total drug absorption may be increased by up to 20% if it is taken with food. Trazodone does not seem to selectively localize in any specific tissue; it has 89 to 95% plasma protein binding. Its volume of distribution is 0.47 to 0.84 L/kg. Trazodone is extensively metabolized in the liver by oxidation and hydroxylation. Cytochrome P450 (CYP) 3A4 and 2D6 are involved in the metabolism of trazodone. When metabolized by CYP 3A4, an active metabolite, m-chlorophenylpiperazine, is produced. Renal excretion is responsible for 70 to 75% of its elimination, 21% eliminated by the fecal route and 0.13% excreted in urine unchanged. In general, the elimination half-life of the parent compound is reported as 7.1 hours; however, a biphasic elimination pattern has been described for trazodone. The initial phase has a half-life of 3 to 6 hours and the second slower phase has a half-life of 5 to 9 hours.

With regard to the pharmacokinetics of Trazodone Contramid<sup>®</sup>, the single-dose study in which 300-mg dose of Trazodone Contramid<sup>®</sup> was compared to 100mg of the immediate release trazodone given every 8 hours, the AUC<sub>0-∞</sub> and AUC<sub>0-t</sub> for Trazodone Contramid<sup>®</sup> were approximately 20% lower than that of the immediate release reference product. The sponsor however reports equivalent AUCs from the multiple dose study. The C<sub>max</sub> was 1.86-fold higher under fed conditions compared to fasted conditions. T<sub>max</sub>, AUC<sub>0-∞</sub> and AUC<sub>0-t</sub> were however not affected by food. Though the trazodone AUC was equivalent after intake of 300 mg Trazodone Contramid<sup>®</sup> in the morning and

Clinical Review

{Victor Crentsil, M.D., M.H.S.}

{NDA 22-411}

{Trazodone Contramid<sup>®</sup> OAD, Extended-Release Caplet}

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evening, the  $C_{max}$  was 1.5-fold higher when taken in the evening. The sponsor reports that the trazodone systemic exposure ( $C_{max}$  and AUC) was equivalent after administration at supertime with food and at night, approximately 4 hours after a meal. The mean  $T_{max}$  after a 300-mg dose of Trazodone Contramid was 8 hours, with a median of 9 hours and a range of 3-16 hours. After a single-dose of 300 mg Trazodone Contramid, the mean apparent terminal half-life reported was 10 hours.

Trazodone Contramid<sup>®</sup> was manufactured at two different sites, the Labopharm Inc. (b) (4) laboratories. The sponsor also reports that bioequivalence with respect to  $AUC_{0-\infty}$  and  $AUC_{0-t}$  was demonstrated for caplets manufactured at the two sites; however, the criterion for bioequivalence was not met for  $C_{max}$ .

*Reviewer's Comments: It appears that food increases the  $C_{max}$  of Trazodone Contramid<sup>®</sup> by 86% and an evening administration of Trazodone Contramid<sup>®</sup> was associated with a 50% increase in  $C_{max}$ , whether this evening increase in  $C_{max}$  is supper-related or not is not clear. The sponsor further reports that the  $C_{max}$  after supertime administration was equivalent to administration four hours after meals. Hence, to avoid  $C_{max}$ -related adverse events, the undersigned reviewer recommends that Trazodone Contramid is taken in the evening (due to the associated somnolence/sedation) but on an empty stomach, i.e., before supper/dinner.*

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

**Table 2: Characteristics of Phase I and III Studies Submitted to Support sNDA Application**

Protocol	Study Design	Dose	No. of Subjects Randomized/Completed and Duration
<b>SINGLE PIVOTAL (PHASE III) STUDY</b>			
04ACL3-001	2-arm, multicenter, randomized, placebo-controlled, double-blind, parallel group study.	Trazodone Contramid or Placebo Dose- 150 mg, 225 mg, 300 mg, 375 mg (once-daily)	412/307  Duration- 8 weeks
<b>PHARMACOKINETIC STUDIES</b>			
04ACL101	open-label, randomized, 4-period crossover, single-dose (test product), multiple-dose (reference products).	Trazodone HCl CR 300mg  Desyrel 100mg TID  Trittico AC 150 mg BID	24/19  Duration- 1 day per period*
04ACL102	open-label, randomized, single-dose, 2-way crossover, fasting condition	Trazodone Contramid 15 mg or 300mg	18/18  Duration- 1 day per period*
04ACL103	open-label, randomized, 4-period crossover, single-dose food effect study	Trazodone Contramid ½ of 300 mg caplet fasting and repeat dose fed  Trazodone Contramid whole 300mg caplet fasting and repeat dose fed	20/16  Duration- 1 day per period*
04ACL104	open-label, randomized, 2-way crossover, single-dose, food effect study	Trazodone Contramid 300 mg fasting then 300 mg fed	36/34  Duration- 1 day per period
04ACL105	open-label, randomized, 5-way crossover, dose-proportionality study, fasting	Trazodone Contramid- 75, 150, 300, and 375 mg	45/43  Duration- 1day per period
04ACL107	open-label, randomized, 3-way crossover, single-dose, chrono-pharmacokinetic, food-effect study	Trazodone- 300 mg	30/24  Duration-1 day per period
04ACL108	open-label, randomized, 2-way crossover, multiple-dose, steady state study	Trazodone Contarmid- 300 mg QD Trazodone HCL IR- 100 mg TID	30/27  Duration- 11 days per period
04ACL109	open-label, randomized, 2-way crossover, single-dose, site transfer bridging study	Trazodone Contramid (Labopharm)- 300 mg Trazodone Contramid (b) (4) labs)- 300 mg	30/26  Duration- 1 day per period
04ACL1-010	open-label, randomized, 2-way crossover, single-dose (test product), multiple-dose (reference products) study, under fasting conditions	Trazodone Contramid- 300 mg Trazodone HCL IR- 100 mg TID (ref)	26/23  Duration- 1 day per period

## 5.2 Review Strategy

For the efficacy review, data submitted from Study 04ACL3-001 (Phase III pivotal study) was reviewed. The safety review included an individual review of the Phase III pivotal study and Phase I studies (04ACL101, 04ACL102, 04ACL103, 04ACL104, 04ACL105, 04ACL107, 04ACL108, 04ACL109, and 04ACL1-010).

## 5.3 Discussion of Individual Studies/Clinical Trials

Overall, studies included in the review were one Phase III study (04ACL3-001), two relative bioavailability studies (04ACL108 and 04ACL1-010), two dose proportionality study (04ACL102 and 04ACL105), two food effect study (04ACL103 and 04ACL104), one chronopharmacokinetic study (04ACL107), one steady-state study (04ACL108), and one site transfer bridging study (04ACL109). The nine phase I studies were performed either in Canada (b) (4) or South Africa (Farmovs- Parexel).

**Study 04ACL3-001:** was a multicenter, 2-arm, randomized, double-blind, placebo-controlled, parallel design Phase III study designed to assess the efficacy, safety, and clinical benefit of Trazodone Contramid® compared with placebo for the treatment of unipolar major depressive disorder (MDD).

**Study 04ACL101:** was an open-label, randomized, single-dose (for the test product) and multiple-dose (for the reference product), four-period cross-over study performed under fasting conditions with the objective of comparing the pharmacokinetics of two prototypes of 300 mg Trazodone Contramid® OAD (Test 1 and Test 2) to two reference products (Reference 1- Trittico AC-two x 150 mg CR tablets and Reference 2- Desyrel®; three x 100 mg IR tablets). The study was also performed to evaluate the controlled release properties of the two formulations and to select a prototype formulation for further drug development.

**Study 04ACL102:** was an open-label, randomized, single-dose, two-way cross-over study performed under fasting conditions with the objective of comparing the rate and extent of absorption as well as dose-proportionality of 150 mg and 300 mg Trazodone Contramid® OAD.

**Study 04ACL103:** was an open-label, randomized, single-dose, 4-way cross-over study performed under fasting and fed conditions with the objective of assessing the effect of food on the rate and extent of absorption of 300 mg Trazodone Contramid® OAD given as a whole extended-release caplet and a half extended-release caplet (150mg) under fasting and then fed conditions. The secondary objective was to

evaluate dose-proportionality of the whole 300 mg caplet and half (150 mg) caplet of Trazodone Contramid.<sup>®</sup>

**Study 04ACL104:** was an open-label, randomized, single-dose, two-way cross-over study performed under fasting and fed conditions with the objective of assessing the effect of food on 300 mg Trazodone Contramid<sup>®</sup> OAD.

**Study 04ACL105:** was an open-label, randomized, single-dose, 5-way cross-over study performed under fasting conditions with the objective of evaluating dose-proportionality of Trazodone Contramid<sup>®</sup> OAD given as a single dose for doses ranging from 75 mg to 375 mg and comparing half- and intact-caplet doses.

**Study 04ACL107:** was an open-label, randomized, single-dose, 3-way cross-over study performed under fasting and fed conditions to assess the impact of time of the day and food on the pharmacokinetics of trazodone following a single-dose administration of 300mg Trazodone Contramid<sup>®</sup> OAD.

**Study 04ACL108:** was an open-label, randomized, multiple-dose, 2-way cross-over study performed under fasting conditions to compare the pharmacokinetic profiles at steady state of the test product, 300mg of Trazodone Contramid<sup>®</sup> OAD, given once daily and the reference product, 100mg trazodone HCL immediate-release tablets, given thrice daily for one week.

**Study 04ACL109:** was an open-label, randomized, single-dose, 2-way cross-over study performed under fasting conditions to compare the pharmacokinetic profile of a single oral dose of 300mg Trazodone Contramid<sup>®</sup> OAD, manufactured in Labopharm. Inc. (Quebec) and 300mg trazodone HCL extended-release caplets (containing Contramid<sup>®</sup>), manufactured at [REDACTED] (b) (4).

**Study 04ACL1-010:** was an open-label, randomized, single-dose, 2-way cross-over study performed under fasting conditions to compare the pharmacokinetic profile of the test profile, 300mg Trazodone Contramid<sup>®</sup> OAD, given as a single dose, and the reference product, 100mg trazodone HCL immediate-release tablets, administered three times daily.

## 6 Review of Efficacy

### Efficacy Summary

The sponsor pursued the development of Trazodone Contramid® OAD under the regulatory approach of a 505(b)(2), referencing the existing efficacy data on trazodone HCL for Unipolar Major Depressive Disorder (MDD). The sponsor therefore submitted a single Phase III study (04ACL3-001) to support the indication sought.

According to Study 04ACL3-001, Trazodone Contramid® OAD demonstrated superior efficacy against placebo for unipolar MDD as evidenced by the results of analysis of the primary efficacy endpoint (Change in HAMD-17 Total Score from baseline) and other analytic approaches (Mixed-effects Model Repeated Measures and Time Weighted Average Analysis).

### 6.1 Indication

The sponsor seeks approval of Trazodone Contramid® OAD for the treatment of Unipolar Major Depressive Disorder.

### STUDIES PERTINENT TO CLAIM

Study 04ACL3-001 is the only study submitted by the sponsor to support the efficacy claim for the proposed indication.

### Study Summary

### Methods/Study Design/Analytic Plan

### 6.2 Methods

#### Study Design

#### Overall Study Design:

The proposed efficacy claim for Trazodone Contramid® OAD for the treatment of Unipolar Major Depressive Disorder is based on data from Study 04ACL3-001, which was a multicenter, two-arm, randomized, double-blind, placebo-controlled, parallel design Phase III clinical trial. Study 04ACL3-001 was conducted in 38 study sites in USA and Canada.

The study proceeded in two phases- The baseline phase [screening and washout] and the double-blind randomized phase (*See Figure 1 for additional information*).

The total study duration was 11 weeks. Up to 3 weeks for screening and the washout of prohibited drugs, then 2 weeks of titration of drug or placebo and 6 weeks of treatment with maximum tolerated dose of drug/placebo (or final titration dose level). Rescue medication for the treatment of MDD was not allowed. Subjects were discontinued if dose adjustment was not successful in treating intolerable symptoms or adverse events (AEs).

Dose titration schedule: (TC.OAD = Trazodone Contramid® OAD)

Dose level I: TC.OAD 150 mg or Placebo once daily (at bedtime) for 4 days  
Dose level II: TC.OAD 225 mg or Placebo once daily (at bedtime) for 3 days  
Dose level III: TC.OAD 300 mg or Placebo once daily (at bedtime) for 4 days  
Dose level IV: TC.OAD 375 mg or Placebo once daily (at bedtime) for 3 days

The patients were re-evaluated at end of baseline period and on Days 7, 14, 21, 28, 42, and 56. The patients were also contacted by telephone 35 days and 49 days post-randomization.

The patients who could not tolerate Dose level I exited the study. Patients stayed on their next high dose level for at least 2 days before a decision was made whether the patient will remain at that dose or decrease to the previous lower dose. Only one dose reduction was permitted during the titration phase. Dose reduction or increase were also permitted during treatment period based on efficacy and tolerability.

**Pertinent Inclusion Criteria** (Source: 04ACL3-001, Clinical Study Report, Page 26-27):

- Aged 18 years or older.
- Fulfilled DSM-IV criteria for Unipolar Major Depressive Disorder (MDD) (Axis I) as confirmed by the MINI International Neuropsychiatric Interview.
- The primary DSM-IV Axis I diagnosis had to be Major Depressive Disorder (296.22, 296.23, 296.32, 296.33); any subject meeting criteria for another, non excluded Axis I disorder, had to demonstrate MDD as the primary disorder.
- The ongoing episode of MDD should have lasted for a minimum of 1 month, whether the patient has been diagnosed with one single episode or recurrent episodes.
- Presence of dysphoria for most days over the prior four weeks.
- Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score of at least 26 at screening and baseline.
- Oral and written language comprehension at a level sufficient to comply with the protocol and to complete study-related materials.

