CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202088Orig2s000

MEDICAL REVIEW(S)

MEMORANDUM

RE	NDA 202088-02 resubmission
Name of drug	Phentermine HCl (Suprenza)
Sponsor	Citius Pharmaceuticals, LLC
Date of Submission	September 29, 2011
PDUFA Goal Date	March 29, 2012
Medical Reviewer	Julie Golden, M.D.

This is a resubmission of a phentermine 505(b)(2) NDA. In the original application, the 37.5 mg strength ODT was formulated with (b) (4) The 15 and 30 mg strengths were approved after the application was unbundled. In this NDA resubmission, the sponsor submitted data for (b) (4) 37.5 mg tablet. CMC and Biopharmaceutics reviewers have found the application acceptable and recommend approval. There were no new clinical data in this application.

There were two studies required post-approval of Suprenza. The approval letter for this NDA should reiterate that the sponsor will be required to conduct: 1) a pharmacoepidemiology study to evaluate drug utilization annually in the first 3 years after market launch to more fully understand and assess off-label use, and 2) a clinical pharmacology study to evaluate the PK of phentermine in patients with renal impairment.

With respect to labeling, I agree with DMEPA that wording should be changed from symbols such as "≥" to wording such as "greater than or equal to" in the package insert. DMEPA has also made recommendations regarding the container label (moving net quantity statement away from product strength). OPDP has no comments at this time.

In order to be consistent with other amphetamine congeners, we will add 'tachycardia' to the overdose section. (b) (4)

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

/s/

JULIE K GOLDEN
03/07/2012

ERIC C COLMAN
03/07/2012

Medical Officer 505(b)(2) NDA Review
Division of Metabolism and Endocrine Products

NDA	202088
Name of drug	Phentermine HCl
Sponsor	Citius Pharmaceuticals, LLC
Date of Submission	August 13, 2010
PDUFA Goal Date	June 13, 2011
Medical Reviewer	Julie Golden, M.D.

BACKGROUND

Regulatory

This 505(b)(2) application for phentermine HCl orally disintegrating tablet (ODT) references phentermine HCl 15 and 30 mg capsules (manufactured by Sandoz Pharmaceuticals) and Adipex-P TEVA 37.5 mg tablet (manufactured by Gate Pharmaceuticals).

Phentermine was first approved by FDA for obesity management in 1959. Drugs initially approved between 1938 and 1962 on the basis of safety alone required an assessment of efficacy under the Drug Efficacy Study Implementation (DESI) process, which began in the late 1960s. In 1973, phentermine, as one of a number of amphetamine congeners, was reviewed under the DESI process and deemed efficacious based on a statistically significantly greater weight loss than placebo; however, given the theoretical concern for abuse and addiction, its use was limited to short-term (a few weeks).[1]

In the 1990s, phentermine was studied in obese patients for up to 4 years in combination with fenfluramine, another anorectant drug approved under DESI, and its use was popularized in the 'fen-phen' combination. Fenfluramine was ultimately withdrawn from the market due to its association with cardiac valvulopathy. Phentermine has generally not been implicated as a contributing cause of valvulopathy. More recently, phentermine was studied in a number of 1-year safety and efficacy trials as a component of Qnexa, an investigational combination of low-dose phentermine and topiramate for the chronic treatment of obesity. In those trials, modest increases in heart rate associated with

[1] Colman E. Anorectants on trial: a half century of federal regulation of prescription appetite suppressants. Ann Intern Med 2005; 143:380-5.

phentermine were noted. No clinical trials of 1-year duration have been conducted with phentermine as monotherapy. Nevertheless, according to a survey published in the journal Obesity in 2009, phentermine is the most widely prescribed obesity medication by bariatric physicians.[2]

Pre-submission activity

Pre-IND 76477 was opened by Citius early 2007. [redacted] the sponsor should proceed with 1 of 2 approaches for development: 1) conduct a bioequivalence study vs. marketed phentermine with conditions of use/claims in their labeling limited to that of marketed phentermine; or 2) examine the safety and efficacy of phentermine ODT vs. placebo in a one-year study, with no restriction of use in product labeling if data supported approval.

IND 76477 was submitted early 2009 with 3 single-dose phase 1 protocols. The development program was designed to evaluate bioavailability of phentermine ODT relative to currently approved phentermine formulations.

Drug in study

Phentermine is α,α-Dimethylphenethylamine hydrochloride, an anorectant agent structurally similar to amphetamine. Its molecular formula is $C_{10}H_{15}N{\cdot}HCl$ and its molecular mass is 185.7 Da.

