

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202088Orig1s000

OTHER REVIEW(S)



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 6, 2011

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Consult on NDA 202088
Suprenza (phentermine orally-disintegrating tablets)
Abuse potential of new formulation
Indication: short-term treatment of obesity
Doses: 15, 30, (b) (4)
Sponsor: Citius Pharmaceuticals

Materials reviewed: NDA (three bioavailability and bioequivalence studies that included pharmacokinetic and adverse event data) Sponsor-proposed drug label

Background:

The Division of Metabolism and Endocrinology Products consulted CSS regarding Suprenza, an orally disintegrating formulation of phentermine flavored with peppermint and sweetened with mannitol and sucralose (NDA 202088). Each tablet of Suprenza contains 15, 30 (b) (4) of phentermine HCl. This NDA is being reviewed as a 505(b)(2) submission. Thus, the Sponsor submitted three bioavailability and bioequivalence studies (b) (4) that included both pharmacokinetic and adverse event data. No specific abuse-related data were submitted, other than psychiatric and neurological adverse events collected during the PK studies. No pharmacology-toxicology studies, including safety pharmacology studies, were conducted with this new formulation. A proposed drug label for Suprenza was also submitted. Phentermine is a Schedule IV substance under the Controlled Substances Act.

Given that Suprenza is a new dosage formulation, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) will apply to this NDA. (b) (4)

Conclusions:

- The Tmax and Cmax produced by the three proposed dosage formulations of Suprenza (15, 30 (b) (4)) are nearly identical to the Tmax and Cmax produced by the currently marketed immediate release formulations of phentermine at the same drug doses. Additionally, the AUC values for Suprenza are lower than those for the immediate release formulations of phentermine at the same drug doses. These pharmacokinetic data demonstrate that Suprenza produces a similar onset time, similar peak plasma concentrations and lower overall plasma concentrations compared to immediate-release phentermine. This suggests that the pharmacokinetic profile of Suprenza does not increase its abuse potential compared to currently marketed Schedule IV immediate release phentermine products.
- The adverse events (AEs) observed during the pharmacokinetic studies with Suprenza show that the degree of euphoria, as indicated by abuse related AEs reported by subjects who received this formulation, is comparable to that reported by subjects who received the positive control, immediate release phentermine. This suggests that Suprenza has an abuse potential that may be similar to that of currently marketed Schedule IV immediate-release phentermine products.

Conclusions and Recommendations (to be conveyed to Sponsor):

- The proposed drug label for Suprenza is acceptable with regard to the abuse related information contained in Section 9.0 “Abuse and Dependence” and Section 7.2 “Drug Interactions: Alcohol”.
- Precautions against misuse, abuse, and diversion should be included in product labeling and any other materials that will be made available for patients and healthcare professionals. The Sponsor should include a statement in the Patient Counseling Information section of the label (Section 17.0) informing patients that Suprenza tablets should be kept in a safe place to prevent accidental overdose, misuse or abuse, and that selling or giving away Suprenza tablets may harm others and is against the law.

- Suprenza is not likely to produce a risk of abuse that is different from that of currently marketed Schedule IV immediate release formulations of phentermine, based on the similarity between the two drug products in terms of their pharmacokinetic profile and the abuse related adverse events reported in these single dose pharmacokinetic studies.
- The Suprenza formulation is a tablet flavored with sweetened peppermint, making it similar to a candy product in appearance and taste. Compared to an unflavored tablet that is swallowed whole, the candy-like properties of Suprenza may increase its desirability to children for nonmedical purposes and may also increase the possibility that an adult or minor would consume higher than recommended doses of Suprenza. These factors may lead to overdose, misuse or abuse of the drug product.



- Additionally, in order to monitor the actual abuse potential of Suprenza after it is marketed, the Sponsor should provide monitoring of selected postmarketing adverse events in addition to current, mandatory pharmacovigilance requirements. The Office of Surveillance and Epidemiology will provide the final determination on the adequacy of the proposed, post-marketing plan and that of the reporting frequency.
- The proposed plan should include maintenance of all adverse events in a centralized safety database with expedited reporting of the “Events of Interest” listed below. Individual case safety reports (ICSRs) that include these events will be submitted to the Agency as expedited reports, 15-day reports, for one (1) year unless a renewal is stated. These Events of Interest based on the latest MedDRA terminology are:
 - Drug administered at inappropriate site
 - Drug administration error
 - Incorrect dose administered
 - Incorrect route of drug administration
 - Wrong technique in drug usage process
 - Intentional drug misuse
 - Accidental exposure
 - Accidental overdose
 - Intentional overdose

- Multiple drug overdose
 - Multiple drug overdose accidental
 - Multiple drug overdose intentional
 - Overdose
 - Drug abuser
 - Substance abuser
 - Dependence
 - Drug dependence
 - Drug tolerance
 - Drug tolerance decreased
 - Drug tolerance increased
-
- In addition to expedited reporting of the above events, a discussion in the quarterly periodic report should provide numbers and trends based upon MSSO's Standardized MedDRA Query (SMQ): "Drug Abuse, Dependence and Withdrawal" and accident related events for the entire period the drug is marketed.
 - The Sponsor should also follow and report relevant data from national abuse databases: Drug Abuse Warning Network (DAWN), and the Toxic Exposure Surveillance System (TESS) report prepared by the American Association of Poison Control Centers (AAPCC), currently the National Poison Data System (NPDS), and any additional product specific databases that are helpful to understand the use in real world conditions.

Appendix

Abuse-Related Data in the NDA for Suprenza

The NDA submission for Suprenza included two types of data related to abuse potential: pharmacokinetic data from three bioavailability/bioequivalence (BA/BE) studies and adverse events data from the three BA/BE studies.

Pharmacokinetic Studies

Three BA/BE studies were conducted by the Sponsor:

- Study #1806KH 15 mg Suprenza compared to 15 mg immediate-release phentermine
- Study # 18089D 30 mg Suprenza compared to 30 mg immediate-release phentermine
- Study #1809PB (b) (4) Suprenza compared to (b) (4) immediate-release phentermine

Each of these pharmacokinetic studies had a randomized, balanced, open-label, single dose crossover design using one of the three phentermine treatments (orally dissolved Suprenza, followed either with or without water, as well as an immediate-release oral dose of phentermine equal to the dose contained in the Suprenza formulation). The washout period between sessions in each study was at least 10 days.