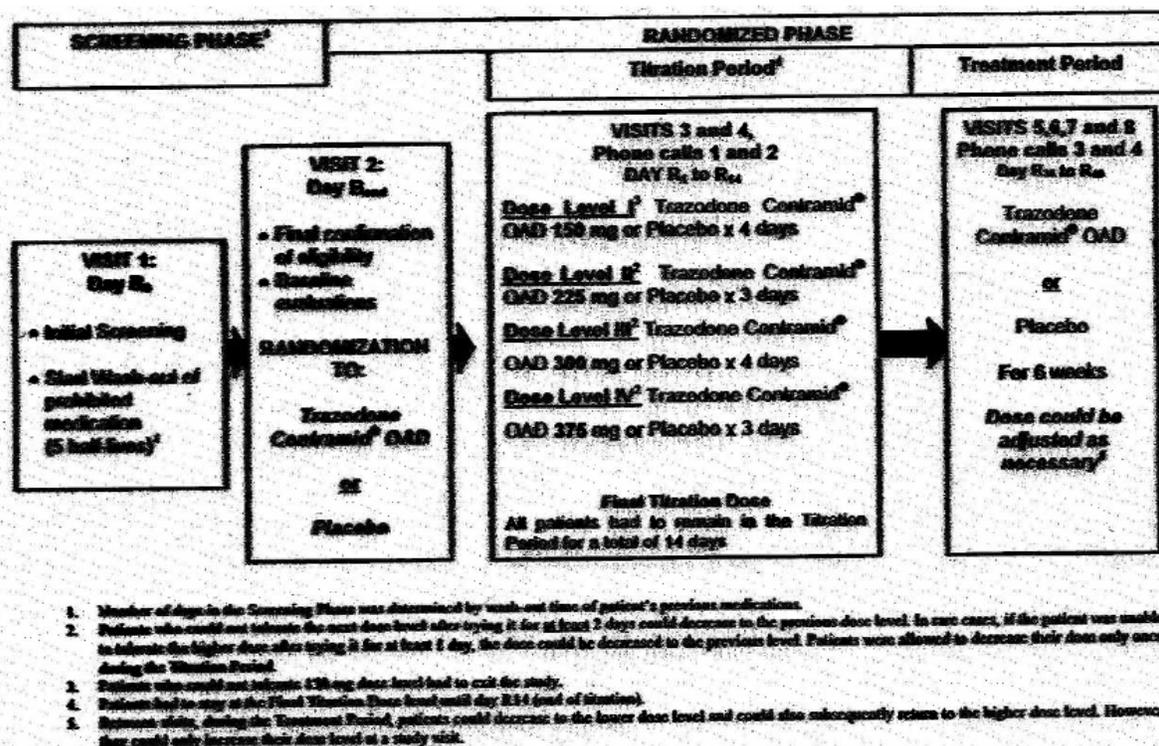
**Pertinent Exclusion Criteria** (Source: 04ACL3-001, Clinical Study Report, Page 26-27):

- DSM-IV Major Depressive Disorder Specifiers: (a) With Catatonic Features; (b) With Postpartum Onset; (c) With Seasonal Pattern;
- Presence of any of the following DSM-IV Axis I disorders: generalized anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, eating disorder, bipolar disorder, alcohol/substance abuse or dependence (caffeine and) nicotine allowed), any psychotic disorder.
- Depression secondary to stroke, cancer, or other severe medical illnesses.
- History or present condition of any DSM-IV Axis II disorder.
- History of treatment refractory major depressive episodes defined as incomplete or no therapeutic response to two prior courses of at least one month of conventional antidepressant drug treatment in adequate dosages.
- In psychotherapy at the time of enrolment (at least one session in the past month with a plan for continuing) with a licensed/registered/certified mental health provider, marriage counselor, or family therapist.
- Met criteria for high suicide risk on the MINI suicide scale, or in the opinion of the investigator was inappropriate for the trial due to clinically significant suicidal or homicidal potential.
- Required hospitalization for treatment of the ongoing episode of depression.
- Uncorrected hypo- or hyperthyroidism.
- A history of seizures other than pediatric febrile seizure.
- A history of cardiac arrhythmias requiring therapy.
- A history of myocardial infarction within 1 year before screening.
- Clinically significant abnormal findings of ECG, laboratory parameters.
- Treatment within the previous 3 weeks with monoamine oxidase (MAO) inhibitors.
- Use of the following concomitant treatment during the study: medications causing QT prolongation (e.g. amiodarone, droperidol, erythromycin); medications causing PR prolongation (e.g. digoxin); anti-psychotics (e.g. haloperidol); and protease inhibitors such as ritonavir and indinavir.
- Hormonal treatment (e.g. estrogen, oral contraceptives) which had started within 3 months of study entry.
- Bowel disease causing malabsorption.
- Significant liver disease, defined as active hepatitis or elevated liver enzymes) 3 times the upper boundary of the normal range.
- Significant renal disease, defined as BUN and/or creatinine) 3 times the upper boundary of the normal range clearance.

Figure 1: Design of Study 04ACL3-001

(Source: Clinical Study Report, Page 33)

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## General Discussion of Endpoints

The primary efficacy endpoint was the change in total score of the Hamilton Depression Rating Scale (17-item scale) [HAMD-17] from baseline (the last measurement before the first dose at Visit 2) to the last visit.

Secondary efficacy endpoints were:

- Percentage of patients who show a response on the HAMD-17 at every post-baseline study visit.
- Percentage of patients who were remitters, defined as subjects who achieved a HAMD-17 total score  $\leq 7$ , at every post-baseline study visit.
- Change from baseline on the HAMD-17 Depressed Mood Item (Item 1) at every post-baseline study visit.
- Change in MADRS total score from baseline to the end of the study (Visit 8).
- Percentage of patients who showed a response on a CGI-I and PGI-I at the last study visit (Visit 8).
- Change from baseline in CGI-S at every post-baseline study visit.

- CGI-I and PGI-I score at the last study visit (Visit 8).
- Quality of Sleep Assessment at every post-baseline study visit.
- Discontinuation due to lack of efficacy.

## **Analytic Plan**

There were three analysis populations for Study 04ACL3-001- The Full Analysis Population (FA), the Safety Population (SP), and Per Protocol Population (PP).

The Full Analysis Population (FA): This population consisted of all randomized patients who received one or more doses of the study medication and had a baseline assessment as well as at least one post-baseline HAMD-17 evaluation.

The Safety Population (SP): All patients who received one or more doses of the study medication.

The Per Protocol Population (PP): All randomized patients who completed the study and had a HAMD-17 rating at the end of the study as well as had no major protocol violations.

The efficacy analyses were based on the FA population using Last Observation Carried Forward (LOCF) for imputation of missing data. The Mixed-effects Model Repeated Measures (MMRM) using an unstructured covariance matrix was used as sensitivity analysis to support the LOCF approach.

The secondary analyses of the efficacy parameters were based on the PP population.

The SP was used for the safety analysis.

The trial had a single primary null hypothesis so no adjustment for multiplicity was necessary.

The primary efficacy endpoint was compared between treatment groups by an Analysis of Covariance (ANCOVA) model including treatment, baseline measurement, and site as covariates. Treatment-by-site and treatment-by-baseline interactions were to be explored.

For the categorical secondary endpoints, remitters and responders in HAMD-17, CGI-I, and PGI-I scores, the Cochran-Mantel-Haenszel test was used to compare the two treatment arms, adjusting for site.

For the continuous secondary endpoints- change from baseline on the HAMD-17 Depressed Mood Item (Item 1) at every post-baseline study visit, change in MADRS total score from baseline to the end of the study (Visit 8), CGI-S, overall quality of sleep, trouble falling asleep and awakening during the night- an analysis of covariance model in which treatment, site, and baseline measurements were used as covariates to compare the two treatment arms. In addition, for the last three variables, a Fisher's exact test was used to analyze the data using a categorical approach.

A blinded interim analysis was performed when half of the total enrolment goal was achieved.

### 6.3 Results

#### Demographics

There were no appreciable differences in the baseline demographic characteristics of the patients in the FA population (*See Table 3 below*).

**Table 3: Baseline Characteristics of Full Analysis Population**  
 (Study 04ACL3-001)

	Trazodone Contramid N=202	Placebo N=204
<b>Gender</b>		
Female	129 (63.9%)	131 (64.2%)
Male	73 (36.1%)	73 (35.8%)
<b>Age (years)</b>		
Mean $\pm$ SD	43.8 $\pm$ 12.8	44.0 $\pm$ 13.5
Median	44.0	44.0
<b>Age Group</b>		
< 65 years	193 (95.5%)	188 (92.2%)
$\geq$ 65 years*	9 (4.5%)	16 (7.8%)
<b>Race</b>		
Asian	4 (2.0%)	3 (1.5%)
Black	41 (20.3%)	44 (21.6%)
Caucasian	139 (68.8%)	140 (68.6%)
Other	18 (8.9%)	17 (8.3%)

\*There were 7 patients who were  $\geq$  75 years of age; 2 in the trazodone group and 5 in the placebo group

## Patient Disposition

As displayed in Table 3, 30.1% of the Trazodone group discontinued from the study, while 20.9% of the placebo patients discontinued. An appreciably higher percentage of patients randomized to Trazodone discontinued due to an adverse event than those randomized to placebo (12.1% versus 2.9%). Otherwise, there were no significant disparities between reasons for discontinuation between the Trazodone and placebo group.

**Table 4: All Randomized Patients Disposition and Reasons for Discontinuation**

(Source: Clinical Study Report, Study 04ACL3-001, Page 63)

	Placebo N = 206	Trazodone Contramid® OAD N = 206	Overall N = 412
<b>Number of patients (%):</b>			
<b>Who were randomized</b>	<b>206 (100.0%)</b>	<b>206 (100.0%)</b>	<b>412 (100.0%)</b>
<b>Who received at least one dose of study medication</b>	<b>204 (99.0%)</b>	<b>202 (98.1%)</b>	<b>406 (98.5%)</b>
<b>Who Discontinued</b>	<b>43 (20.9%)</b>	<b>62 (30.1%)</b>	<b>105 (25.5%)</b>
<i>Reasons for Discontinuation:</i>			
Adverse Event	6 (2.9%)	25 (12.1%)	31 (7.5%)
Lack of Efficacy	9 (4.4%)	8 (3.9%)	17 (4.1%)
Patient Request	9 (4.4%)	11 (5.3%)	20 (4.9%)
Investigator Initiated Discontinuation <sup>1</sup>	19 (9.2%)	16 (7.8%)	35 (8.5%)
Administrative Reason	0 (0.0%)	2 (1.0%)	2 (0.5%)
<b>Who Discontinued During Titration (Visit 2-Visit 4)</b>	<b>8 (3.9%)</b>	<b>22 (10.7%)</b>	<b>30 (7.3%)</b>
<i>Reasons for Discontinuation</i>			
Adverse Event	2 (1.0%)	13 (6.3%)	15 (3.6%)
Lack of Efficacy	2 (1.0%)	1 (0.5%)	3 (0.7%)
Patient Request	2 (1.0%)	2 (1.0%)	4 (1.0%)
Investigator Initiated Discontinuation	2 (1.0%)	6 (2.9%)	8 (1.9%)
<b>Who Discontinued During Treatment Phase (Visit 5-Visit 8)</b>	<b>35 (17.0%)</b>	<b>40 (19.4%)</b>	<b>75 (18.2%)</b>
<i>Reasons for Discontinuation</i>			
Adverse Event	4 (1.9%)	12 (5.8%)	16 (3.9%)
Lack of Efficacy	7 (3.4%)	7 (3.4%)	14 (3.4%)
Patient Request	7 (3.4%)	9 (4.4%)	16 (3.9%)
Investigator Initiated Discontinuation	17 (8.3%)	10 (4.9%)	27 (6.6%)
Administrative Reason	-	2 (1.0%)	2 (0.5%)

<sup>1</sup>The investigator initiated discontinuations were mainly: patients lost to follow-up (Trazodone-11/16 and Placebo- 15/19), non-compliance (Trazodone-4/16 and Placebo-2/19), dental abscess (Trazodone- 1), and took prohibited drug (Placebo-1).

### 6.2.3 Efficacy Findings

This subsection includes data from the analysis of the FDA biometrics reviewer (Dr. George Kordzakhia, Ph.D) [See *biometrics review for more information*] and the sponsor.

#### **Primary Efficacy Analysis**

The mean HAMD-17 Total Score at baseline was 23.2 and 22.4 for patients randomized to Trazodone and Placebo, respectively. The mean change from baseline in HAMD-17 Total Score at Week 8 was 11.17 for Trazodone and 9.25 for Placebo. A statistically significant treatment effect of -1.93 (95% CI, -3.42, -0.43) in favor of Trazodone was observed. The treatment effect of Trazodone was larger than that of placebo across all visits (See *Figure 2*) with the largest treatment difference observed at Week 3-4 (See *Table 5 below*). The LOCF analysis indicated that a statistically significant difference between Trazodone versus Placebo was achieved within the first 7 days of treatment initiation ( $p= 0.0049$ ).

The sponsor also reports that MMRM analysis was consistent with the LOCF analysis, with a change in HAMD-17 Total Score from baseline to last visit in favor of Trazodone with a statistically significant difference ( $p=0.0055$ ). The sponsor also reports that the statistically significant difference between Trazodone and placebo in reference to the primary efficacy endpoint was also supported by a non-parametric ANCOVA ( $p=0.0045$ ). Furthermore, the sponsor performed a Time Weighted Average analysis with results consistent with the previously mentioned analytic approaches used.