Excipients in the ODT drug product are: Mannitol powder [redacted] Citric Acid powder, Povidone CL [redacted] Povidone K 30 [redacted] Sucralose, Magnesium Stearate, Peppermint flavor, Talc, Sodium Lauryl Sulfate, Mannitol pregranulated [redacted] FD&C Blue # 1 lake [redacted] and FD&C Yellow # 5 lake [redacted]

[redacted]

Biopharmaceutical studies

The applicant conducted three studies to compare the bioavailability and bioequivalence of the test drug phentermine HCl ODT (15, 30 and 37.5 mg) to the immediate release listed drug formulations (15, 30 and 37.5 mg). The applicant also evaluated the food effect, the effect of swallowing and potential mucosal irritation by the ODT formulation, and the proposed labeling claim that the ODT can be taken with or without water. These

[2] Hendricks EJ, et al. How physician obesity specialists use drugs to treat obesity. Obesity 2009; 17:1730-5.

studies were reviewed in detail by Dr. Immo Zadezensky from the Office of Clinical Pharmacology.

STUDY SUMMARIES

No trials evaluating clinical safety and efficacy were conducted.

Study 01806KH

All 15 subjects enrolled were administered 3 single doses of phentermine 15 mg, one per study period. Dosing in the 3 study periods was separated by a 10-day washout period.

The bioequivalence between the 15 mg phentermine HCl ODT administered with or without water and the 15 mg dose of the reference listed drug was established based on C_{max} and AUC (AUC_{last} and AUC_{inf}). The 90% confidence intervals of the comparisons were within the accepted 80% to 125% limits (Table 1). Of note, one subject in this study had an outlier (high) C_{max} at one time point (t=4 hours) with the reference drug. Bioequivalence was established after the exclusion of that subject's data.

The bioequivalence between the 15 mg phentermine HCl ODT administered with water and the 15 mg phentermine HCl ODT administered without water was established based on C_{max} and AUC. The 90% confidence intervals of the comparisons were within the accepted 80% to 125% limits (Table 1).

Table 1: Summary of Study 01806KH

<table>
<tr><th>Study Reference No.</th><th>Study Objective</th><th>Study Design</th><th>Treatments (Dose, Dosage Form, Route)</th><th>Subjects (No. (M/F) type Age: mean (range)</th><th>Parameters</th></tr>
<tr><td>01806KH</td><td>Compare bioavailability of phentermine HCl 15 mg ODT when administered in each instance by oral disintegration and followed by water and swallowed after disintegration without water with phentermine HCl Reference 15 mg capsule when administered with water.

Monitor safety including mucosal irritation</td><td>Randomized, balanced, open-label, single-dose, 3-treatment, 3-sequence, 3-period, crossover</td><td>Phentermine HCl 15 mg ODT by i) oral disintegration and followed by water and ii) swallowed after disintegration without water;

Reference Phentermine HCl 15 mg Capsule when administered with water</td><td>15</td><td>
Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation Administered with Water (T1) to the Reference Product with Water (Primary Analysis, n = 14).
<table>
<tr><th rowspan="2">Dependent Variable</th><th colspan="2">Geometric Mean[a]</th><th rowspan="2">Ratio (%)[b] (Test/Ref)</th><th colspan="2">90% CI[c]</th><th rowspan="2">Power</th><th rowspan="2">ANOVA CV%</th></tr>
<tr><th>Test</th><th>Ref</th><th>Lower</th><th>Upper</th></tr>
<tr><td>ln(C_{max})</td><td>47.2656</td><td>47.8895</td><td>98.70</td><td>95.21</td><td>102.31</td><td>1.0000</td><td>5.56</td></tr>
<tr><td>ln(AUC_{last})</td><td>1631.6223</td><td>1729.1990</td><td>94.36</td><td>88.83</td><td>100.22</td><td>0.9999</td><td>9.32</td></tr>
<tr><td>ln(AUC_{inf})</td><td>1742.6066</td><td>1861.1115</td><td>93.63</td><td>87.67</td><td>100.00</td><td>0.9998</td><td>10.17</td></tr>
</table>
Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation Administered without Water (T2) to the Reference Product with Water (Primary Analysis, n = 14).
<table>
<tr><th rowspan="2">Dependent Variable</th><th colspan="2">Geometric Mean[a]</th><th rowspan="2">Ratio (%)[b] (Test/Ref)</th><th colspan="2">90% CI[c]</th><th rowspan="2">Power</th><th rowspan="2">ANOVA CV%</th></tr>
<tr><th>Test</th><th>Ref</th><th>Lower</th><th>Upper</th></tr>
<tr><td>ln(C_{max})</td><td>49.1671</td><td>47.8895</td><td>102.67</td><td>99.04</td><td>106.43</td><td>1.0000</td><td>5.56</td></tr>
<tr><td>ln(AUC_{last})</td><td>1620.1964</td><td>1729.1990</td><td>93.70</td><td>88.21</td><td>99.52</td><td>0.9999</td><td>9.32</td></tr>
<tr><td>ln(AUC_{inf})</td><td>1736.8013</td><td>1861.1115</td><td>93.32</td><td>87.38</td><td>99.67</td><td>0.9998</td><td>10.17</td></tr>
</table>
[a] Geometric Mean for the Test Formulation without water, T2 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
</td></tr>
</table>