The three drug treatment conditions produced pharmacokinetics (Tmax, Cmax and AUCinf) that were largely equivalent (Tables 1, 2 and 3, below), based on a comparison between Suprenza and identical doses of immediate-release phentermine:

Table 1: Pharmacokinetic Profile of Suprenza (With and Without Water) Compared to Immediate-Release Phentermine at 15 mg (p.o.)

Treatment (oral administration)	PK Parameter	Suprenza with Water	Suprenza without Water	Immediate-Release Phentermine
15 mg phentermine	Tmax (hr)	3.0	3.7	3.8
(n 15)	Cmax (ng/ml)	48.2	49.7	48.9
	AUCinf (hr*ng/ml)	1775	1780	1901

As shown in Table 1 (above), the 15 mg oral Suprenza formulation produced a Tmax of ~3-4 hours when taken either with or without water, which is similar to that of the ~4 hr

Tmax produced by the 15 mg oral immediate-release phentermine formulation. The Suprenza formulation (either with or without water) produced a Cmax of 48-50 ng/ml, which is similar to that of the Cmax produced by the immediate-release formulation (~49 ng/ml). However, Suprenza (either with or without water) produced an AUCinf of 1775-1780 hr*ng/ml that was slightly lower than that produced by the immediate-release formulation of phentermine (1901 hr*ng/ml).

Table 2: Pharmacokinetic Profile of Suprenza (With and Without Water) Compared to Immediate-Release Phentermine at 30 mg (p.o.)

Treatment (oral administration)	PK Parameter	Suprenza with Water	Suprenza without Water	Immediate-Release Phentermine
30 mg phentermine	Tmax (hr)	3.7	4.5	3.8
(n 15)	Cmax (ng/ml)	94.0	98.8	100
	AUCinf (hr*ng/ml)	3746	3632	4114

As shown in Table 2 (above), the 30 mg oral Suprenza formulation produced a Tmax of ~4-5 hours when taken either with or without water, which is similar to that of the ~4 hr Tmax produced by the 30 mg oral immediate-release phentermine formulation. The Suprenza formulation (either with or without water) produced a Cmax of ~94-99 ng/ml, which is similar to that of the Cmax produced by the immediate-release formulation (100 ng/ml). However, Suprenza (either with or without water) produced an AUCinf of 3632-3746 hr*ng/ml that was slightly lower than that produced by the immediate-release formulation of phentermine (4114 hr*ng/ml).

Table 3: Pharmacokinetic Profile of Suprenza (Without Water, Fasted and Fed) Compared to Immediate-Release Phentermine (Fasted) at (b) (4) (p.o.)

Treatment (oral administration)	PK Parameter	Suprenza without Water (Fasted)	Suprenza without Water (Fed)	Immediate-Release Phentermine (Fasted)
(b) (4) phentermine	Tmax (hr)	3.0	4.5	2.7
(n 18)	Cmax (ng/ml)	119	112	121
	AUCinf (hr*ng/ml)	4595	4033	4509

As shown in Table 3 (above), the (b) (4) oral Suprenza formulation produced a T_{max} of 3 hours when taken without water in the fasted state, which is similar to the ~3 hr T_{max} produced by (b) (4) oral immediate-release phentermine formulation when taken in the fasted state. The T_{max} for Suprenza when taken without water in the fed state was slightly longer, at 4.5 hr. The Suprenza formulation (without water, either fasted or fed) produced a C_{max} of 112-119 ng/ml, which is similar to that of the C_{max} produced by the immediate-release formulation in the fasted state (121 ng/ml). The Suprenza formulation produced an AUC_{inf} of 4594 hr*ng/ml when taken without water in the fasted state, which is similar to that of the 4509 hr*ng/ml AUC_{inf} of immediate-release phentermine formulation when taken in the fasted state. The AUC_{inf} for Suprenza when taken without water in the fed state was slightly smaller, at 4033 hr*ng/ml

Abuse-Related Adverse Events in Pharmacokinetic Studies

Adverse events were monitored during each of the three pharmacokinetic studies conducted with Suprenza and immediate-release phentermine. All subjects were monitored for adverse events up to 7-10 days after administration of the last drug treatment in each study.

In the 15 mg phentermine condition (Suprenza, with and without water, compared to immediate-release phentermine), there were 10 AEs reported by 6 of the 15 subjects following initiation of drug administration. Three of these 10 AEs were determined to be probably or possibly related to study treatment. Euphoria was reported by one subject who received Suprenza without water. Restlessness was reported by one subject who received Suprenza with water. Thirst was reported by one subject who received Suprenza without water. There were no other abuse-related AEs reported, including any additional reports of euphoria.

In the 30 mg phentermine condition (Suprenza, with and without water, compared to immediate-release phentermine), there were 8 AEs reported by 6 of the 15 subjects following initiation of drug administration. The number of AEs reported at the 30 mg dose is less than that reported with the 15 mg dose. Seven of these 8 AEs in the 30 mg condition were determined to be probably or possibly related to study treatment. Euphoria was reported by one subject who received Suprenza with water. Headache was reported by three subjects: two in the Suprenza with water condition and one in the Suprenza without water condition. Dizziness was reported by three subjects who received Suprenza with water. There were no other abuse-related AEs reported, including any additional reports of euphoria.

In the (b) (4) phentermine condition (Suprenza, without water, in the fasted and fed state, compared to immediate-release phentermine in the fasted state), there were 19 AEs reported by 9 of the 18 subjects following initiation of drug administration. Thirteen of these 19 AEs were determined to be probably or possibly related to study treatment. Notably, euphoria was not reported by any subjects in any of the treatment conditions with the (b) (4) dose. Anorexia was reported by 3 subjects: one in the Suprenza

condition without water in fed state and two in the immediate-release phentermine condition in fasted state. Headache was reported by 2 subjects: one in the Suprenza condition without water in fasted state and one in the Suprenza condition without water in fed state. Nausea was reported by 2 subjects: one in the Suprenza condition without water in fasted state and one in the Suprenza condition without water in fed state. There were no other abuse-related AEs reported, including any additional reports of euphoria.