**Table 5: Analysis Results of HAMD-17 Total Scores**

[Mean Change from Baseline to Visit with missing data imputed by LOCF]  
 (Source: FDA Biometrics Reviewer’s Analysis)

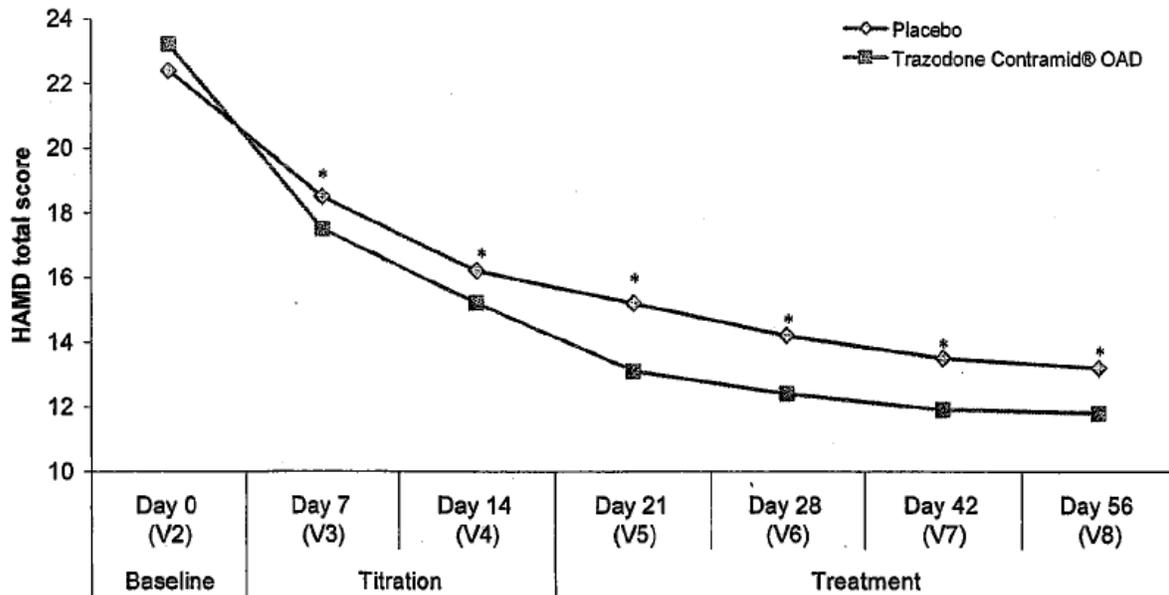
Week (Visit)	Placebo	Trazodone	Treatment Difference: Trazodone - Placebo	
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	95% CI
Week 1 (3)	-3.88 (0.35)	-5.29 (0.36)	-1.41 (0.50)	(-2.38, -0.43)
Week 2 (4)	-6.30 (0.42)	-7.69 (0.43)	-1.39 (0.59)	(-2.55, -0.23)
Week 3 (5)	-7.23 (0.45)	-9.82 (0.46)	-2.59 (0.64)	(-3.84, -1.33)
Week 4 (6)	-8.21 (0.49)	-10.38 (0.50)	-2.17 (0.69)	(-3.52, -0.81)
Week 6 (7)	-8.97 (0.49)	-10.95 (0.50)	-1.98 (0.69)	(-3.33, -0.62)
Week 8 (8)	-9.25 (0.54)	-11.17 (0.55)	-1.93 (0.76)	(-3.42, -0.43)

Note: The reported 95% CIs are nominal and not adjusted for multiplicity.

**Figure 2: HAMD-17 Total Score by Visit**

**(LOCF, Full Analysis Population)**

**[Source: Study 04ACL3-001, Clinical Study Report, Page 76]**



Note: \*Statistically Significant in favor of Trazodone versus Placebo ( $p < 0.05$ ) based on absolute change from baseline

### 6.3 Cross-cutting Issues

#### 6.3.1 Subgroup Analyses

George Kordzakhia, PhD (The FDA Biometrics Reviewer for this NDA) conducted subgroup analyses of the primary efficacy results and below are a summary of his findings (See biometrics review for details):

Age (See Table 6): For subjects younger than 65 years of age, the treatment effect was in favor of Trazodone and the difference was statistically significant. In the patients aged 65 years and above, though there seemed to be a difference in favor of Trazodone, albeit not statistically significant, the reliability is questionable due to the small sample size.

**Table 6: Subgroup Analysis by Age Group: HAMD-17 Total Score**

[Mean Change from Baseline to Endpoint/Last Visit- Study 04ACL3-001]

		Placebo	Trazodone
<b>Younger than 65 years</b>			
No patients		188	193
Change from Baseline	LS Mean (SE)	-9.41 (0.56)	-11.28 (0.57)
Placebo-adjusted difference	LS Mean (SE)	NA	-1.86 (0.79)
	95% CI	NA	(-3.42, -0.31)
<b>65 years or older</b>			
No patients		16	9
Change from Baseline	LS Mean (SE)	-3.18 (2.67)	-11.14 (3.63)
Placebo adjusted difference	LS Mean (SE)	NA	-7.96 (5.27)
	95% CI	NA	(-19.89, 3.97)

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Gender (See Table 7): The treatment effect is numerically in favor of Trazodone in both gender subgroups. The effect size seems larger in females than males. The difference between both arms is not statistically significant in males probably because of the smaller sample size of the males.

**Table 7: Subgroup Analysis by Gender: HAMD-17 Total Score**

[Mean Change from Baseline to Endpoint/Last Visit- Study 04ACL3-001]

		Placebo	Trazodone
<b>Female</b>			
No patients		131	129
Change from Baseline	LS Mean (SE)	-9.22 (0.71)	-11.22 (0.72)
Placebo-adjusted difference	LS Mean (SE)	NA	-2.00 (0.98)
	95% CI	NA	(-3.93, -0.06)
<b>Male</b>			
No patients		73	73
Change from Baseline	LS Mean (SE)	-9.71 (0.90)	-10.92 (0.98)
Placebo adjusted difference	LS Mean (SE)	NA	-1.21 (1.29)
	95% CI	NA	(-3.76, 1.33)

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Race (See Table 8): The Caucasian racial subgroup was the only racial subgroup in which the treatment effect appeared numerically in favor of Trazodone compared to

placebo; however, reliable conclusions can not be made about the other racial subgroups because of their appreciably smaller sample sizes.

**Table 8: Subgroup Analysis by Race: HAMD-17 Total Score**

[Mean Change from Baseline to Endpoint/Last Visit- Study 04ACL3-001]

		Placebo	Trazodone
<b>Black</b>			
No patients		44	41
Change from Baseline	LS Mean (SE)	-14.19 (1.61)	-13.25 (1.71)
Placebo-adjusted difference	LS Mean (SE)	NA	0.93 (1.96)
	95% CI	NA	(-2.99, 4.85)
<b>White</b>			
No patients		140	139
Change from Baseline	LS Mean (SE)	-7.89 (0.70)	-10.86 (0.73)
Placebo adjusted difference	LS Mean (SE)	NA	-2.97 (0.89)
	95% CI	NA	(-4.73, -1.22)
<b>Other</b>			
No patients		20	22
Change from Baseline	LS Mean (SE)	-10.68 (2.35)	-10.35 (2.38)
Placebo adjusted difference	LS Mean (SE)	NA	0.33 (3.13)
	95% CI	NA	(-6.09, 6.75)

Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

### 6.3.2 Dose Response

Study 04ACL3-001 used an optional titration design; hence, it is less informative for dose-response relationships.

### 6.3.3 Secondary Endpoints

- Percentage of patients who show a response on the HAMD-17 at every post-baseline study visit:

From baseline to last study visit, 54% of the patients in the trazodone group were judged as responders versus 41.2% of those in the placebo group.

- Percentage of patients who are remitters:

There was statistically significant difference in percentage of remitters in favor of Trazodone during Visit 5, 6, and 7. For the last visit (Visit 8), there was a 9% increase in remitters among the placebo group such that the difference between the Trazodone and placebo group was not statistically significant (Trazodone 35.6% versus Placebo 31.9%,  $p = 0.218$ ).

## Clinical Review

{Victor Crentsil, M.D., M.H.S.}

{NDA 22-411}

{Trazodone Contramid<sup>®</sup> OAD, Extended-Release Caplet}

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- Change from baseline on the HAMD-17 Depressed Mood Item (Item 1) at every post-baseline study visit:

With the exception of Visit 7, there was a statistically significant reduction in HAMD-17 in the Trazodone group compared to Placebo from baseline to every post-baseline study visit.

- Change in MADRS total score from baseline to the end of the study (Visit 8):

There was a statistically significant reduction from baseline MADRS total score in the Trazodone compared to the Placebo group (Trazodone- 50.9% versus 44.3% in the Placebo group).

- Percentage of patients who show a response on a CGI-I and PGI-I at the last study visit (Visit 8):

CGI-I responders were patients who by the assessment of the investigators were “much improved” or “very much improved” at the last study visit. Though the difference was not statistically significant, the percentage of responders in the Trazodone group was higher than that of the Placebo group (53.3 % versus 48.6%).

PGI-I responders were patients who by the assessment of the investigators were “much improved” or “very much improved” at the last study visit. Though the difference was not statistically significant, the percentage of responders in the Trazodone group was higher than that of the Placebo group (51.1 % versus 43.7%).

- Change from baseline in CGI-S at every post-baseline study visit:

There was a progressive decline in the mean CGI-S from baseline to the last visit in both treatment arms. The difference between both treatment arms was statistically significant at the last visit.

- CGI-I and PGI-I score at the last study visit (Visit 8):

There was no statistically significant difference between Trazodone and Placebo at the last visit for both CGI-I and PGI-I.

- Quality of Sleep Assessment at every post-baseline study visit:

For overall sleep quality, there was a statistically significant difference between Trazodone and Placebo, in favor of Trazodone. Generally, patients on Trazodone had less trouble falling asleep than those on placebo, and the difference was statistically significant at the last visit. Patients randomized to Trazodone had a statistically significant less awakening during the night compared to placebo.

- Discontinuation due to lack of efficacy:

The percentage of patients who discontinued due to lack of efficacy was comparable between both groups. Whereas 4.0% of the patients in the Trazodone group discontinued due to lack of efficacy, 4.4% of placebo discontinued due to the same reason.

#### 6.3.4 Effect Size

The effect size of Trazodone Contramid® by the primary efficacy endpoint (HAMD-17 -1.93] is comparable to that of previous studies for the proposed indication.

#### 6.3.5 Long-term Efficacy

Though trazodone has been marketed for depression for several years, this submission does not provide information on the long-term efficacy of Trazodone Contramid.®

#### 6.3.6 Pediatric Development

Trazodone Contramid® has not been studied in the pediatric population. The sponsor has requested a partial waiver for pediatric studies in infants and children 6 years and below, and deferral for pediatric assessment in children aged 7-11 years of age since they believe their product is ready for approval for adult use but pediatric studies have not yet been completed. (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

## 6.4 Efficacy Conclusions

Based on the results of the pivotal study (04ACL3-001), Trazodone Contramid® OAD demonstrated superior antidepressant efficacy against placebo evidenced by the analysis of the primary efficacy endpoint (Change in HAMD-17 Total Score from baseline). Other analytic approaches (MMRM and TWA) supported the results of the primary efficacy analysis. Majority of the results of secondary efficacy endpoints were consistent with that of the primary efficacy endpoint.

## 7 Review of Safety

### Safety Summary

The integrated review of safety did not reveal any reason to preclude recommendation of approval, from a clinical safety perspective. The person-time exposure to trazodone in this sNDA was less than 100 person-years; however, it was not a significant limitation since the sponsor referenced the accumulated safety data on trazodone HCL in the literature. No serious adverse events (SAEs) or fatalities were reported for the Phase I studies. For the Phase III study, one death (a patient randomized to placebo) and 4 non-fatal SAEs were reported. The SAEs are suicide attempt, viral pericarditis, bacterial endocarditis, and pulmonary embolism; none of which is directly attributable to exposure to trazodone without confounding. The propensity of trazodone to prolong QT interval and induce cardiac arrhythmia appears to be consistent from multiple sources of evidence.

### 7.1 Methods

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

The data used to evaluate safety was obtained from a single Phase III study and 9 open-label or pharmacokinetic studies submitted by the sponsor. All the subjects or patients who received at least one dose of the study treatment were included in the analysis of safety. Overall, 454 subjects/patients were exposed to Trazodone Contramid® (See Section 7.2.1 and Table 9 for further details on safety population).

The single pivotal trial (04ACL3-001), which contributed majority of the data for the evaluation of safety, was a two-arm, multicenter, randomized double-blind, placebo-controlled, parallel-design study. The safety population consisted of 406 subjects (202 in the Trazodone Contramid OAD arm and 204 in the Placebo arm) who received at least one dose of medication. The dose range was 150 to 375 mg once daily, with approximately majority of the patients exposed to the 300-mg daily dose (*See Table 12*). Therefore, an adequate number of patients were exposed to clinically relevant doses.

The Phase I studies were all open-label studies. Approximately 252 healthy human volunteers were exposed to Trazodone Contramid® in the pharmacokinetic studies (*See Table 10 for details on subjects involved in Phase I studies*). Eight of the 9 studies were single dose studies; Study 04ACL108 was the only Phase I study that involved exposure to multiple doses of Trazodone Contramid.

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

Adverse events (AEs) were verbally elicited and recorded in a source document and the Adverse Event page of the Case Report Form. AEs that occurred within 30 days of the last dose of treatment were also identified and recorded. MedDRA version 9.1 terminology was used to classify AEs. A comparison of verbatim and MedDRA preferred terms of adverse events was conducted and was found to be adequate. In addition, an audit of the submission in which the data on the Case Report Forms, Narrative Summaries, and JMP Listings of a random sample of patients did not reveal any inconsistencies in the data submitted.

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

No pooling of data across studies was done because the submitted data consisted of a single Phase III trial, which had design features that precluded pooling it with the 9 Phase I studies.

## **7.2 Adequacy of Safety Assessments**

In general, the safety assessments were adequate. Though the 10 studies included in the safety assessment were short-term studies, trazodone (the active pharmaceutical ingredient of Trazodone Contramid®) has a long history of human exposure and its safety profile is well-characterized.

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

### **Demographics:**

The Phase I study populations consisted of non-smoking mostly Caucasians (98.3%) healthy male and female subjects with a mean age of  $29.4 \pm 11.9$  years.

In the pivotal study, except for patients  $\geq 65$  years of age (7.8%- Placebo; 4.5%- Trazodone Contramid® OAD), the baseline demographic characteristics of the safety population is similar between Trazodone Contramid OAD and placebo.

The average age was 43.9 years and 6.2% were at least 65 years of age. Only 7 subjects were 75 years of age or older. Sixty-four percent was female and the racial breakdown is Caucasians (69%), Blacks (21%), Asians (2%) and others (9%).