Adverse events from this study are listed below; no AEs were serious or severe:

Table 2: Adverse Events, Study 01806KH

	Treatment T1 (N=15)		Treatment T2 (N=15)		Reference Product (N=15)	
Number of Treatmen-Emergent Adverse Events Reported	2		6		3	
Number of Subjects Reporting One or More Events (Percent of Subjects)	1 (7%)		5 (3%)		2 (13%)	
Adverse Events	**Subject**	**Event**	**Subject**	**Event**	**Subject**	**Event**
Angular cheilitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (33%)
Euphoria	0 (0%)	0 (0%)	1 (7%)	1 (17%)	0 (0%)	0 (0%)
Eye Pain	0 (0%)	0 (0%)	1 (7%)	1 (17%)	0 (0%)	0 (0%)
Headache	0 (0%)	0 (0%)	1 (7%)	1 (17%)	0 (0%)	0 (0%)
Increased thirst	0 (0%)	0 (0%)	1 (7%)	1 (17%)	0 (0%)	0 (0%)
Low back pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (33%)
Pharyngitis	0 (0%)	0 (0%)	1 (7%)	1 (17%)	0 (0%)	0 (0%)
Prolonged bleeding at draw site	1 (7%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Restlessness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (33%)
Right arm pain	0 (0%)	0 (0%)	1 (7%)	1 (17%)	0 (0%)	0 (0%)
Right shoulder pain	1 (7%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Percentages of subjects (Incidence of AE) are based on the number of subject exposure to each study drug.
Percentages of events are based on the number of events reported.

Note is made of one subject who developed an AE of euphoria on T2. Dr. Zadezensky reviewed the pharmacokinetics (PK) profiles for this subject on the different treatments. He found that the subject's C_{max} was 71.56 ng/mL for T1, 68.53 ng/mL for T2, and 65.79 ng/mL for the reference product (Ref). Although the phentermine C_{max} for this subject was ~50% higher than the mean C_{max} for all treatments, the C_{max} for the 3 different formulations were similar in this particular subject.

It was reported that the effect of ODT on oral mucosa was examined and that no clinically significant abnormalities were observed.

Study 018089D

All 15 subjects enrolled were administered 3 single doses of phentermine 30 mg, one per study period. Dosing in the 3 study periods was separated by at least a 10-day washout period.

The bioequivalence between the 30 mg phentermine HCl ODT swallowed whole or disintegrated and the 30 mg dose of the reference listed drug was established based on the C_{max} and the AUC_{last} and AUC_{inf}. The 90% confidence intervals of the comparisons were within the accepted 80% to 125% limits (Table 3).

The bioequivalence between the 30 mg phentermine HCl ODT swallowed whole with water (T1) and the 30 mg phentermine HCl ODT disintegrated followed by water (T2) was established based on the C_{max} and the AUC_{last} and AUC_{inf}. The 90% confidence intervals of the comparisons were within the accepted 80% to 125% limits (Table 3).

Table 3: Summary of Study 018089D

Study Reference No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route)	Subjects (No. (M/F) type Age: mean (range)	Parameters
018089D	Compare bioavailability of phentermine HCl 30 mg ODT when administered orally swallowed with water (T1) and disintegrated followed by water (T2) with phentermine HCl Reference 30 mg Capsule, swallowed with water under fasting conditions Monitor safety including mucosal irritation	Randomized, balanced, open-label, single-dose, 3-treatment, 3-sequence, 3-period, crossover	Phentermine HCl 30 mg ODT when administered orally by i) swallowed with water and ii) disintegrated followed by water; Reference Phentermine HCl 30 mg Capsule, swallowed with water under fasting conditions		**Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation-Swallowed with Water (T1) to the Reference Product with Water (Primary Analysis, n = 15).**

Dependent Variable	Geometric Mean[a] Test	Geometric Mean[a] Ref	Ratio (%)[b] (Test/Ref)	90% CI[c] Lower	90% CI[c] Upper	Power	ANOVA CV%
$\ln(C_{max})$	92.1244	98.6089	93.42	90.35	96.61	1.0000	5.38
$\ln(AUC_{last})$	3430.0518	3625.4359	94.61	89.74	99.75	1.0000	8.51
$\ln(AUC_{inf})$	3685.5871	4012.1922	91.86	86.89	97.11	1.0000	8.95

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation-Disintegrated followed by Water (T2) to the Reference Product with Water (Primary Analysis, n = 15).