Pharmacokinetic Evaluation of Euphoria Reports

An evaluation of the pharmacokinetics of phentermine was conducted by Dr. Zdrojewski, the clinical pharmacologist in the Division of Metabolism and Endocrinology Products, for the two incidents of euphoria reported as an AE during the clinical studies with Suprenza, as described above.

15 mg Phentermine Condition

In the 15 mg phentermine condition (Suprenza, with and without water, compared to immediate-release phentermine), there was a single incidence of euphoria reported by a subject who received Suprenza without water. The phentermine C_{max} value for this subject was 69 ng/ml, which is higher than the mean C_{max} for subjects who received Suprenza without water (50 ng/ml). Although this would seemingly explain the report of euphoria, the other two test conditions produced similar C_{max} values in this subject (72 ng/ml for Suprenza with water condition and 66 ng/ml for phentermine immediate-release condition) without producing euphoria.

30 mg Phentermine Condition

In the 30 mg phentermine condition (Suprenza, with and without water, compared to immediate-release phentermine), there was a single incidence of euphoria reported by a subject who received Suprenza with water. The phentermine C_{max} value for this subject was 82 ng/ml, which is lower than the mean C_{max} for subjects who received Suprenza with water (94 ng/ml). Additionally, euphoria was not reported in the other two test conditions, where the C_{max} values were higher than those in the Suprenza with water condition (93 ng/ml for Suprenza without water condition and 92 ng/ml for phentermine immediate-release condition).

Proposed Drug Label for Suprenza

The proposed drug label text for Suprenza is nearly identical to the drug label for currently-marketed immediate-release formulations of phentermine, with the following exceptions:

- The proposed drug label for Suprenza uses the most recent standardized format, including a Section 9.0 Abuse and Dependence and its subheadings of 9.1

“Controlled Substance”, 9.2 “Abuse” and 9.3 “Dependence”. The drug labels for the currently-marketed formulations of phentermine do not use this format.

- The proposed drug label for Suprenza states that phentermine as a Schedule IV controlled substance under Section 9.1 “Controlled Substance”. There is no statement in the text of the drug label for the currently marketed formulations of phentermine regarding the controlled substance status of phentermine (although the “C-IV” designation does appear on the first page of the label).
- For the currently-marketed formulations of phentermine, the Drug Abuse and Dependence section of the label is comprised of a single paragraph. In the proposed drug label for Suprenza, the text has been appropriately separated, based on content, into Sections 9.2 “Abuse” and 9.3 “Dependence”.
- The information from the drug label for the currently-marketed formulations of phentermine presented under the heading “Usage with Alcohol” has been placed into Section 7.2 “Drug Interactions: Alcohol” of the proposed drug label for Suprenza.

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/s/

KATHERINE R BONSON
05/06/2011

SILVIA N CALDERON
05/06/2011

MICHAEL KLEIN
05/06/2011

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: October 25, 2010

TO: CT Viswanathan,
Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Patricia Madara, Regulatory Project Manager, Division of Metabolism and
Endocrinology Products, HFD-510

SUBJECT: Request for Biopharmaceutical Inspections
NDA 202088
(b) (4) (phentermine hydrochloride) ODT, 15 mg, 30 mg, (b) (4)
Citius Pharmaceuticals, LLC

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
018089D And 01809PB	CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217	(b) (4)
	Phone: 210-635-1515	
	FAX: 1-210-635-1646	
	No specific contact see website:	
	http://www.cedraresearch.com/wct-management-team.asp	
	(same sites for both studies)	(same sites for both studies)

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **May 02, 2011**. We intend to issue an action letter on this application by **June 13, 2011**.

Should you require any additional information, please contact Patricia Madara, Project Manager, 310-796-1249.

Concurrence: (Optional)

Immo Zdrojewski, Ph.D., Clinical Pharmacology Reviewer
Sally Choe, Ph.D., Clinical Pharmacology Team Leader

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/s/

PATRICIA J MADARA
10/25/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 202088 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: phentermine HCl orally dissolving tablet Dosage Form: orally dissolving tablet Strengths: 15, 30, (b) (4)		
Applicant: Citius Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: August 11, 2010 Date of Receipt: August 13, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: June 13, 2010	Action Goal Date (if different):	
Filing Date: October 12, 2010	Date of Filing Meeting: September 30, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): Indicated as a short term a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m ² , or ≥ 27 kg/m ² in the presence of other risk factors (e.g. hypertension, diabetes, hyperlipidemia)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>): N/A				
List referenced IND Number(s): 76477				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system? <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?			X		
<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5 year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3 year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?				X	
<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>					

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: N/A <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input checked="" type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	Requested datasets, cmc, and dissolution info are electronic			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).		X		This is primarily a paper NDA – only electronic info are datasets
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: X legible X English (or translated into English) X pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it</i>				

<i>did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vi)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: not yet sent</i></p>		X		

Pediatrics	YES	NO	NA	Comment
<u>PREA</u>	X			
<p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Required documents will arrive shortly
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?		X		Will be submitted shortly – requested in 74-day letter
<i>If no, request in 74-day letter</i>				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>		X		
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Will be submitted shortly
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>		X		
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		Will be consulted when tradename approved
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	No PPI, IFU, or Medguide
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		X		Requested but not yet received
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>			X	Not held
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>			X	Not held

<p>Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>		X		None submitted for review
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ATTACHMENT

MEMO OF FILING MEETING

DATE: September 30, 2010

NDA #: 202088

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: phentermine hydrochloride

DOSAGE FORM/STRENGTH: 15, 30, (b) (4) orally dissolving tablet

APPLICANT: Citius Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Indicated as a short term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g. hypertension, diabetes, hyperlipidemia)

BACKGROUND: This 505(b)(2) application for a new formulation of phentermine hydrochloride. Various formulations of phentermine have been approved for short term use in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g. hypertension, diabetes, hyperlipidemia) since the 1950s.