**Table 9 : Baseline Characteristics and Demographics of Safety Population**

(Source: Clinical Study Report, Study 4ACL3-001, Page 91)

	Placebo N = 204	Trazodone Contramid® OAD N = 202	Overall N = 406
<b>Gender</b>			
Female	131 (64.2%)	129 (63.9%)	260 (64.0%)
Male	73 (35.8%)	73 (36.1%)	146 (36.0%)
<b>Age (years)</b>			
Mean ± SD	44.0 ± 13.5	43.8 ± 12.8	43.9 ± 13.1
Median	44.0	44.0	44.0
<b>Age groups</b>			
< 65 years	188 (92.2%)	193 (95.5%)	381 (93.8%)
≥ 65 years <sup>1</sup>	16 (7.8%)	9 (4.5%)	25 (6.2%)
<b>Race</b>			
Caucasian	140 (68.6%)	139 (68.8%)	279 (68.7%)
Black	44 (21.6%)	41 (20.3%)	85 (20.9%)
Other	17 (8.3%)	18 (8.9%)	35 (8.6%)
Asian	3 (1.5%)	4 (2.0%)	7 (1.7%)

<sup>1</sup>Seven of the patients were ≥ 75 years of age; 5 were in the placebo group and 2 in trazodone group

**Table 10: Demographics of Safety Population for Phase I Studies**

<b>Characteristics</b>	<b>Number of Subjects in Category</b>	<b>Percentage of Subjects in Category</b>
<b>Gender</b>		
Female	103	39.8%
Male	156	60.2%
<b>Age (years)</b>		
Mean $\pm$ SD	29.0 $\pm$ 11.8	NA
Median	23.5	NA
Min, Max	18, 72	NA
<b>Age Group</b>		
< 65 years	257	99.2%
$\geq$ 65 years	2	0.8%
<b>Race</b>		
American Hispanic	1	0.4%
Black	2	0.8%
Caucasian	255	98.5%
Oriental	1	0.4%
<b>BMI (kg/m<sup>2</sup>)</b>		
Mean $\pm$ SD	23.9 $\pm$ 2.5	NA
Median	24.1	NA
Min, Max	18.4, 29.7	NA

\*NA= Not Applicable

### Extent of Exposure

Exposure in the pharmacokinetic studies lasted from 1 to 8 days. In the pharmacokinetic studies, 8 were single dose studies and one multiple dose steady state study (04ACL108). The dose range for the Phase I studies was 75 to 375 mg daily.

The person-years exposure in the Trazodone Contramid® group of the pivotal study was approximately 25.9 and that of the placebo group was 28.8. The mean duration of exposure to Trazodone Contramid® OAD was 46.8 days and that for placebo- 51.6 days. While 23.3% of the subjects were exposed to Trazodone Contramid® OAD for

more than 56 days, 29.9% were exposed to placebo for more than 56 days. The dose range for the Phase I studies was 150 to 375 mg daily.

The mean dose of Trazodone Contramid® OAD taken was 310 mg (n=175) and that of placebo was 355 mg (n=193). Approximately 66.8% of the subjects on Trazodone Contramid® OAD tolerated the 300-mg and above dose level and 88.7% of subjects on placebo tolerated 300 mg and above.

**Table 11: Safety Population- Extent of Exposure**

(Source: Clinical Study Report, Study 4ACL3-001, Page 92)

<b>Days of Therapy</b>	<b>Trazodone Contramid (N=202)</b>	<b>Placebo (N=204)</b>
1-7	13 (6.4%)	3 (1.5%)
8-14	8 (4.0%)	6 (2.9%)
15-21	7 (3.5%)	5 (2.5%)
22-28	9 (4.5%)	3 (1.5%)
29-35	7 (3.5%)	8 (3.9%)
36-42	5 (2.5%)	6 (2.9%)
43-49	6 (3.0%)	7 (3.4%)
50-56	100 (49.5%)	105 (51.5%)
> 56	47 (23.3%)	61 (29.9%)
Mean (SD)	46.8 (17.56)	51.6 (12.75)
Q1	47.0	54.0
Median	56.0	56.0
Q3	56.0	57.0
Min/Max	1/64	1/74
<b>Total Person-Days</b>	<b>9448</b>	<b>10526</b>
<b>Reviewer calculated person-years*</b>	<b>25.9</b>	<b>28.8</b>

<sup>†</sup>Days of therapy were calculated as: [last dose date-first dose date +1]; the last date of assessment was used in place of the last dose date, if the last dose date was missing.

\*Reviewer calculated person-years= person-days provided by sponsor divided by 365 days

**Table 12: Number of Subjects Exposed to Various Dosages of Trazodone Contramid in Phase I Studies**

**[Note: some subjects were exposed to more than one dose]**

Dose (mg/day)	Number of Subject Exposed
75	43
150	83
300	245
375	44

*Reviewer's Comment: In general, although exposure to clinically relevant doses was adequate, exposure of geriatric patients to Trazodone Contramid® was limited. These disparities in exposure durations between Trazodone Contramid® and placebo may be explained by the earlier drop out for subjects on Trazodone Contramid® OAD than placebo. It seems, in general, Trazodone Contramid® was less tolerated than placebo and patients in clinical practice are more likely to terminate treatment from AEs and not lack of efficacy.*

#### 7.2.2 Explorations for Dose Response

For the pharmacokinetic studies, Study 04ACL105 explored treatment emergent adverse events by dose (See Section 7.5.1 for details).

Majority (61%) of the patients in the pivotal study were on the 375 mg dose during the randomized treatment phase. Less than 16% of the patients were exposed to each of the other dose levels during the randomized treatment phase; hence, there was not adequate diversity of dose for a reliable exploration of dose response.

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

See Pharmacological/ Toxicological review for any relevant animal or *in vitro* testing.

#### 7.2.4 Routine Clinical Testing

The routine clinical testing was adequate for this sNDA.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolism, clearance, and interaction profile of trazodone HCL is well characterized. No further studies were performed to assess the metabolism, clearance, and interaction profile of Trazodone Contramid.® The metabolic, clearance, and interaction characteristics of trazodone HCL is most likely applicable to Trazodone Contramid.®

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

Serzone (Nefazodone), which is in the same class of trazodone, has been associated with hepatotoxicity including liver failure. The sale of serzone was discontinued in the United States in 2004. Unlike nefazodone, for which non-clinical studies including human *in vitro* assays have demonstrated its hepatotoxicity, trazodone has not been demonstrated to be hepatotoxic. Indeed, the effects of nefazodone on the human biliary system has not been demonstrated in trazodone.

## 7.3 Major Safety Results

No serious adverse events (SAEs) or fatalities were reported for the Phase I studies. For the Phase III study, one death and 5 non-fatal SAEs ( in 4 patients) were reported.

### 7.3.1 Deaths

Patient # 127011: The only death in the pivotal study was a patient in the placebo group. The patient was a 43-year-old black male with a history of unipolar major depression, stomach ulcer, bronchitis, chronic low back pain syndrome, rotator cuff tear, and a gun shot wound to his femur (in the past). On his last study visit it is reported that he had moderate depression without suicidal ideation, mild to moderate low back pain, and sinus tachycardia on his ECG. The patient had stopped taking the study drug and did not come for his scheduled subsequent follow-up visit. The sponsor reports that the sister of the patient called, informing the study of the death of the patient, which occurred 2 days after his last study visit and 20 days after dose of study medication. The cause of death is yet to be known and the sponsor claims the family had not consented to the release of autopsy findings.

*Reviewer's Assessment of Death: The sponsor reported that numerous attempts to obtain information from the patient's family has not be successful; hence, the sponsor could not provide any further details on the probable cause of death of patient #*

*127011. The patient was randomized to placebo. Therefore, trazodone is unlikely to have contributed to the death of this patient.*

### **7.3.2 Nonfatal Serious Adverse Events**

The five non-fatal SAEs were reported by four patients during the randomized phase of Study 04ACL3-001.

Patient # 001-021-1089: A 52-year-old postmenopausal Caucasian female with a medical history of carpal tunnel surgery in 2007. She entered the study with a diagnosis of unipolar MDD and attempted suicide twice during the period she was involved with the study. The subject was randomized to placebo. Her first suicide attempt was by taking 20 tablets of aspirin, which was initially unnoticed because she neither reported it nor sought health care for it. She attempted suicide for the second time by ingesting 40 tablets of aspirin in addition to drinking 1-2 bottles of wine. The next day she was sent to the emergency room, observed and discharged without hospitalization. She was discontinued from the study due to the suicide attempts.

Patient # 001-022-1097: A 42-year-old Caucasian female with a past medical history of diabetes mellitus, hyperlipdemia, tubal ligation and cholecystectomy who was started on Trazodone Contramid® for unipolar MDD. Her concomitant medications included Lipitor, metformin, diamicon, and advil. On day 43 of trazodone treatment, she experienced difficulty in breathing and was treated and discharged from an emergency room. On Day 45, she returned to the hospital because she felt unwell and was diagnosed with viral pericarditis. She had leucocytosis and an ultrasound revealed that she had a moderate pleural effusion. After 19 days of inpatient treatment, she was discharged and her illness was considered resolved.

Patient # 111-021-1176: A 22-year-old Black male, who has a past medical history of headaches and seasonal allergies, was hospitalized on treatment day 12, after he was randomized to Trazodone for the management of unipolar major depressive disorder. He was hospitalized with chief complaints of a fever and a rash. He reportedly stated in the hospital that he had been ill for 2 weeks. He later became unstable in the hospital and was transferred to the intensive care unit. He was diagnosed with endocarditis when his echocardiogram showed vegetations. The patient however denied intravenous drug abuse. He was also found to have a thyroid disorder (reported by the sponsor to be hyperthyroidism but was treated with synthroid, so the exact diagnosis is unclear), a coagulopathy, and methicillin-resistant staphylococcal bacteremia, elevated liver enzymes, chest x-ray changes suggestive of septic embolism, rhabdomyolysis, and acute renal failure during the hospitalization. Other than the persistently positive blood culture, the other abnormalities the patient developed had resolved when he was transferred to another hospital. In the second hospital, the patient underwent excision of a large vegetation on his mitral valve and debridement of a mitral valve abscess as well

as mitral valve repair. He subsequently had an improvement in his ejection fraction from 35-40% to 60% and his blood culture became negative. He was then discharged home for outpatient follow-up. The patient was discontinued from the study the day he was admitted to the first hospital.

Patient # 128-002-1014: A 56-year-old Caucasian male with an extensive medical and surgical history including obesity (weight 360 pounds), musculoskeletal pain, right leg nerve damage, right knee repair, cholecystectomy, and hip surgery. His study medication was Trazodone Contramid.® On treatment Day 29, he was hospitalized for the management of multiple pulmonary emboli after two episodes of chest pain associated with dysnea and diaphoresis on the previous day. Deep vein thrombosis was excluded and he required treatment for an elevated blood pressure and blood sugar. He was discontinued from study treatment on the day before hospitalization.

*Reviewer's Comment: the SAEs elicited above are suicide attempt, viral pericarditis, bacterial endocarditis, and pulmonary embolism. Patient # 001-021 was randomized to placebo therefore a link between trazodone and her suicidal attempts are unlikely. The relationship between exposure to Trazodone Contramid® and viral pericarditis is confounded by the patient's medical history of diabetes. Immune defects associated with diabetes, may increase the risk for a viral infection in a diabetic such as Patient # 001-022. Therefore, the viral pericarditis is more likely to have occurred because of her history of diabetes, especially if it was poorly controlled, than exposure to Trazodone Contramid. Patient# 111-02's endocarditis may have preceded the initiation of Trazodone treatment. He reportedly stated that he had been ill for 2 weeks, while the treatment with trazodone was initiated 12 days prior to hospitalization. With doubt as to the whether his endocarditis preceded exposure to Trazodone and the unclear biological plausibility of a link between trazodone and endocarditis, attributability of the endocarditis to exposure to Trazodone Contramid is unlikely. Patient #128-002 has risk factors for pulmonary embolism that confounds the relationship between Trazodone Contramid® exposure and pulmonary embolism. The patient is morbidly obese and with right leg nerve damage and musculoskeletal pain it is likely that the patient is physically inactive or sedentary. These factors may have contributed to his pulmonary embolism and confounds a link between trazodone and pulmonary embolism.*

## **Dropouts and/or Discontinuations**

In the Phase I studies, 12 (4.8%) of the subjects discontinued because of AEs.

In the pivotal study, of the 412 patients who were randomized, 206 received Trazodone Contramid® OAD and the other 206, placebo. One hundred and five patients (25.5%) discontinued treatment before the end of the study. The most common reason for discontinuation from treatment was an investigator-initiated reason (8.5%) and adverse

events (7.5%). Investigator-initiated reasons for discontinuation were mainly loss to follow-up and non-compliance.

During the titration period, 22 (10.7%) of the Trazodone Contramid® OAD group versus 8 (3.9%) of the Placebo group discontinued from the study. Among the 15 patients who discontinued from the study due to AEs during the titration period, 13 were from the Trazodone Contramid® OAD group and 2 from the placebo group. During the treatment phase 16 patients discontinued due to AEs; 12 were from the Trazodone Contramid® OAD group and 4 from the Placebo group.

### **Significant Adverse Events**

Below are significant adverse events reported on the Case Report Forms (CRFs) of the other 8 open-label studies:

**Study 04ACL101** (a randomized four-way crossover pilot study to compare the relative bioavailability of two prototype once-a-day trazodone hydrochloride products and two marketed reference products following an equivalent daily dose administration under fasting conditions in healthy volunteers), 2 subjects became hypotensive on treatment and one of them had a convulsion with the hypotension.

Subject #2 (South Africa site- data obtained from CRF): A 23-year-old Caucasian male with a predose BP 137/79 and pulse 55 beats per minute (bpm) underwent study procedures uneventfully on the first study day. During the second study day (one week after the first), he had a transient period of reduction in blood pressure (BP 122/57 to nadir of 94/50) and bradycardia (nadir of 47 bpm). It seems he had a convulsion with the hypotension, so he was withdrawn from the study. The other complaints of the patient were dizziness, nausea, and a headache.

Subject #15 (South Africa site- data obtained from CRF): A 19-year-old Caucasian female with an orthostatic change in her BP (supine BP 134/63 pulse 72 and standing BP 116/71 pulse 92) who also had a history of seasonal hay fever. She was withdrawn from the study on the first day after her BP dropped from 120/66 predose to 88/53 four hours postdose. Her concurrent pulse change was 73 bpm to 81 bpm. Her BP recovered after an apparent treatment with intravenous fluids.

**Study 04ACL103** (Canada site- data obtained from CRF) - Pilot, randomized, open-label, 4-way crossover study evaluating the effect of food on the bioavailability of trazodone CR 300mg and 150 mg in healthy volunteers):

Subject #3: A 47-year-old Caucasian male without any significant past medical history.

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AEs recorded: weakness, dizziness, nausea, abdominal pain, headache, feeling sleepy, fainting, bruise right and left arm, and cut right fifth finger. He was discontinued from treatment due to fainting (10/10/06). The lowest BP recorded was 98/64 and pulse 87bpm (9/26/06).