Dependent Variable	Geometric Mean[a] Test	Geometric Mean[a] Ref	Ratio (%)[b] (Test/Ref)	90% CI[c] Lower	90% CI[c] Upper	Power	ANOVA CV%
$\ln(C_{max})$	97.3409	98.6089	98.71	95.46	102.08	1.0000	5.38
$\ln(AUC_{last})$	3182.3721	3625.4359	87.78	83.26	92.55	1.0000	8.51
$\ln(AUC_{inf})$	3540.2612	4012.1922	88.24	83.46	93.29	1.0000	8.95

[a] Geometric Mean for the Test Formulation-Disintegrated followed by water, T2 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

Adverse events are listed below; no AEs were serious or severe:

Table 4: Adverse Events, Study 018089D

	Treatment T1 (N=15)		Treatment T2 (N=15)		Reference Product (N=15)	
Number of Treatmen-Emergent Adverse Events Reported	6		2		0	
Number of Subjects Reporting One or More Events (Percent of Subjects)	5 (33%)		1 (7%)		0 (0%)	
Adverse Events	**Subject**	**Event**	**Subject**	**Event**	**Subject**	**Event**
Dizziness	3 (20%)	3 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Euphoria	1 (7%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache	2 (13%)	2 (33%)	1 (7%)	1 (50%)	0 (0%)	0 (0%)
Tenderness of temporal areas	0 (0%)	0 (0%)	1 (7%)	1 (50%)	0 (0%)	0 (0%)

Percentages of subjects (Incidence of AE) are based on the number of subject exposure to each study drug.
Percentages of events are based on the number of events reported.

Note is made of one subject who developed an AE of euphoria on T1. Dr. Zadezensky reviewed the PK profiles for this subject on the different treatments. He found that C_{max} was 82.12 ng/mL, 92.51 ng/mL, and 91.86 ng/mL for T1, T2, and Ref, respectively.

These values are in fact lower than the mean phentermine C_{max}, and furthermore, this subject's C_{max} with T1 was lower than with T2 or Ref.

It was reported that the effect of ODT on oral mucosa was examined and that no clinically significant abnormalities were observed.

Study 01809PB

Sixteen of the 18 subjects enrolled were administered 3 single doses of phentermine 37.5 mg, one per study period. Dosing in the 3 study periods was separated by at least a 10-day washout period.

The bioequivalence between the 37.5 mg phentermine HCl ODT under fasting and fed conditions and the 37.5 mg dose of the reference listed drug was established based on the C_{max} and the AUC_{last} and AUC_{inf}. The 90% confidence intervals of the comparisons were within the accepted 80% to 125% limits (Table 5).

The bioequivalence between the 37.5 mg phentermine HCl ODT administered under fed conditions (T2) and the 37.5 mg phentermine HCl ODT administered under fasted conditions (T1) was established based on the C_{max} and the AUC_{last} and AUC_{inf}. The 90% confidence intervals of the comparisons were within the accepted 80% to 125% limits (Table 5).

Table 5: Summary of Study 01809PB

<table>
<tr><th>Study Reference No.</th><th>Study Objective</th><th>Study Design</th><th>Treatments (Dose, Dosage Form, Route)</th><th>Subjects (No. (M/F) type Age: mean (range)</th><th>Parameters</th></tr>
<tr><td>01809PB</td><td>Compare the bioavailability of phentermine HCl 37.5 mg ODT under fasting (T1) and fed (T2) with phentermine HCl Reference 37.5 mg tablets under fasting condition

Monitor safety including mucosal irritation</td><td>Randomized, balanced, open-label, single-dose, 3-treatment, 3-sequence, 3-period, crossover</td><td>Phentermine HCl 37.5 mg ODT administered i) fasting and ii) fed;