The 2007 FDA Draft Guidance for developing drugs to treat obesity defines it as a chronic illness that requires long-term treatment.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pat Madara	Y
	CPMS/TL:	Lina Al Juburi	N
Cross-Discipline Team Leader (CDTL)	Sally Choe		Y
Clinical	Reviewer:	Monique Falconer	Y
	TL:	Eric Colman	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Immo Zdrojewski	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mukesh Summan	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Elsbeth Chikhale	N
	TL:	Su Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	Elsbeth Chikhale	N
	TL:	Su Tran	Y
Facility Review/Inspection	Reviewer:	CDER DMPQ Review	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	TBD	
	TL:	TBD	
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/DCRMS (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (DSI)	Reviewer:	Martin Yau	Y
	TL:	Jean Mulinde	
Controlled Substance Staff (CSS)	Reviewer:	TBD	
	TL:		
Other reviewers	Tapash Ghosh, ONDQA Biopharmaceutics reviewer		Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>Comments:</p> <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments: <u>probably not applicable since this is a 505b2</u></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Application sent to Biostats TL, Todd Sahlroot. No reviewer assigned.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: a potential refuse-to-file issue was eliminated after obtaining additional information from the sponsor prior to the 60-day filing date.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: a potential refuse-to-file issue was eliminated after obtaining additional information from the sponsor prior to the 60-day filing date.</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Eric Colman, M.D.; Deputy Director of DMEP</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p>done</p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p>N/A</p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p>N/A</p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>

N/A	BLA/BLA supplements: If filed, send 60-day filing letter
N/A	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
done	Send review issues/no review issues by day 74
TBD	Conduct labeling review and include labeling issues in the 74-day letter
N/A	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

PATRICIA J MADARA
11/30/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medication Error Prevention and Risk Management

Date: May 13, 2011

Application Type/Number: NDA 202088

To: Mary Parks, Director
Division of Metabolism and Endocrinology Products

Through: Melina Griffis, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Lubna Merchant, M.S., Pharm.D, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name and Strength(s): Phentermine Orally Disintegrating Tablets, 15 mg, 30 mg (b) (4)
(b) (4)

Applicant/sponsor: Citius Pharma.

OSE RCM #: 2011-43

CONTENTS

EXECUTIVE SUMMARY	3
1. INTRODUCTION	3
2. METHODS AND MATERIALS.....	3
2.1. Adverse Event Reporting System (AERS) search criteria	3
2.2 Labels and Labeling	3
3. RESULTS	4
3.1 AERS Results	4
3.2 Labels and Labeling	4
4. DISCUSSION.....	4
5. CONCLUSION AND RECOMMENDATIONS.....	4
5.1 Comments to the Division	4
5.2 Comments to the Applicant.....	4

EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Phentermine Orally Disintegrating Tablets (NDA 202088) for areas of vulnerabilities that could lead to medication errors.

(b) (4)

1. INTRODUCTION

The labels and labeling were submitted by the Applicant on March 15, 2011. The proposed proprietary name is evaluated under separate review (OSE # 2011-1013).

2. METHODS AND MATERIALS

Since Phentermine is currently marketed, the Division of Medication Error Prevention and Analysis (DMEPA) conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors relevant to the labels or labeling of Phentermine and reviewed proposed labels and labeling.

2.1. ADVERSE EVENT REPORTING SYSTEM (AERS)

An AERS search was conducted on March 22, 2011 using the search terms tradename “Fastin,” active ingredients “Phentermine” and verbatim terms “Phentermin%” and “Fasti%.” The reactions used were the HLG T term, “Medication Errors,” and the PT term, “Product Quality Issue.”

Reports were manually reviewed to determine if a medication error occurred. Reports that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse events related to Phentermine or concomitant medications, accidental or intentional overdose, lack of efficacy or product quality complaints, and accidental ingestion) were excluded. If an error occurred, the reports were categorized by type of error and evaluated for contributing factors to the medication errors. Additionally the reports were reviewed to determine if the error could be applicable to the labels and labeling of (b) (4) and thus pertinent to this review. Duplicate reports were combined into cases.

2.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA)¹, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed labels and labeling submitted by the Applicant on March 15, 2011.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3. RESULTS

The following section describes the results of AERS and our label and labeling review.

3.1 AERS RESULTS

A total of 88 cases were retrieved in the AERS search, however after excluding cases as described in section 2.1, 9 cases involved a medication error. These cases are categorized below:

- Wrong drug errors (n = 6). Two cases involved Adipex and Aciphex, one case involved Fastin and Prozac, one case involved Pondimin and Reglan, one case the prescription was filled with Fastin and Generic Phentermine in the same bottle. One case did not specify the medications involved in the confusion.
- Wrong route error (n = 1), in this case the patient dissolved the Phentermine in water and injected the solution.
- Wrong frequency error (n = 2). In one case, the pharmacy technician interpreted the sig code QD as QID. In the second case the pharmacist typed “Take 1 Fastin 4 times daily” instead of the prescribed once daily.

None of these cases are related to the label and labeling of Phentermine and are therefore not relevant to this review.

3.2 LABELS AND LABELING

The label and labeling risk assessment identified the following deficiencies:

- (1) The D&A section of the insert labeling is confusing
- (2) The established name and dosage form is not presented with the proprietary name
- (3) The company symbol and the size of the schedule IV symbol are distracting.

(b) (4)

4. DISCUSSION

(b) (4)

5. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations to the insert labeling in Section 5.1 Comments to the Division for discussion during the labeling meetings. Section 5.2 Comments to the Applicant for the container labels and carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Margarita Tossa at 301-796-4053.

5.1 COMMENTS TO THE DIVISION:

Full Prescribing Information- Dosage and administration- Section 2

1.

2. The following two statements appear separately within this section. “The usual adult dose is one tablet as prescribed by the physician, administered (b) (4) (b) (4)” and “(b) (4) can be administered with or without food.” We recommend these statements be combined and revised as follows:

“The usual adult dose is one tablet as prescribed by the physician, administered in the morning with or without food.”

5.2 COMMENTS TO THE APPLICANT:

A. Proposed Container Label (All sizes and strengths)

1. Revise the product name presentation on the Principal Display Panel to include the established name and the dosage form as shown below.