*Reviewer's observation: ECG showed QTc prolongation, baseline QTc 352 (9/14/06) maximum QTc 413 (10/10/06), increase in QT= 61 (about 3 hours after fainting). ECG read as from normal at baseline to incomplete bundle branch block post-baseline.*

### **7.3.5 Submission Specific Primary Safety Concerns**

The submission specific primary safety concern with exposure to trazodone is whether trazodone prolongs QTc interval or not. The Office of Surveillance and Epidemiology at FDA suggested a potential signal of QTc prolongation associated with exposure to trazodone. The Division of Cardiorrenal Products was consulted for their opinion on the need for a thorough QT study and their recommendations (See Section 7.4.5 for details).

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

The most common TEAEs in the Phase I studies were dizziness, headache, somnolence, nausea, and nasal congestion. For the Phase III study, the most frequent TEAEs with a higher occurrence rate in the trazodone group than the placebo group were somnolence/sedation (trazodone- placebo difference, 27.4%), dizziness (trazodone-placebo difference, 13%), dry mouth (trazodone-placebo difference, 12.5%), nausea (trazodone-placebo difference, 8.6%), fatigue (trazodone-placebo difference, 6.5%), headache (trazodone-placebo difference, 12.5%), constipation (trazodone-placebo difference, 6%) and blurry vision (trazodone-placebo difference, 5.5%).

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**Table 13: Treatment Emergent Adverse Events Occurring in 5% or more in the Phase I Studies**

Preferred Term	Trazodone Contramid (N=252)	
	N	%
Dizziness	70	27.8
Headache	60	23.8
Nausea	46	18.3
Somnolence	24	9.5
Nasal Congestion	13	5.2

**Table 14 : Most Frequent Treatment Emergent Adverse Events**  
 (≥ 5% of Patients on Active Treatment in Study 04CL3-001)

Preferred Term	Trazodone Contramid (N=202)	Placebo (N=204)
Somnolence/Sedation	46.0%	19.1%
Headache	33.2%	27.0%
Dry Mouth	25.2%	12.7%
Dizziness	24.8%	12.3%
Nausea	20.8%	12.7%
Fatigue	14.9%	8.3%
Diarrhea	9.4%	11.3%
Constipation	7.9%	2.0%
Back pain	5.4%	3.4%
Blurry Vision	5.4%	0.0%

Source: Clinical Study Report, Page 105. Data verified by reviewer, who re-analyzed the submitted data.

#### 7.4.2 Laboratory Findings

The section will highlight the findings of interest in this sNDA since trazodone has long history of human exposure.

In general, there was no clinically significant changes in the laboratory values in both the Phase I studies and Phase III study.

**Hematology:** While 3.4% and 4.0% of the safety population in the Phase III study had abnormal hematocrits in the placebo and Trazodone Contramid® groups respectively, none of the patients had in either group had a clinically relevant hematocrit value at any post-baseline assessment. With regard to platelet counts, 3.4% of the safety population on placebo had abnormal counts at baseline and 2.5% of those on Trazodone has abnormal counts at baseline; only 0.5% in each group had a clinically abnormal counts at any post-baseline assessment.

**Hepatic:** There were no consistent changes from baseline suggestive of trazodone-associated liver damage. There were no patients identified with hepatic transaminases increases greater than 3-fold the upper limit of normal and total bilirubin increases greater than 2-fold above upper limit of normal.

**Glucose:** There was no trend suggestive of an increased trazodone-associated tendency to glycemic events. Approximately 13.4% patients had an abnormal blood glucose level at baseline in the Trazodone group, the corresponding proportion among the patients randomized to placebo was 13.2%. In Study 04ACL3-001, 5.0% of the patients given Trazodone had an abnormal blood sugar during any of the post-baseline assessment and 8.8% of the placebo patients had an abnormal blood glucose during the same period.

#### 7.4.3 Vital Signs

In general, there were no notable changes in vital signs attributable to trazodone exposure.

The change in systolic blood pressure (SBP) among patients treated with Trazodone Contramid® was minimal and was not significant compared to the infinitesimal change among placebo patients. There was no consistent pattern of change from Visit 3 to Visit 8. While the median SBP of patients treated with Trazodone Contramid® was 118 mmHg from Visit 3 to Visit 8 that of the patients on placebo was 120 mmHg. The median absolute change from baseline in SBP among patients treated with Trazodone Contramid® ranged from -3.0 to 0.0 mmHg. In the patients treated with placebo the change ranged from -1.0 to 0.0 mmHg. Similarly, the change in diastolic blood pressure was not appreciable among both the patients treated with Trazodone Contramid® and placebo.

The change in heart rate among patients treated with Trazodone Contramid<sup>®</sup> was minimal and was not significant compared to the change among placebo patients. There was no consistent discernable change in heart rate from Visit 3 to Visit 8. While the median heart rate of patients treated with Trazodone Contramid<sup>®</sup> was 70 to 74 bpm from Visit 3 to Visit 8, that of the patients on placebo was 72 to 73 bpm. The median absolute change from baseline in heart rate among patients treated with Trazodone Contramid<sup>®</sup> ranged from -2.0 to 0.0 bpm. In the patients treated with placebo the change was 0.0 bpm.

No appreciable change in respiratory rate in both the Trazodone Contramid<sup>®</sup> group compared to the placebo group was reported.

No significant weight change from baseline was reported in both the Trazodone Contramid<sup>®</sup> group and the placebo group. While the mean ( $\pm$  standard deviation) absolute change in weight from baseline was  $0.1 \pm 2.1$  kg for the Trazodone Contramid<sup>®</sup> group, that of the placebo group was  $0.2 \pm 3.1$  kg.

#### **7.4.4 Electrocardiograms (ECGs)**

During the Phase I studies, no clinically significant ECG changes were reported.

In the Phase III study, ECGs were obtained at Visit 1 and Visit 8. Approximately 108 patients who participated in the Phase III study were reported to have ECG abnormalities, regardless of the significance of the abnormality. Displayed in Tables 15 and 16 are summaries of QT changes observed during the Phase III study.

**Table 15: Analysis of QTcF Changes in Phase III Study (04ACL3-001)**

Parameter	<i>Mean Change in QTcF from Baseline</i>		
	Placebo	Trazodone	Trazodone-Placebo Difference
QTcF (All patients)	-0.7msec 95%CI:-3.17, 1.86 (N=183)	6.1msec 95%CI: 3.11, 8.99 (N=177)	6.8 msec
QTcF (Normal ECG at baseline to Abnormal ECG at last visit)	0.4 msec 95%CI:-9.33, 10.18 (N=19)	8.3 msec 95% CI: 1.39-15.28 (N=21)	7.9 msec
QTcF (Abnormal ECG at baseline to Normal ECG at last visit)	0.9 msec 95%CI:-8.28, 10.11 (N=24)	8.0 msec 95%CI:-1.05, 17.05 (N=26)	7.1 msec
QTcF (Normal ECG at baseline to Normal ECG at last visit)	-1.7 msec 95%CI:-4.67, 1.27 (N=110)	4.5 msec 95%CI:0.91, 8.05 (N=96)	6.2 msec

*Reviewer's Comments: There seem to be a consistent trend of a small but important mean increase in QTcF from baseline in the order of magnitude of 4.5 to 8.3 mseconds among patients treated with Trazodone Contramid.® In 3 out of the 4 categories of subject ECG groups evaluated in the patients given trazodone, the 95% CI for mean change in QTcF did not include zero. On the contrary, in all 4 categories of subject ECG groups evaluated in the patients given placebo, the 95% CI for mean change in QTcF included zero. In all the patients included in this analysis, regardless of whether their ECG qualitatively remained normal or not, there was an increase in QTc attributable to trazodone exposure .*

**Table 16: Analysis of QT Status of Abnormal ECGs in Study 04ACL3-001**

(Reference: Clinical Study Report, Page 148-155)

Dose	Trazodone (N=58)		Placebo (N=50)	
	No QT Prolongation Reported	QT Prolongation Reported	No QT Prolongation Reported	QT Prolongation Reported
150 mg	10 (17%)	1 (1.7%)	1 (2%)	0 (0%)
225 mg	4 (6.9%)	0 (0%)	1 (2%)	0 (0%)
300 mg	11 (19%)	1 (1.7%)	8 (16%)	0 (0%)
325 mg	0 (0%)	0 (0%)	1 (2%)	0 (0%)
375 mg	28 (48.3%)	0 (0%)	38 (76%)	1 (2%)
unknown	3 (5.4%)	0 (0%)	0 (0%)	0 (0%)
<b>Totals</b>	<b>56 (96.6%)</b>	<b>2 (3.4%)</b>	<b>49 (98%)</b>	<b>1 (2%)</b>

*Reviewer's Comment: In the limited number of patients who had abnormal ECGs in the pivotal study, 3.4% of the patients who had abnormal ECGs in the Trazodone group had QT prolongation reported and 2% of the patients who had abnormal ECGs on placebo had QT prolongation reported. Although the numbers are small, the higher report rate of QT prolongation in the Trazodone group than in the placebo group adds to the concern for the propensity of Trazodone on prolong QT interval and potential induction of cardiac arrhythmias.*

#### 7.4.5 Special Safety Studies/Clinical Trials

Though no special safety clinical trials were conducted, the FDA's Office of Surveillance and Epidemiology (OSE) has expressed a concern for a link between exposure to Trazodone and prolonged QT as well as cardiac dysrhythmias. We consulted the Division of CardioRenal Products (DCRP) of the Office of New Drugs of FDA for an opinion on the relationship between exposure to Trazodone and prolonged QT as well as cardiac dysrhythmias and below are excerpts from the review of OSE and DCRP:

## Clinical Review

{Victor Crentsil, M.D., M.H.S.}

{NDA 22-411}

{Trazodone Contramid® OAD, Extended-Release Caplet}

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### Comments from OSE review:

“Sixty-eight per cent of the trazodone case series for Torsades, ventricular tachycardia and prolonged QT with a reported peak daily dose, were taking an off-label dose of 100mg or less, including two of the three pediatric cases. Currently, the 50mg dose of trazodone is the most widely dispensed strength followed by the 100mg dose. The off-label low doses of 100mg or less do not appear to mitigate the potential risk of QT prolongation and related arrhythmias of Torsades and ventricular tachycardia. The predominant risk factors in the DPV I case series appear to be concomitant administration of a drug metabolized by CYP3A4 and/or concomitant administration of a drug labeled for QT prolongation.

The current labeling does not address the potential risks of QT prolongation and related events such as Torsades and symptomatic ventricular tachycardia. Also unaddressed are the concomitant administration of drugs that prolong the QT interval, and drugs metabolized by CYP3A4. The current labeling is insufficient to alert health care providers to these potentially life-threatening cardiac adverse events at both labeled doses and at off-label doses of 100mg or less.”

### Comments from Cardiorenal Consult/Review:

“Trazodone does have potential for QT prolongation and pro-arrhythmic risk. Similar to some other drugs of this class (tricyclic antidepressants and re-uptake inhibitors-see reviewer’s assessments below), this seems more likely to occur in patients with other risk factors (concomitant QT prolonging drugs, drug overdose, congestive heart failure, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit CYP3A4). Although it is possible that this risk could be mitigated to some extent if the C<sub>max</sub> is lower with the controlled release formulation, the potential for QT prolongation and pro-arrhythmia exists. Since there is non-clinical evidence and QT prolongation with related AEs have been seen postmarketing including TdP with trazodone we do not believe a TQT study is required.”

*Reviewer’s Comment: The propensity of trazodone to prolong QT and induce cardiac arrhythmia appears to be consistent from multiple sources of evidence. In addition to sources detailed in the reviews from OSE and DCRP consults, there is notable data from this sNDA. In Study 04ACL103, one patient developed QT prolongation of 61mseconds. For Study 04ACL3-001, as shown in Table 15, in all the patients included in the analysis, regardless of whether their ECG qualitatively remained normal or not, there was a consistent trend of increase in QTc attributable to trazodone exposure. In the literature review submitted by the sponsor as part of this sNDA, the sponsor admits that QT prolongation and syncope have been reported in the literature on trazodone. The undersigned reviewer is therefore of the opinion that a Thorough QT (TQT) study is more likely to be positive than negative; hence, a TQT is not recommended at this time, especially since it is not necessary for the suggested labeling changes and it is not without risks to research subjects. The undersigned reviewer recommends that the*

*labeling of Trazodone Contramid<sup>®</sup> reflect its propensity to prolong QT and induce cardiac arrhythmia even at therapeutic dosages.*

#### **7.4.6 Immunogenicity**

No human immunogenicity study was conducted as part of this sNDA.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

In the pharmacokinetic studies (Study 04ACL105), the incidence of TEAE seemed to increase by dose, and the severity of TEAEs was dose-dependent except for dizziness in which the incidence of mild dizziness increased  $\geq 300$  mg/day and moderate dizziness emerged at doses  $\geq 300$  mg/day. In the dose-proportionality study (04ACL105), the dose range explored was 75 mg to 375 mg/day. TEAE with incidence  $> 5\%$  in any group of subjects were dizziness, headache, and syncope. Syncope seemed to occur when the 375 mg dose was administered as a single dose without titration. The most common ( $\geq 5\%$ ) TEAEs reported by subjects who received the 300 mg dose were dizziness, somnolence, nausea, and headache.

#### **7.5.2 Time Dependency for Adverse Events**

In general, with a few exceptions, the time-to-onset of TEAEs were shorter in the Trazodone group than the Placebo group. In the Trazodone group, except for diarrhea, the mean time-to-onset of common TEAEs was 6 to 10 days. In the Placebo group, except for diarrhea, the mean time-to-onset of common TEAEs was 9 to 13 days. For dry mouth, dizziness, somnolence/sedation, constipation, and fatigue, the mean time-to-onset were shorter in the Trazodone than the Placebo group. For nausea, headache, diarrhea, and constipation, the mean time to onset was comparable in both groups of patients. The mean time-to-onset for back pain was longer in the Trazodone than the Placebo group. The time-to-onset for blurry vision in the Trazodone group was 8.6 days; no placebo patient was reported to have complained of visual blurring.

The mean duration of TEAEs in the Trazodone group ranged from 5 days (diarrhea) to 30 days (dry mouth). TEAEs that lasted longer in Trazodone treated patients than the placebo group were dry mouth (29.9 versus 24.2 days), dizziness (12.8 versus 10.6 days), sedation/somnolence (18.6 versus 12.2 days), fatigue (28.0 versus 19.9 days),

and constipation (16.7 versus 12.8 days). Visual blurriness lasted 17.3 days on the average.