Reference Phentermine HCl 37.5 mg Tablet administered under fasting condition</td><td></td><td>
Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation under Fasting Conditions, T1 to the Reference Product under Fasting Conditions.
<table>
<tr><th rowspan="2">Dependent Variable</th><th colspan="2">Geometric Mean[a]</th><th>Ratio (%)[b]</th><th colspan="2">90% CI[c]</th><th colspan="2">Power ANOVA</th></tr>
<tr><th>Test</th><th>Ref</th><th>(Test/Ref)</th><th>Lower</th><th>Upper</th><th></th><th>CV%</th></tr>
<tr><td>ln(C_{max})</td><td>116.4055</td><td>118.4320</td><td>98.29</td><td>94.40</td><td>102.33</td><td>1.0000</td><td>6.70</td></tr>
<tr><td>ln(AUC_{last})</td><td>4099.3519</td><td>4054.3170</td><td>101.11</td><td>95.59</td><td>106.95</td><td>1.0000</td><td>9.34</td></tr>
<tr><td>ln(AUC_{inf})</td><td>4467.8094</td><td>4394.7729</td><td>101.66</td><td>94.99</td><td>108.80</td><td>0.9997</td><td>11.30</td></tr>
</table>
Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation under Fed Conditions, T2 to the Reference Product under Fasting Conditions.
<table>
<tr><th rowspan="2">Dependent Variable</th><th colspan="2">Geometric Mean[a]</th><th>Ratio (%)[b]</th><th colspan="2">90% CI[c]</th><th colspan="2">Power ANOVA</th></tr>
<tr><th>Test</th><th>Ref</th><th>(Test/Ref)</th><th>Lower</th><th>Upper</th><th></th><th>CV%</th></tr>
<tr><td>ln(C_{max})</td><td>110.7577</td><td>118.4320</td><td>93.52</td><td>89.82</td><td>97.37</td><td>1.0000</td><td>6.70</td></tr>
<tr><td>ln(AUC_{last})</td><td>3661.5895</td><td>4054.3170</td><td>90.31</td><td>85.38</td><td>95.53</td><td>1.0000</td><td>9.34</td></tr>
<tr><td>ln(AUC_{inf})</td><td>3956.0526</td><td>4394.7729</td><td>90.02</td><td>84.11</td><td>96.34</td><td>0.9997</td><td>11.30</td></tr>
</table>
[a] Geometric Mean for the Test Formulation-Disintegrated followed by water, T2 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
</td></tr>
</table>

Adverse events are listed below; no AEs were serious or severe:

Table 6: Adverse Events, Study 01809PB

	Treatment T1 (N=17)		Treatment T2 (N=17)		Reference Product (N=17)	
Number of Treatmen-Emergent Adverse Events Reported	6		8		5	
Number of Subjects Reporting One or More Events (Percent of Subjects)	5 (29%)		6 (35%)		3 (18%)	
Adverse Events	**Subject**	**Event**	**Subject**	**Event**	**Subject**	**Event**
Abdominal pain	1 (6%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anorexia	0 (0%)	0 (0%)	1 (6%)	1 (13%)	2 (12%)	2 (40%)
Back pain	0 (0%)	0 (0%)	1 (6%)	1 (13%)	0 (0%)	0 (0%)
Chapped lips	0 (0%)	0 (0%)	1 (6%)	1 (13%)	0 (0%)	0 (0%)
Dizziness	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dry skin	0 (0%)	0 (0%)	1 (6%)	1 (13%)	0 (0%)	0 (0%)
Dyspepsia	0 (0%)	0 (0%)	1 (6%)	1 (13%)	0 (0%)	0 (0%)
Early satiety	1 (7%)	1 (17%)	1 (6%)	1 (13%)	1 (6%)	1 (20%)
Headache	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	1 (20%)
Headache, Intermittent	1 (6%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Irregular pulse	0 (0%)	0 (0%)	1 (6%)	1 (13%)	0 (0%)	0 (0%)
Nausea	1 (6%)	1 (17%)	1 (6%)	1 (13%)	0 (0%)	0 (0%)
Right arm contusion	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	1 (20%)
Swollen lip	1 (6%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Upper Respiratory Infection	1 (6%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Percentages of subjects (Incidence of AE) are based on the number of subject exposure to each study drug.
Percentages of events are based on the number of events reported.

As above, no adverse events of euphoria were seen in this study.

It was reported that the effect of ODT on oral mucosa was examined and that no clinically significant abnormalities were observed.

AUDITS

Division of Scientific Investigations (DSI) inspection reports are still pending as of this writing. The preliminary information suggests deficiencies at the site unrelated to the bioequivalence data, primarily related to not conducting mouth checks twice to be sure subjects did not get mouth ulcers from the phentermine swallowed 2 to 4 hours earlier.

CMC

No CMC deficiencies were identified. See Dr. Chikhale's review for details.

PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology deficiencies were identified. See Dr. Summan's review for details.

FINANCIAL DISCLOSURE

The sponsor provided a signed form FDA 3454, certifying that no financial arrangements or interests were held by the listed clinical investigators for the clinical pharmacology studies conducted to support approval of this application.

LABELING

Suprenza will be the first phentermine product to be in Physician Labeling Rule format. A detailed labeling review will be conducted separately from this document.

The following are some of the clinical issues we have considered with this label:

- The duration of use is limited to a few weeks: this duration limitation is a hold-over from the phentermine labels for the reference listed drug. The PLR label will for the most part mirror currently approved phentermine labeling.

- In 2007, as part of a relisting determination for Ionamin (phentermine resin complex), I reviewed the NDA file for Ionamin, relevant literature, and postmarketing reports. At that time, 11 case reports involving phentermine were identified from the published literature. In the past, phentermine was often taken with a second anorexigenic agent, such as fenfluramine, and therefore, adverse reactions associated with fenfluramine, such as primary pulmonary hypertension (PPH) and valvulopathy are occasionally attributed to phentermine. PPH and valvulopathy are in the Warnings section of the phentermine label. Adverse event reports with a plausible relationship to the sympathomimetic effect of phentermine in patients on phentermine monotherapy included: cerebrovascular ischemic event (2 reports), ischemic colitis (1 report), and acute nonarteritic ischaemic optic neuropathy (1 report). At that time it was recommended that 'ischemic events' be included in the Adverse Reactions section of labeling; not all phentermine product labeling appears to have been updated. 'Ischemic events' should be added to this PLR.

