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APPLICATION NUMBER:

202088Orig1s000

SUMMARY REVIEW

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 (b) (4)
Proposed Indication(s)	Short-term weight reduction
Recommended Action:	Approve the 15 mg and 30 mg tablets (b) (4)

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 (b) (4) 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 (b) (4) mg (followed by water after disintegration) fasted
   T2. Phentermine ODT (b) (4) mg (followed by water after disintegration) fed
   Ref. (b) (4) 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))

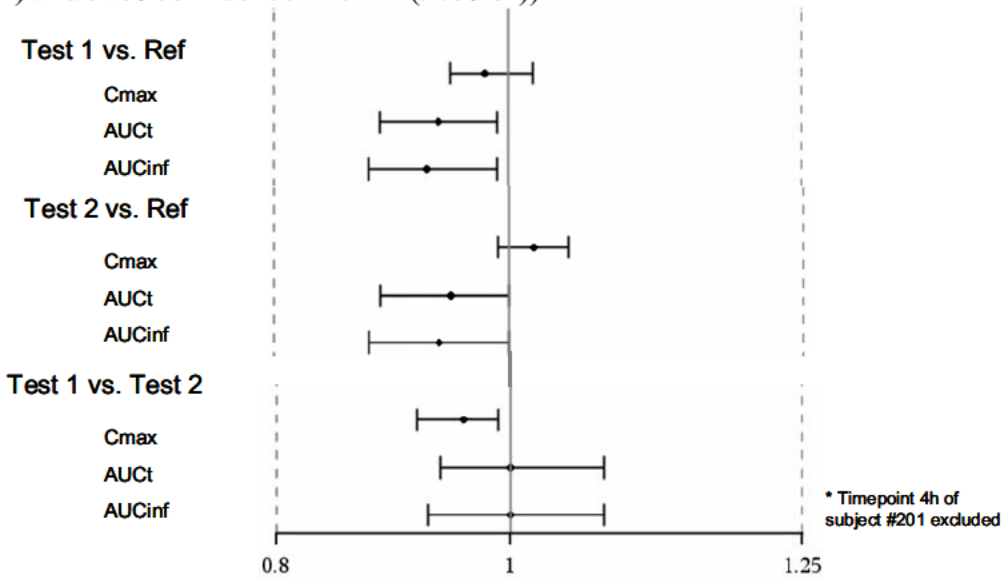


Figure 2 Study 018089D Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine (30 mg) for 018089D (Geometric mean ratio (GMR) and 90% confidence interval (90% CI))

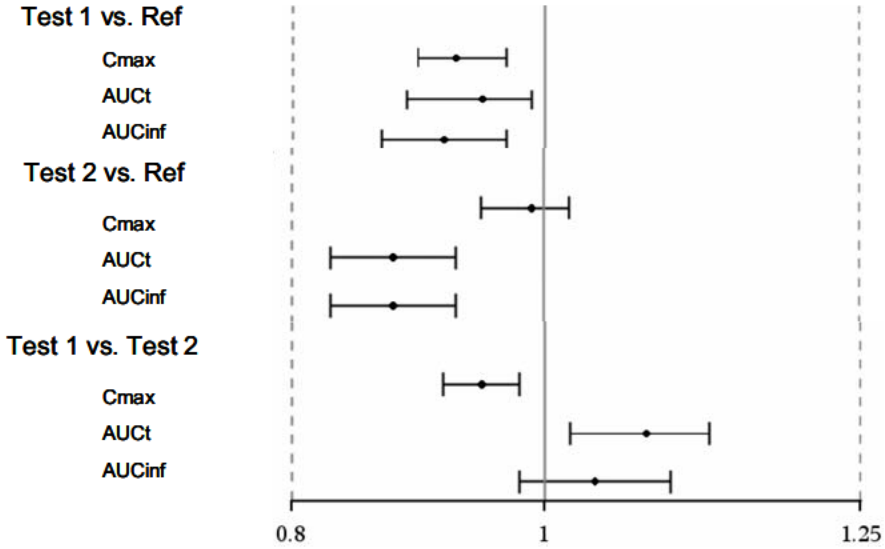
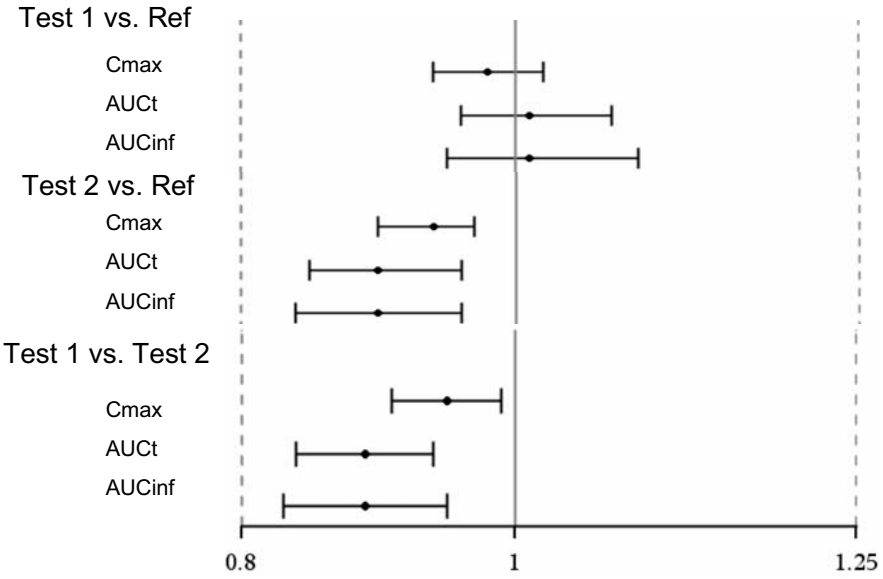


Figure 3 Study 01809PB Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine ([(b) (4)] mg) for 01809PB (Geometric mean ratio (GMR) and 90% confidence interval (90% CI))



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. (b) (4)

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)

(b) (4)

The NDA for the 15 mg and 30 mg ODT will be approved. (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 (b) (4)

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/s/

ERIC C COLMAN
06/13/2011