It must be noted that TEAEs with an earlier time of onset in the trazodone group versus the placebo group (dry mouth, dizziness, somnolence/sedation, constipation, and fatigue) also lasted longer in duration comparing their duration in the trazodone group to that of the placebo group.

### 7.5.3 Drug-Demographic Interactions

**Age:** The interaction between age and Trazodone TEAEs can not be reliably assessed because patients <18 years of age were not included in the submitted clinical studies and of the 406 patients included in the safety population only had 25 were aged  $\geq$  65 years.

*Reviewer's Comments:* In spite of the limited number of older adults in the study, there seemed to be an age-related premature termination from Study 04ACL3-001 due to TEAE. Despite a lower placebo-trazodone difference in percentage of patients reporting  $\geq$  1 TEAE (4.4% in the  $\geq$  60 years age group; 10.2% in the 40 to < 60 years age group; and 9.3% in the less than 40 years age group), the  $\geq$  60 years age group had the highest percentage of patients terminating prematurely due to TEAE (13.1% in the  $\geq$  60 years age group; 9.5% in the 40 to < 60 years age group; and 8.2% less than 40 years age group).

All of the 9 subjects aged  $\geq$  65 years who were randomized to Trazodone Contramid® included in the safety population experienced at least one TEAE which was possibly drug related. This contrasts with 61.2% of subjects younger than 65 years of age given Trazodone Contramid® experiencing at least one TEAE possibly drug related.

Such findings suggest that older adults may be more susceptible or less tolerant to trazodone-related AEs thus closer monitoring of older patients, especially at high dosages, may be prudent.

**Sex:** Females seemed to be more susceptible to trazodone-related TEAEs than males.

Among females in Study 04ACL3-001, there was a statistically significant placebo-trazodone difference in the number of patients with at least one TEAE (placebo-80.9% vs. trazodone-92.2%,  $p=0.01$ ),  $\geq$  1 severe TEAE (placebo-8.4% vs. trazodone-17.1%;  $p=0.04$ ),  $\geq$  1 possibly drug related TEAE (placebo-67.2% vs. trazodone-87.6%;

p<0.0001), and patients who terminated the study early due to TEAE (placebo-3.8% vs. trazodone-14.0%; p=0.0043).

In males, the only TEAE category that had a statistically significant difference between placebo and trazodone was the number of patients with  $\geq 1$  possibly drug related TEAE (placebo- 50.7% vs. trazodone-78.1%; p=0.0009).

**Race:** Though the racial diversity of the study patients were limited, Caucasians seemed to be appreciably susceptible to trazodone related TEAE. Due to the low number of non-Caucasians in the study, it is unclear if Caucasians are more susceptible than non-Caucasians.

Among Caucasians in Study 04ACL3-001, there was a statistically significant placebo-trazodone difference in the number of patients with at least one TEAE (placebo-77.9% vs. trazodone-92.8%, p=0.0006),  $\geq 1$  severe TEAE (placebo-7.1% vs. trazodone-19.4%; p=0.026),  $\geq 1$  possibly drug related TEAE (placebo-60.7% vs. trazodone-87.8%; p<0.0001), and patients who terminated the study early due to TEAE (placebo-3.6% vs. trazodone-15.8%; p=0.0005).

In Blacks and Asians, none of the placebo-trazodone differences in TEAEs was statistically significant.

#### 7.5.4 Drug-Disease Interactions

No drug-disease interaction was examined with this application.

#### 7.5.5 Drug-Drug Interactions

Drug-drug interactions were not evaluated as part of this application. As stated in approved labeling of trazodone (Desyrel®), in vitro drug metabolism studies have shown that trazodone is a CYP 3A4 substrate; hence, trazodone plasma concentration may be affected by co-administration of Trazodone Contramid with CYP3A4 inhibitors or inducers. Further details on the drug-drug interaction profile of trazodone is contained in the approved labeling for trazodone HCL (or Desyrel®).

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

No human carcinogenicity study was submitted with this sNDA.

### **7.6.2 Human Reproduction and Pregnancy Data**

Three pregnancies were reported in the Trazodone Contramid® development program. Two in the Phase I studies and one in the Phase III study. The two cases in the early phase study occurred in the same study- Study 04ACL108.

Subject #1 in Study 04ACL108 was a 25-year-old female with a prior history of a Down's Syndrome pregnancy that was electively terminated at 6.5 months gestation. For the pregnancy associated with the study for this sNDA, her pregnancy test was reported as positive at the end of the study. Her first dose of Trazodone Contramid® was 2 days prior to the first day of her last normal menses. At her last follow-up, she was 24 weeks pregnant and her pregnancy was reported to be uncomplicated so far.

Subject #29 in Study 04ACL108 was a 29-year-old female whose pregnancy test was reported as positive before the second part of the study. Her first dose of trazodone was about 3 weeks after the first day of her last menstrual period. At her last follow-up she was 24 weeks pregnant and her pregnancy was reportedly uncomplicated thus far.

Subject #127-0009-1238, Study 04ACL3-001, a 33-year-old female who was treated with 300 mg daily of Trazodone Contramid,® found to have a positive pregnancy test at her last study visit. The sponsor reports that the patient was referred to a gynecologist and was supposed to follow-up at the study site but she did not show up at her follow-up appointment and no further information is available on her pregnancy.

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

The Phase I and III studies did not include pediatric patients, therefore the impact of Trazodone Contramid® on growth was not evaluated.

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

No overdose was reported in the Phase I and III studies submitted.

The submitted data did not include information for the determination of the abuse potential of Trazodone Contramid.<sup>®</sup>

Although the Phase I and III studies submitted did not evaluate the potential for withdrawal and rebound phenomena after treatment with Trazodone Contramid,<sup>®</sup> the literature indicates that symptoms suggestive of withdrawal has been reported with trazodone. Some of the reported symptoms are agitation, anxiety, and sleep disturbance. Dose tapering has been recommended with termination of therapy with trazodone.

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

Contramid<sup>®</sup> belongs to a class of modified starches, chemically identical to starch used for food. The sponsor reports no adverse events attributable to Contramid.<sup>®</sup>

## **8 Postmarket Experience**

Trazodone Contramid<sup>®</sup> has not been approved for marketing; therefore, there is no post-marketing data accompanied this submission.

## 9 Appendices

### 9.1 Literature Review

The literature databases searched by the sponsor were Medline, PubMed, EmBase, Current Content, and Biosys. A cut-off data for publication records used was June 25, 2008. Upon request by FDA, a literature search on the cardiovascular effects of trazodone was conducted. The search was conducted by the sponsor and an independent regulatory affairs consulting firm (CanReg). Of the 656 records in English language on use in humans identified, 117 were duplicates, leaving 539 unique records. The sponsor reports that their literature review resulted in the following findings:

**Suicidality:** No report of an association between the use of trazodone and suicidal behavior was identified. Like other antidepressants, Trazodone however retains the boxed warning on suicidality.

**Priapism:** Thirteen cases of priapism associated with intake of Trazodone have been reported.

**Cardiovascular Events:** The sponsor reports that QT prolongation, syncope, and hypotension have been reported in the literature. The sponsor believes these effects were often associated with drug interaction and overdose. It is further stated that the cardiovascular effects of trazodone is more pronounced in patients with pre-existing heart disease.

**Serotonin Syndrome:** The sponsor states that several cases of serotonin syndrome has been reported with use of trazodone, especially with the use of serotonergic drugs.

**Abnormal bleeding:** Although postmarketing reports have suggested a link between drugs that interfere with serotonin reuptake and gastrointestinal bleeding, the sponsor reports that their literature review did not reveal an association between trazodone use and bleeding events.

#### **Reference (Cited by Reviewer Under Section 2.4):**

Brodie-Meijer CC, Diemont WL, Buijs PJ. Nefazodone-induced clitoral priapism. Int Clin Psychopharmacol 1999; 14:257-258

## 9.2 Labeling Recommendations

This labeling review includes sections that changes are recommended.

Change the word “Caplet” to tablet (*See recommendations of the FDA’s Office of New Drug Quality Assessment*).

### Highlights of Prescribing Information

#### Dosage and Administration

*Add that Trazodone Contramid should be taken in the evening on an empty stomach, before supper/dinner (See reviewer’s comments under 4.4 Clinical Pharmacology).*

#### Warning and Precautions:

*Add that Trazodone has been associated with prolonged QT interval, ventricular tachycardia, and Torsade de Pointes.*

#### Adverse Reactions

*Change incidence > 5% to incidence  $\geq$  5%. Start the list with somnolence or sedation*

#### Use in Specific Populations

*Add Geriatric: Caution should be used (8.5)*

### Full Prescribing Information

#### 2 Dosage and Administration

*Add that Trazodone Contramid® should be taken in the evening on an empty stomach, before supper/dinner (See reviewer’s comments under 4.4 Clinical Pharmacology).*

#### 5.1 Warnings- Clinical Worsening and Suicide Risk

*Add years to statement of ages in the paragraph.*

#### 5.4 Use in patients with heart disease

*Modify this section minimizing the information on QT prolongation and cardiac arrhythmia since it is recommended that the information needs its own subsection.*

*Create a new subsection under Section 5 on QT prolongation and Cardiac Arrhythmia and put details on available data on the subject matter under this subsection.*

## 6.1 Clinical Studies Experience

*In Table 2, combine somnolence with sedation and make it the first item in the table.*

### Adverse Events:

*Remove (b) (4) under Renal and Urinary Disorders and leave the clearer description of the condition- "excessive frequent urination."*

## 6.2 Postmarketing Experience

*Under cardiovascular system effects add Torsade de Pointes and delete the phrase (b) (4) at the end of the paragraph.*

## 14 Clinical Studies

*Modify the third sentence of the third paragraph to read "Of this population, 25 patients were 65 years old or older and 9 of the 25 received Oleptro™."*

*Remove Figure 1 and 2.*

*Remove the phrase (b) (4) from the beginning of the last paragraph, i.e., the paragraph on sleep quality, because there were visits where the difference had a p-value >0.05.*

## 17.2 General Information for Patients

*Under "Patients should be warned that:" add language to communicate the potential for cardiac arrhythmia, especially for patients with pre-existing cardiac disease as well as those on concomitant drugs that prolong QT or inhibit CYP 3A4.*

## 17.3 Supplemental Patient Material

### Medication Guide

*Under "What are the rare but important side effects of Oleptro™?" Add information on QT prolongation and cardiac arrhythmias.*

## 9.3 Advisory Committee Meeting

An advisory committee meeting will not be necessary since there are no newly recognized safety issues in this sNDA and the efficacy results are not disputed.

## Data Audit

**Table 17: Results of Audits of Case Report Forms, Narrative Summaries, and JMP Adverse Events Listings of Study 04ACL3-001**

ID	Case Report Form AEs	Narrative Summary	JMP AE listing
101001	Dizziness, nausea, chemical taste, dry mouth, daytime somnolence	Dizziness, nausea Somnolence, Chemical taste, Dry mouth	Dizziness, nausea, chemical taste, dry mouth, daytime somnolence
107014	Pinched nerve in the neck, muscle ache generalized, agitation, nausea, dry mouth, heart burn, insomnia, anxiety worsened, chapped lips	Anxiety, insomnia, agitation, heart burn, nausea, dry mouth, generalized muscle aches	Pinched nerve in the neck, muscle ache generalized, agitation, nausea, dry mouth, heart burn worsened, insomnia, anxiety worsened, chapped lips
006005	Dizziness, aching all over, tremor, short of breath, weakness in ankles, swollen ankles, forgetfulness, fall	Weakness in ankle Dizziness Tremors, Fall General aches Shortness of breath Forgetfulness Swelling of ankle	Dizziness, aching all over, tremor, short of breath, weakness in ankle, swollen ankles, forgetfulness, fall
103006	Bilateral ear ache/infection, sore throat, headache,	Sore throat Headache Bilateral ear ache	Bilateral ear pain/infection, sore throat, headache
103001	Nausea, nasal congestion, headache, dizziness	Headache Nausea Dizziness Nasal congestion	Nausea, nasal congestion, headache, dizziness
108005	Eye twitch, groggy, sedation, vivid dreams, slowed speech, headache, agitated, hypothyroidism	Hypothyroidism Eye twitch, Agitation Grogginess Sedation, Headache Vivid dreams Slowed speech	Eye twitch, groggy, sedation, vivid dreams, slowed speech, headache, agitated, hypothyroidism
111021	MRSA septicemia, endocarditis, acute renal failure, pain, hyperthyroidism, left ventricular dysfunction, hyperphosphatemia,	Endocarditis, hyperthyroidism, MRSA bacteremia, acute renal failure, rhabdomyolysis,	MRSA septicemia, endocarditis, acute renal failure, hyperthyroidism, left ventricular dysfunction, pain, hyperphosphatemia,
105027	Blurred vision, heaviness in legs, Dry mouth, Ringing in ears, Poor coordination, Constipation, Muscle pain, Rash on rt. Leg and stomach, floaters in lt. eye, ringing in ears,	Poor co-ordination Blurred vision, Dry mouth, Tinnitus, Constipation, Skin rash Leg heaviness, muscle pain	Heaviness in legs, dry mouth, ringing in ears, poor coordination, constipation, muscle pain, rash on rt leg/stomach, ringing in ears, c/o floater in left eye.
106012	Dizziness, poor coordination, decreased blood pressure, difficulty concentrating	Dizziness, poor coordination, low blood pressure, difficulty concentration	Dizziness, poor coordination, decreased blood pressure, increased difficulty concentrating
107008	Agitation Elevated systolic "BP"	-Agitation -Increased systolic "blood pressure"	Agitation Elevated systolic

Clinical Review  
{Victor Crentsil, M.D., M.H.S}  
{NDA 22-411}  
{Trazodone Contramid® OAD, Extended-Release Caplet}

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/s/

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Victor D Crentsil  
5/1/2009 06:52:31 PM  
MEDICAL OFFICER

Gwen Zornberg  
5/1/2009 07:51:13 PM  
MEDICAL OFFICER

I concur with Dr. Crentsil that based on absence  
of new safety concerns in the 9 Phase  
I Clinical Pharmacology studies and the one positive  
flexible dose RCT, there appear to be no  
clinical issues that would preclude approval.