- Phentermine's current labeling does not include clinical trial information. The applicant has proposed to include adverse events from their single dose BA/BE studies in the Adverse Reactions section. Experiences from these studies should be not be considered to reflect the full range of experiences of patients prescribed phentermine, who may take it for longer and have greater background risk. In addition, these were small studies not designed to assess safety.

- All weight loss drugs will now be labeled as Pregnancy Category X, due to obligatory maternal weight gain for the health of the developing fetus. Labeling will be updated to reflect this new Agency policy. See the Maternal Health staff's review for more details.

- Labeling will reflect that phentermine is known to be cleared by the kidney, and that this product is to be used with caution in patients with renal impairment (see Dr.

Zadezensky's review). A post-marketing study to evaluate the PK of this drug in renally-impaired patients will be required.

- Because of the potential for misuse – both because of its amphetamine properties as well as its peppermint flavoring – the Controlled Substance Staff (CSS) has recommended language for Section 17 (Patient Counseling Information).

- DDMAC has made some labeling recommendations in order to limit the company's ability to (b) (4)

- A Medication Guide (MG) is not being required by OSE at this time. As OSE notes, requiring a MG for this product would impact other approved phentermine products. After conducting a thorough safety review of phentermine (all dosage forms), OSE may make a determination that patient labeling or other labeling updates are needed.

PROPRIETARY NAME

The sponsor proposed the following proprietary names: (b) (4) Suprenza. DDMAC has found two of these names (b) (4) unacceptable for the following reasons:

(b) (4)

(b) (4)

DDMAC does not have any promotional issues with the name Suprenza. I have no objections to or issues with DDMAC's assessment.

The name Suprenza was also submitted to the Office of Surveillance and Epidemiology for safety review. DMEPA reviewed Suprenza based on the product characteristics and known safety profile, and found the name acceptable. I have no objections to or issues with DMEPA's assessment.

PEDIATRIC STUDY REQUIREMENTS

In consultation with the Pediatric Review Committee (PeRC), pediatric study requirements are being waived. The committee felt that there was not enough evidence of long-term phentermine safety in adults to justify exposing children for a year-long study. (b) (4) If indeed the drug utilization study demonstrates significant off-label use in children, FDA may determine if further study (non-clinical or clinical) is needed to evaluate this potential safety risk.

POST-MARKETING REQUIREMENTS

The sponsor will be required to conduct a pharmacoepidemiology study to evaluate drug utilization annually in the first 3 years after market launch to more fully understand and assess off-label use (in particular, use beyond a few weeks duration), as well as a clinical pharmacology study to evaluate the PK of phentermine in patients with renal impairment.

RECOMMENDATION

I recommend approval of this 505(b)(2) application for the short-term use of phentermine 15 mg and 30 mg for weight loss in adults with BMI (b) (4) (b) (4) with co-morbidities based on bioequivalence to the reference drugs, pending final DSI inspection reports and agreement on product labeling. Post-marketing required studies include a drug utilization study and a renal impairment study. I also recommend that periodic safety update reports (PSURs) be reviewed for reports of oral mucosal irritation.

(b) (4)

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

/s/

JULIE K GOLDEN
06/01/2011

ERIC C COLMAN
06/01/2011

CLINICAL FILING MEMORANDUM

NDA Number: 202088 **Applicant:** Citius Pharmaceuticals, LLC

Drug: Phentermine HCl ODT 15, 30, 37.5mg **NDA Type:** 505(b)(2)

Clinical Reviewer: Monique Falconer, MD, MS
Filing Meeting: September 30, 2010
Filing Date: October 16, 2010
74-day Filing Issues: Under the Pediatric Research Equity Act (PREA) of 2007 the applicant is required to submit a pediatric plan outlining the pediatric studies the applicant plans to conduct or documentation for a deferral or biowaiver.
PDUFA Date: August 12, 2011

Introduction
Phentermine is a sympathomimetic amine. Its pharmacologic activity is similar to the amphetamines, which are the prototype drugs for this class of obesity drugs. However, the precise mechanism of action for phentermine mediated weight loss has not been elucidated. The applicant Citius Pharmaceutical (Citius) has developed an orally disintegrating tablet (ODT) formulation of phentermine HCl, and asserts that this formulation will make administration of the tablet easier for patients. The applicant is submitting a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for the approval of phentermine HCl ODT 15, 30 and 37.5mg. The submission references the listed drugs phentermine HCl 15 and 30mg capsules (manufactured by Sanoz Pharmaceuticals) and Adipex-P TEVA 37.5mg tablet (manufactured by Gate Pharmaceuticals).