Tradename
Phentermine HCl Orally Disintegrating Tablets
15 mg

2. Ensure the established name is ½ the size of the proprietary name, and similar in prominence as the proprietary name taking into account all pertinent factors,

including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

3. Relocate the company logo and name to the bottom of the principal display panel or to the side panel.
4. We note that the control substance symbol is more prominent than the proprietary name. Revise the label so that the proprietary and established names are more prominent than the control substance symbol.

Appendices:

Appendix A: Proposed Container Labels



Appendix B: ISR numbers

ISR #		ISR #		ISR #		ISR #	
96391	5	3018574	4	3211655	1	3676639	8
464944	8	3027424	1	3231521	5	3753055	1
610597	5	3075129	3	3253799	4	3753336	1
620436	4	3076519	5	3265985	8	3755981	6
682777	4	3076717	0	3271394	8	3779865	2
1577859	9	3087291	7	3280471	7	3870612	2
1685038	X	3089919	4	3285142	9	3873182	8
1745325	3	3091762	7	3290513	0	3875498	8
1750623	3	3092509	0	3290580	4	3877740	6
1766045	5	3093388	8	3336331	6	3894523	1
1774864	4	3095577	5	3341221	9	3971852	4
1777146	X	3103751	4	3370095	5	3978176	X
1783897	3	3136862	8	3385361	7	4067914	6
1812965	2	3146053	2	3418496	0	4071886	8
1835692	4	3164339	2	3472017	5	4091500	5
1842902	6	3165723	3	3472253	8	4182409	7
1955762	X	3173692	5	3536433	5	4191001	X
1989673	0	3176046	0	3564084	5	4349035	8
2040107	X	3200792	3	3600803	7	4415059	5
7101250	6	5872836	1	5567658	5	4562545	3
7170683	4	6867848	5	5754990	5	4712950	7
5043284	1	5386059	6	5386157	7	4938639	7

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/s/

MELINA N GRIFFIS
05/13/2011

CAROL A HOLQUIST
05/13/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 17, 2011

To: Pat Madara, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 202088 TRADENAME (phentermine HCl) orally dissolving tablets (ODT)
DDMAC labeling comments for phentermine ODT

DDMAC has reviewed the proposed Prescribing Information (PI) and carton/container labeling for phentermine ODT that was consulted on January 21, 2011 [accessed from the eRoom on May 17, 2011].

General Comment

Comments regarding the PI are provided in the marked version of the PI below.

Carton and Container Labeling

DDMAC does not have any comments at this time.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Sam Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
05/17/2011

INTRODUCTION

On August 11, 2010, Citius Pharmaceuticals submitted a 505(b)(2) New Drug Application (NDA 202088) for phentermine HCL 15,30, (b) (4) mg orally-disintegrating tablets (ODT), for the short-term adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia).

On May 2, 2011, the Division of Metabolic and Endocrine Products (DMEP) consulted the Pediatric and Maternal Health Staff (PMHS) - Maternal Health Team (MHT) to review and provide appropriate revisions to the pregnancy subsection of labeling. PMHS-MHT's review also provides suggested revisions to the nursing mothers subsection of labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Phentermine

Phentermine, a sympathomimetic amine, is used as an anorectic or appetite suppressant in obesity treatment. Phentermine was initially approved on May 4, 1959, under the tradename Ionamin[®] (UCB, Inc.), and was found to be effective under DESI on July 19, 1974. Ionamin[®] was withdrawn from the market (for reasons other than safety and efficacy) in 2008. Phentermine has pharmacologic activity similar to the prototype drugs of this class used in obesity treatment (d-amphetamine and d/l-amphetamine)¹ and is the most commonly prescribed medication for treatment of obesity in the U.S.²

Phentermine is currently classified as a pregnancy category C drug. No animal reproductive studies or studies in pregnant women have ever been conducted with phentermine. Limited human pregnancy data were located in reproductive risk databases. REPROTOX[®]³ summarizes phentermine reproductive risk as follows:

There are small series of human pregnancies exposed to phentermine without an increase in congenital malformations. Phentermine is avoided during pregnancy due to concerns about effects of weight loss on embryo development.

And REPROTOX additionally reports:

A 1962 study described the use of phentermine by 118 women in their 3rd trimester of pregnancy until delivery. In this population there were 5 stillborn infants; one was due to abruptio placentae and a second was associated with mild preeclampsia.

¹ See Sponsor Proposed Labeling, March 9, 2011

² Hendricks EJ, Rothman RB, Greenwaw FL. How physician obesity specialists use drugs to treat obesity. Obesity 2009 Sep;17(9):1730-5

³ REPROTOX[®] is a subscription information system on environmental hazards to human pregnancy, reproduction and development developed by the Reproductive Toxicology Center for its members. REPROTOX contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development.

Because phentermine has pharmacologic activity similar to amphetamines, it is important to consider amphetamine vascular side effects, including vasoconstriction and a rise in blood pressure, on a pregnancy. REPROTOX[®]⁴ reports that studies in pregnant sheep with methamphetamine demonstrated the following:

Administration of methamphetamine to pregnant sheep results in transfer of the agent to the fetus. Because the fetus has a longer elimination half-life than the mother, total exposure of the fetus is high. Drug administration in this model is associated with an elevation in maternal and fetal blood pressure, and a decrease in fetal oxyhemoglobin saturation and pH. A transient increase in umbilical vascular resistance and a decrease in uterine blood flow accompanied these changes.

Pregnancy and Weight Gain Guidelines

Weight gain guidelines exist for pregnancy, because both excessive weight gain and weight loss or poor weight gain during pregnancy have been associated with adverse maternal and fetal outcomes. The Institute of Medicine (IOM) published the following new pregnancy weight gain guidelines in May 2009, to address current research that had been conducted on the effects of weight gain in pregnancy on the health of both mother and baby:⁵

TABLE S-1 New Recommendations for Total and Rate of Weight Gain During Pregnancy, by Prepregnancy BMI

Pregpregnancy BMI	Total Weight Gain		Rates of Weight Gain* 2nd and 3rd Trimester	
	Range in kg	Range in lbs	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (< 18.5 kg/m ²)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5-24.9 kg/m ²)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0-29.9 kg/m ²)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥ 30.0 kg/m ²)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

An obligatory weight gain occurs in maternal tissues (the uterus, breasts, blood volume, and in the fetal-placental unit) during pregnancy. Weight gain in pregnancy is partly a gain in adipose tissue, accompanied by some degree of insulin resistance and other metabolic alterations that serve as an adaptive response to allow a more efficient transfer of fuels across the placenta to the fetus.