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 6, 2009

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Bill Bender  
Regulatory Project Manager  
Division of Psychiatry Products

Subject: QT-IRT Consult to NDA 22411

This memo responds to your consult to us dated 9 Feb 2009 regarding QT prolongation and pro-arrhythmic potential for Trazodone under NDA 22411, sponsored by Labopharm. The QT-IRT received and reviewed the following materials:

- Your consult
- OSE Review
- ECG summaries from the Study Report 04ACL3-001 (NDA 22411)

**Question 1: Please review the attached data provided in the OSE review and relevant data, including ECG waveforms, from NDA 22-411 (Trazodone Extended Release Caplets for Unipolar Major Depression), available in the EDR. Please comment on the potential for trazodone to prolong the QT interval and/or induce cardiac dysrhythmias, and whether a thorough QT study is warranted?**

Trazodone does have potential for QT prolongation and pro-arrhythmic risk. Similar to some other drugs of this class (tricyclic antidepressants and re-uptake inhibitors-see reviewer's assessments below), this seems more likely to occur in patients with other risk factors (concomitant QT prolonging drugs, drug overdose, congestive heart failure, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit CYP3A4). Although it is possible that this risk could be mitigated to some extent if the C<sub>max</sub> is lower with the controlled release formulation, the potential for QT prolongation and pro-arrhythmia exists.

Since there is non-clinical evidence and QT prolongation with related AEs have been seen post-

marketing including TdP with trazodone we do not believe a TQT study is required.

**Question 2: Please comment on whether there is adequate nonclinical evidence to support an association between trazodone and QT prolongation or cardiac dysrhythmias?**

There is adequate non-clinical evidence for QT prolongation. This has already addressed by Dr. John Koerner to Dr. Gwen Zornberg.

Background

Trazodone (Desyrel®) labeling for the treatment of major depression recommends an initial dose of 150 mg/day in divided doses, with dose increases in increments of 50 mg/day every 3 or 4 days, and a maximum recommended dose of 400 mg/day for outpatients and 600 mg/day for inpatients (in divided doses). Off label use in doses less than 100 mg for anxiety and insomnia is widespread.

The division is reviewing an NDA for a controlled release formulation of trazodone, 150-375 mg/day (Trazodone Contramid® OAD, NDA 22-411). They have consulted the QT-IRT with respect to potential for QT prolongation and the need for a TQT study. In study 04AC13-001, 406 subjects were exposed to Trazodone Contramid® OAD. The sponsor collected ECGs on Visit 1 and at the end of Study. The sponsor reports that no ECG findings were recorded as AEs by the investigators and no cases of discontinuation were linked to ECG findings which were also evaluated by a cardiologist.

In an OSE review dated 8 January 2009, the Division of Pharmacovigilance (DPV) identified several findings from the AERS database suggesting a possible risk of QT prolongation and pro-arrhythmia associated with trazodone. Pre-clinical information for this drug is also suggestive of possible prolongation of the QTc interval.

OSE Findings and Recommendations

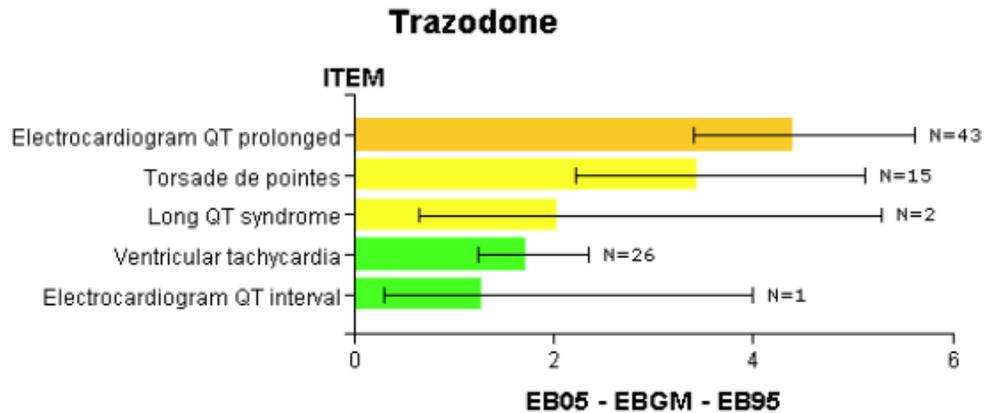
Data mining

“OSE routinely uses an EB05>2.0 as the “suspicious level” for a signal. An EB05 score > 2.0 indicates, with 95% confidence that the drug-event combination in question occurs at least at twice the expected rate when considering all other drugs and events in the AERS database. Data mining does not determine causality or degree of risk, but quantifies potential drug-event associations by producing a ranked set of scores which indicate varying strengths of reporting relationships between drugs and events.

“The data mining scores below show an EB05 score >2.0 for the MedDRA preferred terms “Long QT syndrome, Torsades de pointes and Electrocardiogram QT prolonged” which indicates the drug/event occurs at least twice the expected rate with trazodone therapy, when compared to drug-event associations in AERS.

**Figure 1: Data Mining Scores**

*Source: Figure 2 from OSE Review*



“OSE searched AERS for torsades, QT prolongation, and ventricular arrhythmias received by the FDA from December of 1981 through May 30, 2008 and retrieved 74 AERS reports. One case of NMS, 17 overdose cases, 1 case in which the event occurred after the patient had discontinued trazodone and 16 duplicates were excluded

#### Case Series Results

##### **“Sudden Death in AERS (n=1)**

A physician reported the case (AERS ISR #1989265) of a 60 year old female prescribed trazodone for depression. The patient experienced sudden death due to Torsades. The physician questioned a possible overdose. Peak daily dose and time to onset was not reported. The concomitant medication was klonopin, which is metabolized by CYP3A (Daily Med, Klonopin).

##### **“Torsades Cases in AERS (n=8)**

Four of the eight reported decreased potassium and one of the eight reported a decreased hemoglobin and hematocrit. Two of the eight cases were received by the FDA in 1996 and six of the eight were received from 2001 through 2006. One case of death was reported with a cause of death of leukemia; however, the death occurred after the reported resolution of the Torsades. Four cases reported an off-label dose of 100mg or less and all four reported a concomitant medication metabolized by CYP3A4. One of the four was >age 65. All eight cases reported concomitant administration of a drug labeled for QT prolongation. Four of the eight cases were also published in the medical literature.

*Reviewer’s Comments: On review of table 8.5 from the OSE review, only one patient was on itraconazole and 2 patients were on amiodarone (weak CyP 3A4 inhibitor). The remaining patients only received CyP3A4 substrates. They all received concomitant medications that prolong the QT interval and hypokalemia was reported in 4 cases.*

##### **“Ventricular Tachycardia in AERS (n=15)**

Nine cases were received by the FDA from 1982 through 1995 and five from 2000 through 2008. One death was reported (AERS # 777305); however, the case contains a diagnosis of ventricular tachycardia and a copy of the EKG, without additional clinical information; thus preventing a meaningful clinical assessment. Eight cases reported an off-label dose of 100 mg or less and three of the eight reported concomitant use of a drug

metabolized by CYP3A4. One of the three was >age 65. Four of the cases reported concomitant administration of a drug labeled for QT prolongation.

**“AERS ISR# 568370**

A physician reported the case of a 63 year old female who was admitted to the hospital due to a syncopal episode. The patient had been taking trazodone 100mg daily for 180 days for an unknown indication. The patient developed ventricular tachycardia during a stress test. Trazodone was discontinued. The patient did not experience ventricular tachycardia during a repeat stress test. Trazodone was rechallenged and the patient again experienced ventricular tachycardia during a stress test. The echocardiogram was normal. Cardiac catheterization and coronary angiography did not reveal coronary artery disease. An electrophysiology test was unsuccessful in inducing ventricular tachycardia. The patient had no history of cardiac disease. The physician concluded that the patient was experiencing exercise-induced ventricular tachycardia. Prednisone was the concomitant medication. A history of temporal arteritis was reported.

**“Ventricular Tachycardia in the Published Medical Literature (n=1)**

Vitullo, Wharton, Allen, and Pritchett, 1990, reported the case of 79 year old female, prescribed 50mg BID for depression, who experienced a rechallenge of exercise-induced ventricular tachycardia with trazodone therapy. A syncopal episode had occurred 30 minutes after climbing a flight of stairs at home. After the syncopal episode, the patient was examined and discharged as her EKG was normal, no arrhythmias were seen during several hours of monitoring, and serum tests were normal. The patient was later admitted for further evaluation and experienced ventricular tachycardia during two stress tests, while on trazodone therapy. The patient’s cardiac catheterization revealed no abnormalities. An EPS was unable to induce the arrhythmia and a stress test performed 48 hours after discontinuation of trazodone did not result in ventricular tachycardia. As the patient had no history of cardiac disease, no abnormalities were seen during the cardiac work-up, and no subsequent events occurred during the 11 months of follow-up, the authors associated the stress-induced ventricular tachycardia with trazodone therapy. Concomitant medications were lorazepam and prednisone which did not have “complicating cardiovascular effects.”

*Reviewers Comments: QT prolongation is not reported but the ventricular tachycardia was clearly drug-induced.*

**“OSE RECOMMENDS:**

1. Add Drug Interaction labeling regarding the use of two or more QT/QTc interval prolonging drugs and note the potential increased risk has been seen at both labeled doses and off-label doses of 100 mg or less.
2. Modify the Warning for patients with pre-existing cardiac disease as follows:
  - A. Add Torsades to the identified arrhythmias in the warning for patients with cardiac disease.
  - B. Replace “short episode of ventricular tachycardia” with tachycardia with syncope
  - C. Add prolonged QT to the warning.

- D. Note that these events have occurred at off-label doses of 100 mg or less.
- E. Add language to indicate that concomitant administration of a drug that prolongs the QT or concomitant administration of a drug metabolized by CYP3A4 may increase the risk of the cardiac arrhythmias for these patients.
3. Add prolonged QT interval, Torsades, and ventricular tachycardia to the Post-introduction Reports section and note that these events have occurred at off-label doses of 100 mg or less.
4. Modify the Drug Interaction section for concomitant administration of drugs metabolized by CYP3A4 to note that Torsades, ventricular tachycardia and prolonged QT have been seen even when the dose is decreased.”

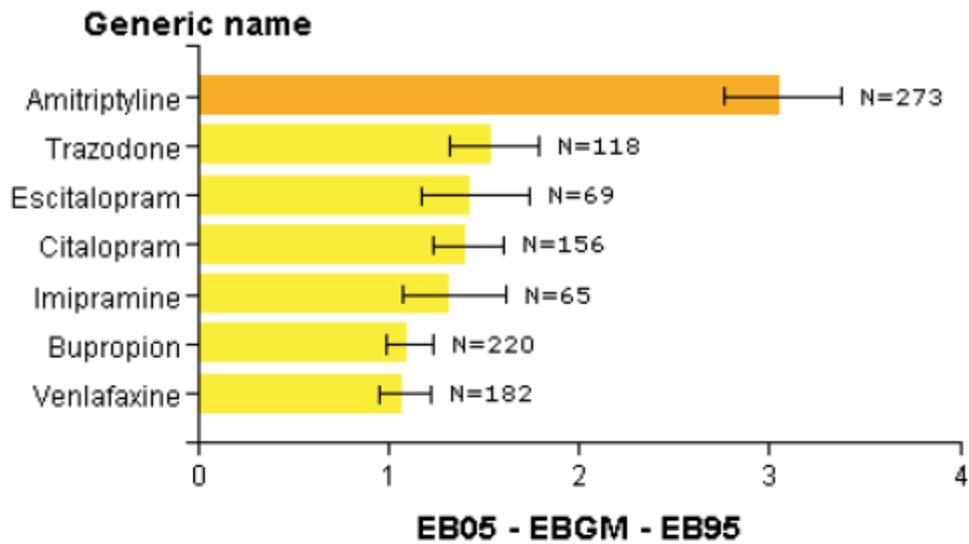
*Reviewer’s Comments: Concomitant CYP3A4 substrates would not cause QT prolongation or the arrhythmic events. On review of the table 8.5 in the OSE review the drugs listed were predominantly substrates (not inhibitors). The presence of concomitant medications that prolong the QT interval was an additional risk factor/confounder for arrhythmia and QT prolongation. Hence statement E has to be modified (CYP3A4 inhibitors-not metabolizers) and no modifications are required for the drug interactions section.*

Reviewer’s Assessments:

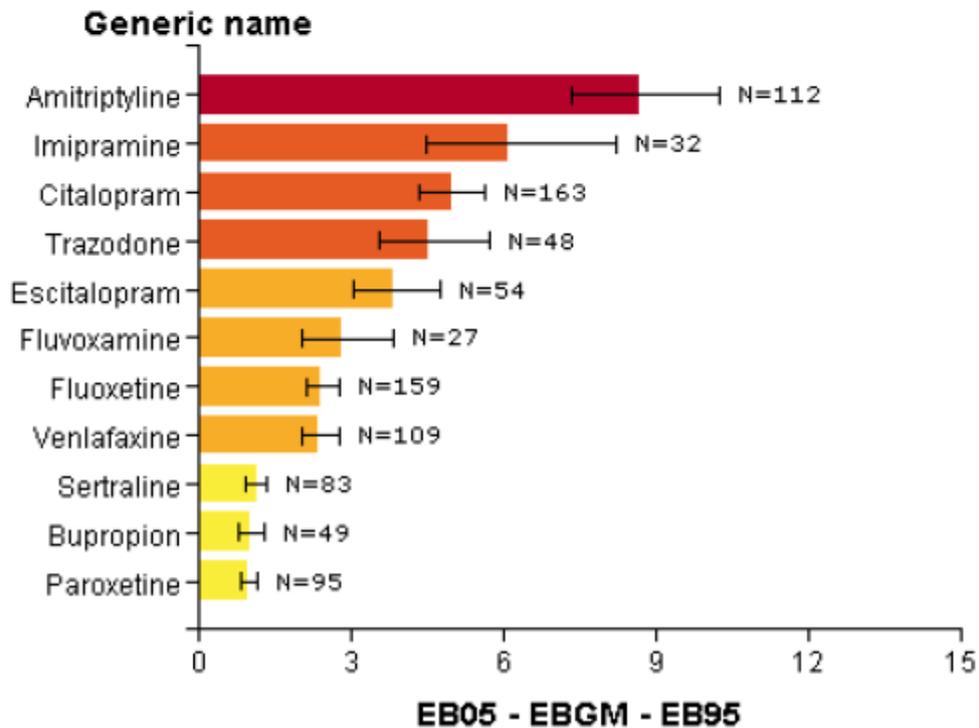
We also performed an MGPS data mining analysis of the AERS database for trazodone and other antidepressants. The number of case reports for TdP, QT prolongation and ventricular tachycardia with trazodone were similar to the OSE analysis (compare to Figure 1). The cases of TdP (n=21) were also reviewed. Similar to the OSE analysis, there were 8 cases after removing the cases of overdose, duplicate reports and 1 case of neuroleptic malignant syndrome (NMS). The signal scores (EBGM value) were greater than 2 for several of the drugs for QT prolongation and TdP and for some of the drugs for ventricular tachycardia and ventricular fibrillation (see figure below)

