CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202088Orig2s000

SUMMARY REVIEW

MEMORANDUM

March 21, 2012

NDA: 202088

COMPANY: Citius Pharmaceuticals

DRUG: Phentermine hydrochloride 37.5 mg orally disintegrating tablet (ODT)

INDICATION: Short-term treatment of obesity

DATE of SUBMISSION: September 28, 2011

On June 13, 2011, the Division issued an approval letter for the 15 mg and 30 mg phentermine ODTs and a complete response letter for the 37.5 mg phentermine ODT. The highest dose strength was not approved (b) (4)

Dr. Elsbeth Chikhale, the Chemistry Manufacturer and Control (CMC) and Biopharmaceutics reviewer, evaluated the relevant data submitted by the company and recommends approval of the 37.5 mg ODT.

Dr. Reasol Agustin, the primary reviewer from the Division of Medication Error Prevention and Analysis (DMEPA), provided the company with recommended changes to the package insert and container labels. In a correspondence of March 2, 2012, the company agreed to the recommended labeling changes.

Reviewers from the Controlled Substance Staff (CSS) and the Office of Prescription Drug Promotion (OPDP) have reviewed the proposed labeling and recommend approval of the 37.5 mg ODT.

The 505b2 Assessment Committee cleared this application for approval on February 28, 2012.

There are no outstanding issues. I agree with the recommendation to approve the 37.5 mg phentermine hydrochloride ODT.

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Eric Colman, MD

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/s/

ERIC C COLMAN
03/27/2012

Summary Review for Regulatory Action

Date	June 1, 2011
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	202088
Applicant Name	Citius Pharmaceuticals
Date of Submission	11 August 2010
PDUFA Goal Date	13 June 2011
Proprietary Name / Established (USAN) Name	Suprenza/phentermine
Dosage Forms/Strength	Orally disintegrating tablet: 15 mg, 30 mg, and 37.5 mg
Proposed Indication(s)	Short-term weight reduction
Recommended Action:	Approve the 15 mg and 30 mg tablets Complete Response for the 37.5 mg tablet

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Julie Golden, MD
Statistical Review	NA
Pharmacology Toxicology Review	Mukesh Summan, PhD
CMC Review/OBP Review	Elsbeth Chikhale, PhD/Tapash Ghosh, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Immo Zadezensky, PhD
DDMAC	Samuel Skariah, PharmD
DSI	Abhijit Raha, PhD
CDTL Review	See Deputy Division Director Summary Review
OSE/DMEPA	Lubna Merchant, PharmD
DRISK	NA
Thorough QT Consult	NA
Controlled Substance Staff	Katherine Bonson, PhD
Pediatric and Maternal Health Staff	Jeanine Best, MSN, RN

OND=Office of New Drugs
CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biopharmaceutics
DDMAC=Division of Drug Marketing, Advertising and Communication
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management

Introduction

This memorandum summarizes the Agency review team's assessment of a 505b2 application for phentermine hydrochloride orally disintegrating tablets (ODT). The sponsor is seeking approval as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavior modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 in the presence of other risk factors (e.g., controlled hypertension, diabetes, hyperlipidemia). This language mirrors that for approved phentermine products.

The sponsor indicates that phentermine hydrochloride (HCL) 15 mg and 30 mg capsules manufactured by Sandoz Pharmaceuticals and phentermine HCL 37.5 mg tablet manufactured by Gate Pharmaceuticals are the reference listed drugs. The sponsor is relying on the finding of safety and effectiveness for NDA 11613, Ionamin (phentermine resin complex capsule). This product was discontinued from marketing for reasons not related to efficacy or safety.

1. Background

Phentermine was approved for weight loss in 1959. Following DESI review in the late 1960s/early 1970s, the indication for phentermine and other anorectics was limited to short-term use. This reflected a concern regarding abuse liability and evidence that weight loss with phentermine therapy waned with treatment beyond a few weeks.

2. CMC/Biopharmacuetics

There are no outstanding CMC or biopharmacuetics issues and Dr. Chikhale recommends that the application be approved. I concur.

3. Nonclinical Pharmacology/Toxicology

Nonclinical studies of phentermine ODT were not conducted. The sponsor relied on publically available information, including the approved labeling for Adipex-P, and FDA's finding of efficacy and safety for previously approved phentermine in support of approval.

Because chemical analysis indicated that impurities and degradants in the phentermine ODT drug substance and drug product were within acceptable limits, a nonclinical bridging toxicology study between phentermine ODT and a reference drug was not required.

Because the Division is waiving the requirement for pediatric studies due to the absence of adequate long-term efficacy or safety data in adults, the sponsor will not be required to perform carcinogenicity or juvenile animal studies.

There are no outstanding nonclinical pharmacology or toxicology issues and Dr. Summan recommends approval. I concur.

4. Clinical Pharmacology

As outlined in Dr. Zadezensky's review, three relative bioavailability studies were conducted by the sponsor in support of approval of phentermine ODT. The study titles and treatment groups are shown below (taken from Dr. Zadezensky's review). All told, the studies included 48 healthy men and women between the ages of 18 to 45 years with body mass indices of 18.3 kg/m^2 to 29.1 kg/m^2.