Excessive weight gain during pregnancy can lead to an increased risk of maternal insulin resistance and gestational diabetes mellitus, which can lead to fetal hyperglycemia and increased adiposity. In addition, these babies have a higher risk for childhood obesity and accompanying

⁴ REPROTOX[®] is a subscription information system on environmental hazards to human pregnancy, reproduction and development developed by the Reproductive Toxicology Center for its members. REPROTOX contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development. Available through MicroMedex

⁵ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

metabolic sequelae.⁶ Pre-pregnancy obesity is associated with an increased risk of major malformations, including neural tube defects, omphalocele, heart defects, orafacial clefts, and others. The mechanism for these observed malformations and obesity is not known but may be due to: severe metabolic and hormonal alterations including hyperglycemia, elevated insulin, and elevated estrogen levels; nutritional deficits from dieting or poor quality diets; and/or diabetes.⁷

Despite the association between obesity and major fetal malformations, a minimum weight gain (and no weight loss) is recommended during pregnancy for all women, including those who are already overweight or obese because of the obligatory weight gain that occurs in maternal tissues during pregnancy. The metabolic consequences of weight loss in pregnancy may be associated with adverse neurodevelopmental outcomes in childhood.⁸

Pregnancy and Nursing Mothers Labeling

FDA currently classifies the reproductive and developmental risk of drugs for use during pregnancy into five categories (A, B, C, D, and X)⁹ using available animal and/or human data. Some of the categories require consideration of both the potential risks (to mother and fetus) and the potential benefits (to the mother and indirectly to the fetus) if the drug is used during pregnancy. The classification system does not define a linear increase in fetal risk from pregnancy category A to pregnancy category X (see Appendix A for a description of each pregnancy category). PMHS- MHT notes that the pregnancy category classification will be eliminated when the Final Pregnancy and Lactation Labeling Rule (PLLR) publishes (Proposed Pregnancy and Lactation Labeling Rule published May 29, 2008).¹⁰ When the final regulations publish, the PLLR will complete the requirements on content and format of labeling for human prescription drug and biological products (Physician Labeling Rule, January 24, 2006, 71 FR 3922) by revising the content and format requirements for the pregnancy, labor and delivery, and nursing mothers subsections of labeling. The proposed changes to prescription drug labeling will provide prescribers with clinically relevant and more comprehensive information for making prescribing decisions and for counseling women who are pregnant, human milk-feeding, or of reproductive potential about using prescription medications.

The Pregnancy and Nursing Mothers section of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. PMHS- MHT labeling recommendations comply with current regulations but incorporate “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated

⁶ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

⁷ Watkins M, Rasmussen S, et al. Maternal obesity and the risk for birth defects. *Pediatrics* 2003; 111:1152-58

⁸ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

⁹ See Appendix A for pregnancy category definitions table

¹⁰ See Proposed Pregnancy and Lactation Labeling Rule, 73 FR 30831, May 29, 2008

pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management.

SPONSOR PROPOSED LABELING (dated March 9, 2011)

(b) (4)

DISCUSSION

Pregnancy

Phentermine has been classified as a pregnancy category C drug because of a lack of both adequate and well-controlled studies in pregnant women and developments reproductive studies in animals. Phentermine is related chemically and pharmacologically to amphetamine (d- and d/l-amphetamine); and therefore, has amphetamine-like vasoconstrictive effects, which increase blood pressure, and have the potential to adversely affect uteroplacental blood flow in a pregnant woman. REPOTOX¹¹ reports on methamphetamine effects in pregnant sheep that included high fetal drug exposure and elevated maternal and fetal blood pressure with accompanying transient increases in umbilical vascular resistance and a decrease in uterine blood flow.

Current published guidelines¹² call for a minimum weight gain, and no weight loss, during pregnancy for all women, including those who are already overweight or obese, because of the

¹¹ REPOTOX[®] is a subscription information system on environmental hazards to human pregnancy, reproduction and development developed by the Reproductive Toxicology Center for its members. REPOTOX contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development. Available through MicroMedex

¹² Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

obligatory weight gain that occurs in maternal tissues during pregnancy. Both excessive weight gain and weight loss can lead to adverse maternal and/or fetal outcomes. Because of these current guidelines, weight loss drugs, including phentermine, offer no potential benefit to a pregnant woman, and weight loss resulting from the use of phentermine or other weight loss drugs may lead to fetal harm.

The designation of a particular pregnancy category under the current labeling regulations [21 CFR 201.57(c)(9)(i)] is based on the relative risks and benefits (maternal and fetal) of using a drug during pregnancy. Under the current labeling regulations, a pregnancy category X is the appropriate designation for phentermine ODT, as there is no potential weight loss benefit for a woman during pregnancy and there is potential for adverse amphetamine-like vasoconstrictive maternal and fetal effects.

Nursing Mothers

No literature is available on the use of phentermine during lactation; however, based on its low molecular weight, excretion into human milk is expected. The American Academy of Pediatrics (AAP) Committee on Drugs reports that amphetamines are present in human milk and can have an adverse effect on a human milk fed infant, including irritability and poor sleeping patterns.¹³

CONCLUSIONS

The pregnancy subsection of all phentermine labeling should clearly convey to clinicians that phentermine is contraindicated during pregnancy due to its lack of potential benefit for a woman during pregnancy and the potential for maternal/fetal harm due to amphetamine-like vasoconstrictive effects.

The nursing mothers subsection of phentermine labeling should be revised to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

PMHS-MHT RECOMMENDATIONS

Labeling Recommendations

The following are PMHS-MHT recommended phentermine ODT pregnancy and nursing mothers labeling revisions. A track-changes version of PMHS-MHT recommended pregnancy and nursing mothers labeling revisions can be found in Appendix B of this document.

HIGHLIGHTS OF PRESCRIBING INFORMATION

CONTRAINDICATIONS

- Pregnancy (4)

¹³ AAP Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk. Pediatrics September 2001 108 (3):776-80

-----**USE IN SPECIFIC POPULATIONS**-----

- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother.