**Figure 2: CI graphs for QT prolongation and AEs related to QT prolongation for amitriptyline, imipramine, citalopram, escitalopram, trazodone, fluvoxamine, fluoxetine, venlafaxine, sertraline, bupropion and paroxetine.**

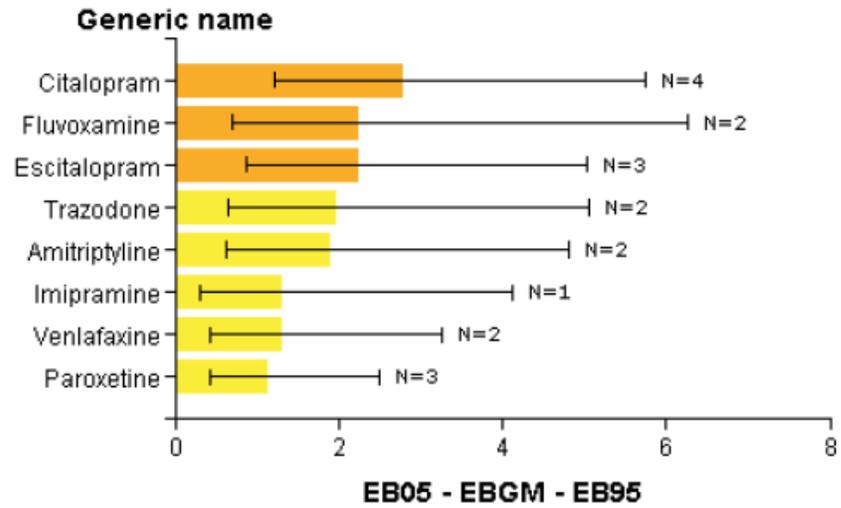
### Event=Cardiac arrest



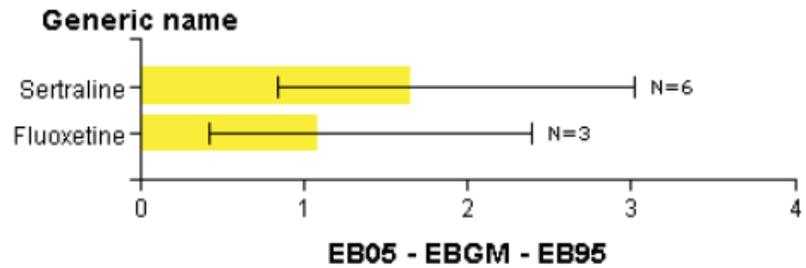
### Event=Electrocardiogram QT prolonged



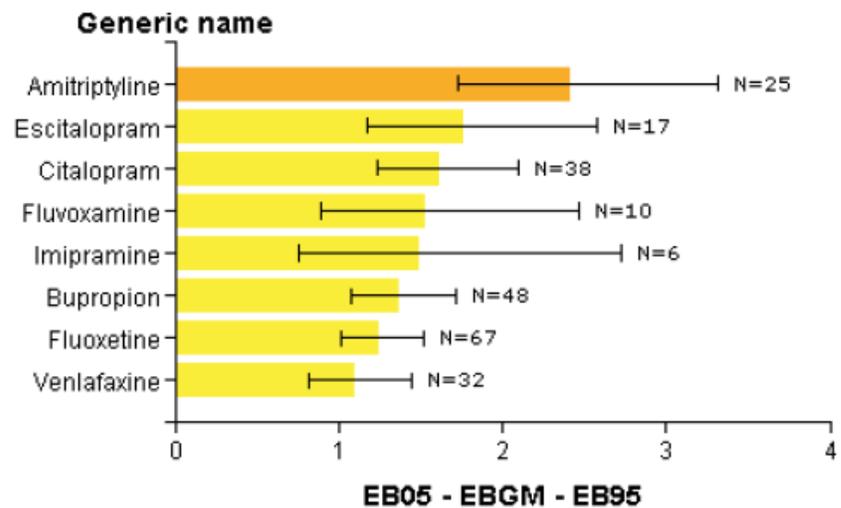
### Event=Long QT syndrome



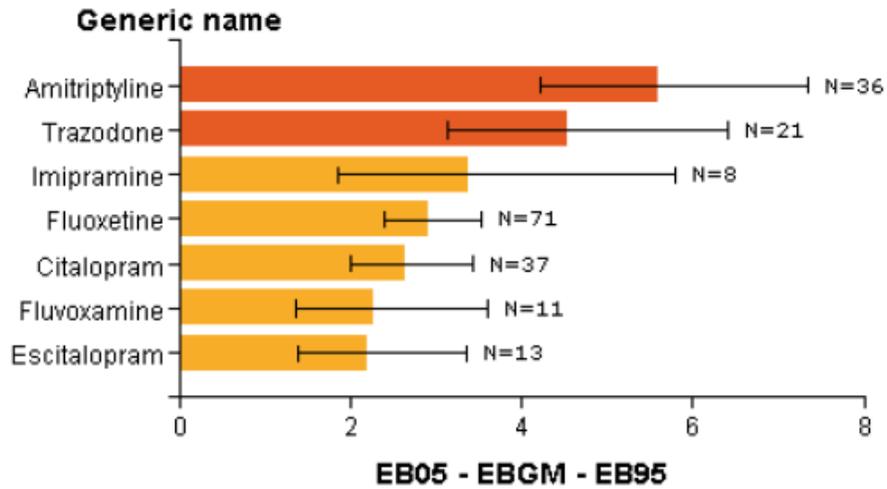
### Event=Sudden cardiac death



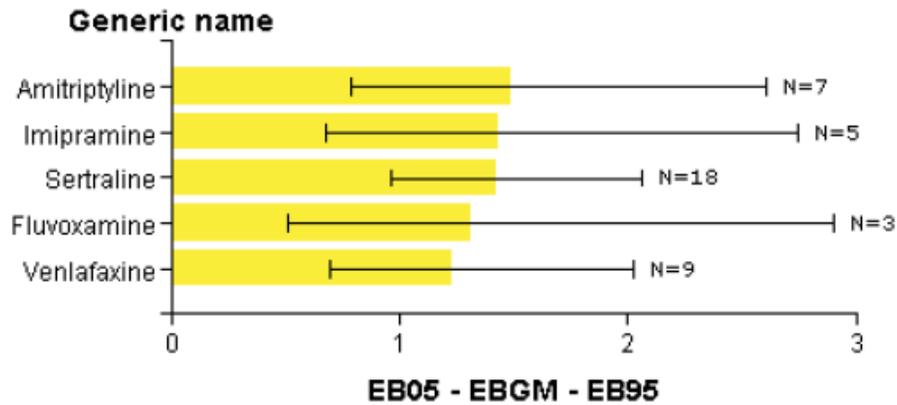
### Event=Sudden death



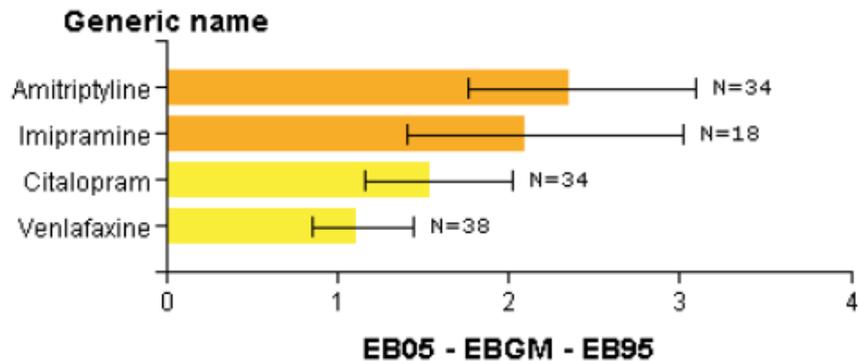
### Event=Torsade de pointes



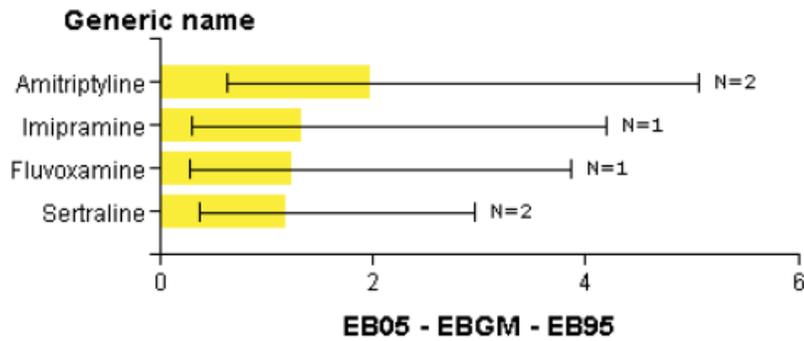
### Event=Ventricular arrhythmia



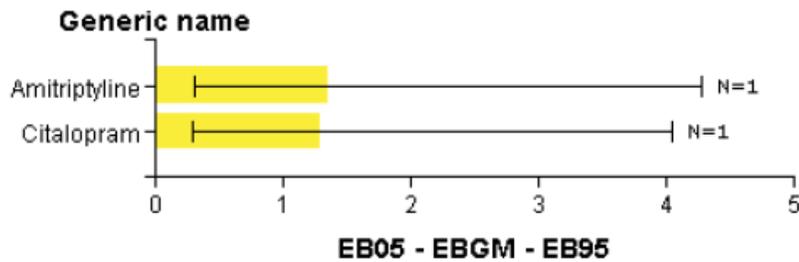
### Event=Ventricular fibrillation



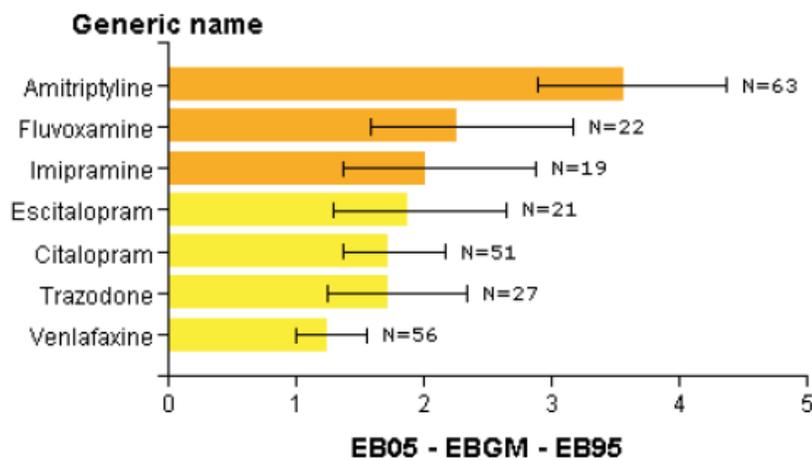
**Event=Ventricular flutter**



**Event=Ventricular tachyarrhythmia**



**Event=Ventricular tachycardia**



$0 \leq \text{EBGM} \leq 1$   
  $1 < \text{EBGM} \leq 2$   
  $2 < \text{EBGM} \leq 4$   
  $4 < \text{EBGM} \leq 8$   
  $8 < \text{EBGM} < \infty$

<b>ID:</b>	515
<b>Type:</b>	MGPS
<b>Name:</b>	Generic (S)
<b>Description:</b>	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
<b>Project:</b>	CBAERS Standard Runs
<b>Configuration:</b>	CBAERS BestRep (S)
<b>Configuration Description:</b>	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
<b>As Of Date:</b>	03/13/2009 00:00:00
<b>Item Variables:</b>	Generic name, PT

<b>Stratification Variables:</b>	Standard strata
<b>Highest Dimension:</b>	2
<b>Minimum Count:</b>	1
<b>Calculate PRR:</b>	Yes
<b>Calculate ROR:</b>	Yes
<b>Base Counts on Cases:</b>	Yes
<b>Use "All Drugs" Comparator:</b>	No
<b>Apply Yates Correction:</b>	Yes
<b>Stratify PRR and ROR:</b>	No
<b>Fill in Hierarchy Values:</b>	Yes
<b>Exclude Single Itemtypes:</b>	Yes
<b>Fit Separate Distributions:</b>	Yes
<b>Save Intermediate Files:</b>	No
<b>Created By:</b>	Empirica Signal Administrator
<b>Created On:</b>	03/20/2009 17:17:38 EDT
<b>User:</b>	Suchitra Balakrishnan
<b>Source Database:</b>	Source Data: CBAERS data from Extract provided by CBER as of 03/13/2009 00:00:00 loaded on 2009-03-19 08:07:45.0

**Dimension: 2 Selection Criteria:** Generic name(Amitriptyline, Bupropion, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Imipramine, Paroxetine, Sertraline, Trazodone, Venlafaxine) + PT(Cardiac arrest, Electrocardiogram QT prolonged, Long QT syndrome, Sudden cardiac death, Sudden death, Torsade de pointes, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia) **Where:** EBGM > 1.0

```
SELECT * FROM OutputData_515 WHERE (DIM=2 AND EBGM>1.0 AND ((P1='D' AND ITEM1 IN ('Amitriptyline','Bupropion','Citalopram','Escitalopram','Fluoxetine','Fluvoxamine','Imipramine','Paroxetine','Sertraline','Tr AND P2='E' AND ITEM2 IN ('Cardiac arrest','Electrocardiogram QT prolonged','Long QT syndrome','Sudden cardiac death','Sudden death','Torsade de pointes','Ventricular arrhythmia','Ventricular fibrillation','Ventricular flutter','Ventricular tachyarrhythmia','Ventricular tachycardia')))) ORDER BY ITEM1,EBGM desc
```

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future.

Please feel free to contact us via email at [cderderpqt@fda.hhs.gov](mailto:cderderpqt@fda.hhs.gov)

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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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Suchitra Balakrishnan  
4/6/2009 09:29:36 AM  
MEDICAL OFFICER

Norman Stockbridge  
4/6/2009 10:22:52 AM  
MEDICAL OFFICER