Background
A resin of phentermine was first approved in 1959. Drugs initially approved between 1938 and 1962 on the basis of safety alone, required an assessment of efficacy under the Drug Efficacy Study Implementation (DESI) process, which began in the late 1960s. In 1973 phentermine hydrochloride, an amphetamine congener, was reviewed under the DESI process and deemed efficacious for short term (a few weeks) treatment of obesity.

On March 13, 2007, Citius opened a pre-IND for an orally disintegrating tablet (ODT) formulation of phentermine hydrochloride and submitted a briefing document and questions to the Division of Metabolism and Endocrinology Products (DMEP).

Summary of DMEP response:
Citius was provided with information on the 505(b)(2) regulatory requirements. DMEP advised the applicant that while the toxicological data and approved short-term clinical use of phentermine appeared adequate to support the proposed development plan, (b) (4) Also, additional clinical studies may be required for additional labeling claims over the currently marketed immediate release formulations to which the ODT would be demonstrating bioequivalence. DMEP also recommended that Citius either conduct a bioequivalence study of phentermine ODT compared to the marketed phentermine with labeling limited to the same conditions of use/claims found in the labeling of currently approved phentermine, or examine the efficacy and safety of ODT compared to placebo in a one-year study (b) (4)

CLINICAL FILING MEMORANDUM

NDA Number: 202088 **Applicant:** Citius Pharmaceuticals, LLC

Drug: Phentermine HCl ODT 15, 30, 37.5mg **NDA Type:** 505(b)(2)

(b) (4)

Clinical Development Program

The applicant conducted 3 studies to compare the bioavailability and bioequivalence of the test drug phentermine HCl ODT (15. 30 and 37.5mg) to the immediate release listed drug formulations (15. 30 and 37.5mg) (Table 1). The applicant also evaluated food effect, the effect of swallowing and potential mucosal irritation by the ODT formulation, as well as the proposed labeling claim that the ODT can be taken with or without water.

Table 1: Biopharmaceutical Studies with Phentermine HCl 15, 30 and 37.5mg ODT

Study Reference number	Study population	Study Objectives	Study Design	Treatment
01806KH	15 healthy male and female subjects 18-45 years old BMI 18-30kg/m^2	Compare the bioavailability of phentermine HCL 15mg ODT to the reference Listed drug when administered: • oral disintegration swallowed with water, fasted (T1) • oral disintegration swallowed without water, fasting (T2) PK data collected Safety including oral irritation monitored	A 30-day, randomized, balanced, open-label, single-dose, 3-treatment, 3-sequence, 3-period, crossover (10-day wash-out period between doses)	• 15mg ODT test drug oral disintegration swallowed with water • 15mg ODT test drug oral disintegration swallowed without water • 15mg phentermine HCl (Reference) capsule swallowed with water
018089D	15 healthy male and female subjects 18-45 years old BMI 18-30kg/m^2	Compare the bioavailability of phentermine HCL 30mg ODT to the reference Listed drug when administered: • no disintegration, swallowed with water (T1) • oral disintegration swallowed with water (T2) PK data collected Safety including oral irritation monitored	Randomized, balanced, open-label, single-dose, 3-treatment, 3-sequence, 3-period, crossover	• 30mg ODT test drug swallowed with water • 30mg ODT test drug oral disintegration swallowed with water • 30mg phentermine HCl capsule (Reference) administered with water, fasted
01809PB	18 healthy male and female subjects	Compare the bioavailability of phentermine HCL 37.5mg ODT to the reference Listed drug when administered: • fasted (T1)	Randomized, balanced, open-label, single-dose, 3-treatment,	• 37.5mg ODT test drug, fasted • 37.5mg ODT test drug, fed • 37.5mg phentermine HCl tablet (Reference), fasted

CLINICAL FILING MEMORANDUM

NDA Number: 202088 **Applicant:** Citius Pharmaceuticals, LLC

Drug: Phentermine HCl ODT 15, 30, 37.5mg **NDA Type:** 505(b)(2)

Study Reference number	Study population	Study Objectives	Study Design	Treatment
	18-45 years old BMI 18-30kg/m^2	• fed (T2) PK data collected Safety including oral irritation monitored	3-sequence, 3-period, crossover	

Applicant's Biopharmaceutics Summary

Study 01806KH:

The test formulation of phentermine 15mg ODT administered with or without water was bioequivalent to the reference listed drug phentermine HCL 15mg capsule in a fasted state. The test formulation of phentermine 15mg ODT administered with water was also bioequivalent to the test formulation of phentermine 15mg ODT administered without water.