1. **01806KH:** This study evaluated the following three treatment arms:
   T1. Phentermine ODT 15 mg (followed by water after disintegration) fasted
   T2. Phentermine ODT 15 mg (disintegration without water) fasted
   Ref. Phentermine HCl capsule Sandoz 15 mg (administered with water) fasted

2. **018089D:** This study evaluated the following three treatment arms:
   T1. Phentermine ODT 30 mg (administered with water, swallow without disintegration) fasted
   T2. Phentermine ODT 30 mg (swallow after disintegrated followed by water) fed
   Ref. Phentermine HCl capsule Sandoz 30 mg (administered with water) fasted

3. **01809PB:** This study evaluated the following three treatment arms:
   T1. Phentermine ODT 37.5 mg (followed by water after disintegration) fasted
   T2. Phentermine ODT 37.5 mg (followed by water after disintegration) fed
   Ref. Adipex-P 37.5 mg tablet (administered with water) fasted

Under all testing conditions, the phentermine ODT doses were bioequivalent to the relevant reference phentermine doses. These results are depicted in the following figures from Dr. Zadezensky's review.

Figure 1 Study 01806KH Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine (15 mg) for 01806KH (Geometric mean ratio (GMR) and 90% confidence interval (90% CI))

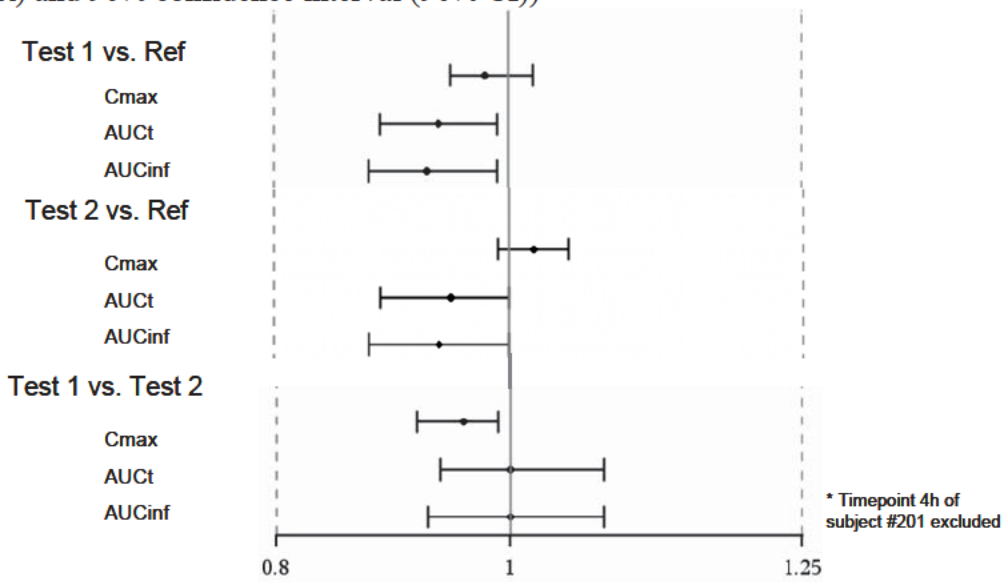


Figure 2 Study 018089D Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine (30 mg) for 018089D (Geometric mean ratio (GMR) and 90% confidence interval (90% CI))

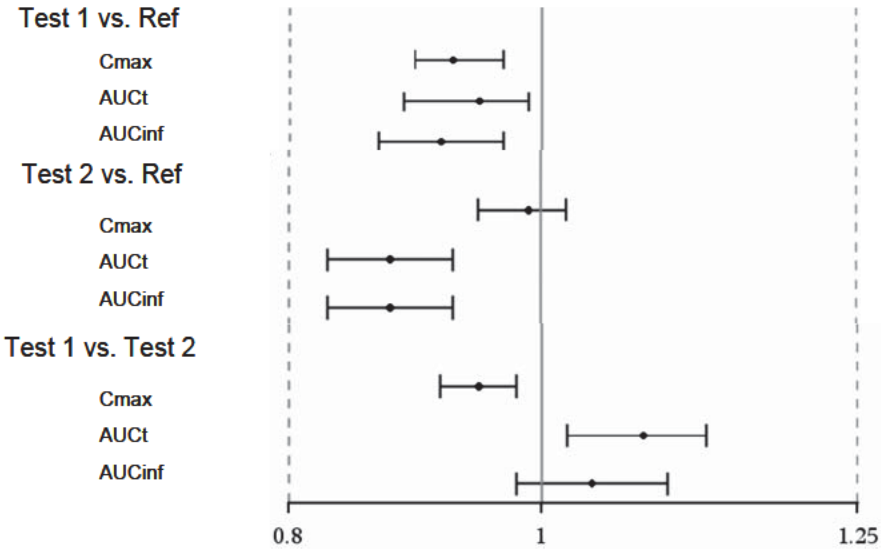
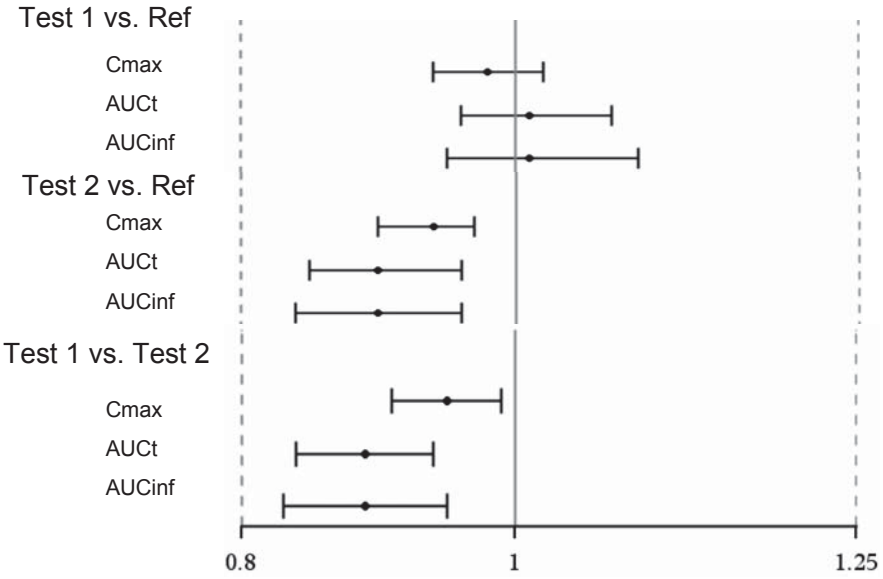