4 CONTRAINDICATIONS

- Pregnancy [*see Use in Specific Populations (8.1)*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

(b) (4)® is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. Phentermine has pharmacologic activity similar to amphetamine (d- and dl-amphetamine) [*see Clinical Pharmacology (12.1)*]. A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to obligatory weight gain that occurs in maternal tissues. Animal reproduction studies have not been conducted with phentermine. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard of to a fetus.

8.3 Nursing Mothers

It is not known if (b) (4)® is excreted in human milk; however, other amphetamines are present in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

17 PATIENT COUNSELING INFORMATION

Advise patients who are pregnant or breastfeeding not to use (b) (4) (see *Use in Specific Populations (8.1, 8.3)*).

Other Recommendations

1. Revise the pregnancy and nursing mothers subsections of all phentermine product labeling for consistency.
2. Consider developing a public health communication to educate female consumers about the importance of: losing weight prior to attempting a pregnancy, achieving a minimum weight gain during pregnancy for both maternal and fetal health, and not using weight loss drugs during pregnancy due to the lack of maternal benefit and potential fetal harm. PMHS-MHT would be happy to assist with the development of any educational pieces for patients and/or healthcare practitioners. Additional assistance could be requested from the Office of Women's Health and/or CDER's Office of Communications or Safe Use program.

**APPENDIX A:
FDA Pregnancy Category Definitions**

Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)	
Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

APPENDIX B – PMHS-MHT Track-Changes Labeling Recommendations

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/s/

JEANINE A BEST
05/06/2011

Karen B FEIBUS
05/06/2011

I concur with the information and recommendations provided in this review. Signing also on behalf of CAPT Lisa Mathis, associate director OND- PMHS

Memorandum to File – Labeling Review

To: NDA 202-088 ORIGINAL-1; Suprenza (phentermine hydrochloride) Orally Disintegrating Tablet

From: Elsbeth Chikhale, Ph.D. – Chemistry Reviewer

Subject: Labeling review

Date: June 10, 2011

Applicant: Citius Pharmaceuticals, LLC

Proposed Proprietary Name: Suprenza

Established Name: phentermine hydrochloride

Dosage form and strength: 15 mg/tablet and 30 mg/tablet

Route of Administration: oral

Indications: Adjunct in weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity.

- The package insert was reviewed in coordination with the clinical division. Minor editorial changes were made to the CMC sections of the package insert.
- After several revisions, the following container labels were submitted on 6/8/11:

(b) (4)



Evaluation: The revised container labels are acceptable from CMC perspective.

Note:

Note that a SPL has not been submitted. There are no remaining CMC issues, therefore NDA 202-088 ORIGINAL-1 is recommended for APPROVAL from CMC perspective.

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/s/

ELSBETH G CHIKHALE
06/10/2011

ALI H AL HAKIM
06/10/2011

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 202088

Name of Drug: Suprenza (phentermine hydrochloride) orally disintegrating tablet (ODT); 15 mg and 30 mg doses only [REDACTED] (b) (4)

Applicant: Citius Pharmaceuticals, LLC

Labeling Reviewed: Package Insert and Container labels

Submission Date: June 6, 2011

Receipt Date: June 7, 2011

Background and Summary Description:

Phentermine is a very old drug, first approved in the 1950s. It is indicated as a short-term adjunct (a few weeks) in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g., controlled hypertension, diabetes, hyperlipidemia).

Phentermine is an anorectic compound related to amphetamine and is a controlled substance. NDAs for phentermine include Wilpo (12737; 8 mg tablet), Ionamin (11613; phentermine resin, 15 and 30 mg capsule), and Fastin (17352; 30 mg capsule). All NDAs for phentermine have been withdrawn from the market but multiple ANDAs remain available by prescription. As mentioned above, it is currently approved for the short-term (a few weeks) use to treat obesity. This indication is no longer accepted for approval of new obesity drugs since obesity is now considered a chronic condition, requiring treatment over long periods of time.

The current application is a new dosing form (orally dissolving tablet) of phentermine and, therefore, was reviewed by DMEP, as a 505(b)(2) application, instead of the Office of Generic Drugs, as an ANDA. It should be noted that the company submitted [REDACTED] (b) (4) dosage strengths in this NDA 15 mg, 30 mg, [REDACTED] (b) (4). However, only the 15 mg and 30 mg doses were approved (Original-1) [REDACTED] (b) (4)

The prescribing information for phentermine has not been updated in many years. It appears that

the last labeling supplement for a phentermine NDA was approved in 2003, adding a geriatric subsection to the PRECAUTIONS section in the prescribing information.

Approval of this 505(b)(2) provided an opportunity to update the label and convert it to the physicians labeling rule (PLR) format. The revisions to the labeling were extensive and reflected significant changes in philosophy related to patient safety. These updates will be incorporated into the labels of all generic phentermine applications.

Review

Package Insert

As mentioned above, the label was converted to PLR format so revisions were extensive. A Highlights section was added and the sections in the Full Prescribing Information were rearranged and revised. The Division waived the 1/2-page limit on the Highlights section.

This project manager reviewed the label submitted on June 6, 2011 and found it to be identical to the wording agreed upon between the Division and sponsor.

After receipt of the label from the company, CSS made two very minor edits to the first sentence in section 5.6. These were incorporated into the version attached to the approval letter and relayed to the sponsor via email. As noted below, the two words underlined, in red font were added.

"Suprenza is related chemically and pharmacologically to amphetamine (d- and d/l-amphetamine) and to other related stimulant drugs that have been extensively abused."

Major revisions from the last approved label include:

1. Conversion to PLR format.
2. Addition of "Pregnancy" to the CONTRAINDICATIONS section.
3. Change from *Pregnancy Category "C" to "X"*

Recommendations

This label was reviewed (and revised) by Drs. Al Hakim, Best, Bonson, Bourcier, Calderon, Chikhale, Colman, Egan, Feibus, Golden, Griffis, Holquist, Mathis, Merchant, Summan, Tran, Vaidyanathan, and Zadezensky. The version submitted on June 6, 2011 is identical to the reviewed version and is acceptable.