Study 018089D:

The test formulation of phentermine 30mg ODT whether swallowed whole or disintegrated was bioequivalent to the reference listed drug phentermine HCL 30mg capsule in a fasted state. The test formulation of phentermine 30mg ODT swallowed whole with water was also bioequivalent to the test formulation of phentermine 30mg ODT disintegrated and swallowed with water.

Study 01809PB:

The test formulation of phentermine 37.5mg ODT whether administered when fasted or fed was bioequivalent to the reference listed drug phentermine HCL 37.5mg tablet in a fasted state. The test formulation of phentermine 37.5mg ODT administered while fed was also bioequivalent to the test formulation of phentermine 37.5mg ODT while fasted.

Test drug disintegration summary:

The stability data showed disintegration times (b) (4).

Efficacy Summary

The applicant will rely on the efficacy data of the reference listed drug.

Safety Summary

The applicant will rely on the safety data from the referenced listed drug. The sponsor has also provided a listing of the postmarketing adverse events from the Adverse Event Reporting System (AERS) from the first quarter of 2009 to the fourth quarter of 2009.

The applicant collected safety data for the three bioequivalence trials. These included physical examinations, vital signs, clinical laboratory tests, ECGs and adverse event

reports during the trial and the follow-up period. The applicant reported that of the 47 subjects who took part in the three studies, 29 (62%) had a total of 38 events. There were no deaths or adverse events leading to discontinuation of the study drug. The adverse events ranged from mild to moderate intensity and all the subjects fully recovered.

Generally, it appeared there were more reports of adverse events while the subjects were on the test formulation, compared to while they were on the reference listed drug (Table 2).

Table 2: Number (%) of Subjects and Adverse Events during the Bioequivalence Studies

Dose		T1	T2	Reference Product
15mg	Number treatment emergent AEs	2	6	3
	Number (%) of subjects	1/15 (7.0)	5/15 (33.0)	2/15 (13.0)
30mg	Number treatment emergent AEs	6	2	0
	Number (%) of subjects	5/15 (33.0)	1/15 (7.0)	0
37.5mg	Number treatment emergent AEs	6	8	5
	Number of subjects	5/17 (29.0)	6/17 (35.0)	3/17 (18.0)

Overall, according to the applicant, the most commonly reported adverse events were in the system organ class nervous system disorders (8 [17%]) and were due to headache (5 [10.6%]) and dizziness (4 [8.5%]). Other commonly reported adverse events by system organ class were gastrointestinal disorders (4 [8.5%]), metabolism and nutritional disorders (3 [6.4%]) and musculoskeletal and connective tissue disorders (3 [6.4%]). Also, there were no reports of oral mucosal irritation.

Proposed Labeling Changes
The applicant submitted draft labeling in the PLR format.

Pediatric Use
The applicant did not submit a pediatric plan or documentation for pediatric biowaiver.

Good Clinical Practices
The applicant did not submit a statement of good clinical practices

Financial Disclosure
The applicant submitted the financial disclosure certification form.

Table 3: Overview of the Phentermine HCL ODT NDA 505(b)(2) Application for Filing

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					

CLINICAL FILING MEMORANDUM

NDA Number: 202088 **Applicant:** Citius Pharmaceuticals, LLC

Drug: Phentermine HCl ODT 15, 30, 37.5mg **NDA Type:** 505(b)(2)

	Content Parameter	Yes	No	NA	Comment
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Paper submission in CTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			X	Paper submission
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?		X		The applicant has committed in writing to submit outstanding CMC data in November 2010
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	The applicant summarized the safety data for the subjects in the three BE studies, as well as included AERS reports (2009 Q1 to 2009 Q4)
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2) Reference drug: Phentermine HCl 15mg capsule, 30mg capsule and 37.5mg tablet
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and			X	No clinical efficacy

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NDA Number: 202088 **Applicant:** Citius Pharmaceuticals, LLC

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	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:				studies were done. The three BE studies are the basis for approval.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	The applicant is relying on the prior findings of safety. (RLD Phentermine HCL)

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

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	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		Neither a pediatric assessment plan nor documentation for a pediatric waiver was submitted
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	The applicant referenced the Adipex-P label.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms			X	

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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NDA Number: 202088 **Applicant:** Citius Pharmaceuticals, LLC

Drug: Phentermine HCl ODT 15, 30, 37.5mg **NDA Type:** 505(b)(2)

	Content Parameter	Yes	No	NA	Comment
	in a legible format (deaths, serious adverse events, and adverse dropouts)?				
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES___

If the application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Under the Pediatric Research Equity Act (PREA) of 2007 the applicant is required to submit a pediatric plan outlining the pediatric studies the applicant plans to conduct or documentation for a deferral or biowaiver.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

MONIQUE FALCONER
10/18/2010

ERIC C COLMAN
10/19/2010