Figure 3 Study 01809PB Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine (37.5 mg) for 01809PB (Geometric mean ratio (GMR) and 90% confidence interval (90% CI))



Following the clinical and analytical site inspections, the Division of Scientific Investigations recommends that the PK data from subject 312 from study 018089D and the PK data from subject 510 from study 01809PB be excluded from the bioequivalence determination. The Division of Scientific Investigations concluded that other data generated at the clinical and analytical sites from studied 018089D and 01809PB be accepted for review.

Dr. Zadezensky confirmed that the overall study results are not affected when subjects 312 and 510 are excluded from the analyses.

Because phentermine is excreted in the urine, Dr. Zadezensky recommends that the sponsor conduct, as a post-marketing requirement, a pharmacokinetics study in subjects with varying degrees of renal insufficiency. I concur with this recommendation.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

No clinical studies were conduced with Suprenza.

7. Safety

There were no signals of concern from the adverse events reported during conduct of the bioavailability studies. Dr. Golden recommends approval of the 15 mg and 30 mg ODTs. I

concur with this recommendation. See section 10 below regarding the approvability of the 37.5 mg ODT.

8. Advisory Committee Meeting

There was no need to convene an advisory committee meeting for this 505b2 application for which bioequivalency to a marketed phentermine product was the basis for approval.

9. Pediatrics

Upon the recommendations of the Pediatric Review Committee, the Division is granting a full waiver for pediatric studies with phentermine ODT. Although phentermine is approved for short-term use only, within the last two decades it has become apparent that obesity is a chronic condition that requires chronic treatment. However, there are inadequate data on the efficacy and safety of phentermine in adults to support long-term studies in pediatric populations. This will be reflected in the Pediatric Use subsection of the labeling.

10. Other Relevant Regulatory Issues

Reviewers from DMEPA and DDMAC reviewed the proposed tradename Suprenza and concluded that it is acceptable.

The company will be required to conduct two post-marketing studies. One study will assess the pharmacokinetics of phentermine ODT in subjects with varying degrees of renal insufficiency. The second, an observational pharmacoepidemiological study, will examine the patterns of use of phentermine ODT in the market place. Specifically, the following information will be obtained and submitted on an annual basis for three years following approval: the distribution of age, sex, and BMI of phentermine ODT recipients, distribution of specialties of physician prescribers, average duration of use, average size of prescriptions, average gap in time between use episodes, average cumulative dose per patient, concomitant drug use, concomitant alcohol use, and concomitant diagnoses.

(b) (4)

I agree with the recommendation by DMEPA that the (b) (4) 37.5 mg ODT not be approved at this time. The original NDA submission will be administratively split into two NDAs: 1) the 15 mg and 30 mg ODT, and 2) the 37.5 mg ODT.

The NDA for the 15 mg and 30 mg ODT will be approved. The NDA for the 37.5 mg ODT will receive a Complete Response. (b) (4)

(b) (4)

11. Labeling

Comments from the DDMAC and Controlled Substance Staff reviewers were taken into account during the Division's review of the proposed labeling. Because there is never a situation when weight loss is recommended during pregnancy, the Pediatric and Maternal Health Staff (PMHS) recommend that the pregnancy category for all weight-loss drugs be "X". The phentermine ODT labeling will incorporate this recommendation along with supportive language provided by the PMHS.

12. Decision

I agree with the review team's recommendation to approve the 15 mg and 30 mg phentermine ODT and issue a Complete Response for the 37.5 mg ODT.

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/s/

ERIC C COLMAN
06/13/2011