Container Labels

Container labels submitted by the company on June 6, 2011 had been revised to comply with all CFR regulations and all safety concerns had been addressed.

Recommendations

The container labels were reviewed by Drs. Al Hakim, Chikhale, Griffis and Tran and determined to be acceptable.

Patricia Madara

June 14, 2011

Regulatory Project Manager

Date

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/s/

PATRICIA J MADARA
06/14/2011

MEMORANDUM

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

DATE: June 6, 2011

TO: Mary H. Parks, M.D.
Director, Division of Metabolism and Endocrinology
Products (DMEP)
Office of New Drugs

Chandrabhas Sahajwalla, Ph.D.
Director,
Division of Clinical Pharmacology II (DCPII)

FROM: Abhijit Raha, Ph.D., Pharmacologist
Arindam Dasgupta, Ph.D., Staff Fellow
Office of Scientific Investigations (OSI)

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Investigations Branch
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering NDA 202-088, (b)(4)
(phentermine hydrochloride) Orally Disintegrating
Tablet (ODT), 15 mg, 30 mg, (b)(4) Sponsored by
Citius Pharmaceuticals, LLC

At the request of DMEP, OSI (formerly DSI) conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

Study 018089D: "A randomized, balanced, open-label, single dose, three-treatment, three-sequence, three-period, crossover, pivotal study to compare the bioavailability of single dose of Test Phentermine HCl 30 mg Orally Disintegrating Tablet (ODT) (from Citius Pharmaceuticals, LLC), when administered orally by two separate modes i.e. swallowed with water (T1) and disintegrated followed by water (T2), with Reference Phentermine HCl 30 mg Capsule (from Sandoz Pharmaceuticals, USA) when swallowed with water in 12 (+3 standby) healthy, adult human (male and female) subjects under fasting condition"

Page 2 - NDA 202-088, (b)(4) (phentermine hydrochloride) orally-disintegrating tablet, 15 mg, 30 mg, (b)(4)

Study 01809PB: "A randomized, balanced, open-label, single dose, three-treatment, three-sequence, three-period, crossover, pivotal, food effect study to compare the bioavailability of single oral dose of Test Phentermine HCl (b)(4) Orally Disintegrating Tablet (ODT) (from Citius Pharmaceuticals, LLC), when administered under two different conditions separately, i.e. fasting (T1) and fed (T2), with Reference Phentermine HCl (b)(4) when administered only under fasting condition in 15 (+3 standby) healthy, adult human (male and female) subjects"

Clinical Site: Worldwide Clinical Trials, San Antonio, TX.

Following the audit of the clinical records of study 018089D and study 01809PB at Worldwide Clinical Trials (formerly CEDRA Clinical Research LLC), San Antonio, TX (February 1-17, 2011), a seven-item Form FDA-483 (**Attachment 1**) was issued. Our evaluation of the seven 483 observations and the firm's written response to Form FDA-483 dated March 8, 2011 (**Attachment 2**) follow.

1. Four employees were not wearing their lab coats properly buttoned during blood draws.
2. A phlebotomist did not follow the Departmental Operating Procedure for Blood Collection since the wound at the puncture site for drawing blood was touched.
3. The "Responsibility Log Completion Process" was not followed as there was no responsibility log that identified Pharmacy staff participating in Study 18089D; not all employees signed the Clinical Trial Daily Personnel Responsibilities Log on days they performed study procedures for studies 18089D and 1809PB.
4. The Departmental Operating Procedure for taking vital signs was not followed.
5. A Cedra memorandum dated 1-5-10 was not followed in that individuals, not authorized do so, performed some 2 and 4-hour post-dose oral exams.
6. Failure to follow study protocols for studies 18089D & 1809PB.
 - a) Pre-dose vital signs were not always taken within 30 minutes of dosing of the subject.
 - b) It was not determined whether all subjects donated more than 300 ml of blood to decide whether they should be excluded.
 - c) In study 18089D, the oral cavity examination was not performed during Period 3 at 48 hours for Subject 301.

Page 3 - NDA 202-088, (b)(4) (phentermine hydrochloride) orally-disintegrating tablet, 15 mg, 30 mg, (b)(4)

- d) Subject 312 (study 018089D) (Obs. 6c) and subject 510 (study 01809PB) (Obs. 6d4) consumed green tea <48 hours prior to being dosed with the study drug.
 - e) In study 1809PB, Subject 501 randomized to the Reference-Fasted group for Period 2 was given breakfast but dropped (Obs. 6d1), the oral cavity examination was not performed during Period 3 at 4 hours for Subject 511 (Obs. 6d2), Subject 517 was not excluded from the study as the systolic blood pressure was 140 mm Hg at screening (Obs. 6d3),
7. Informed consent was performed by individuals not delegated to do so.

DSI EVALUATION: Observations #1, 2, 3, 4, 5, 6a, 6b, 6c, 6e, and 7 are not likely to affect study outcomes.

It is remotely possible that the consumption of green tea by subject 312 (study 18089D) and subject 510 (study 1809PB) within 48 hours prior to dosing with study drug (**Obs. 6c, Obs. 6d4**) could alter the phentermine clearance by subjects 312 and 510. The PK data from these subjects should be excluded.

In their written response, Worldwide Clinical Trials acknowledged these observations and promised corrective actions (**Attachment 2**).

Analytical Site: (b)(4)

Following the inspection at (b)(4) Form FDA-483 was issued (**Attachment 3**). The firm's written response to the inspectional findings was received by DSI on June 6, 2011 (**Attachment 4**). The Form FDA-483 observations for studies 1809PB and 18089D (analytical), the firm's response, and our evaluations follow:

1. **Samples from many analytical runs for phentermine (5 of 15 runs in study 1809PB and 6 of 14 runs in study 18089D) were injected in advance of acquiring final reported data of the analytical runs. (b)(4) SOPs PS-104 (revision 4) at the time the studies were conducted failed to describe selection, evaluation, and reporting of "pre-injection samples."**

Page 4 - NDA 202-088, (b)(4) (phentermine hydrochloride) orally-disintegrating tablet, 15 mg, 30 mg, (b)(4)

Although the samples used for pre-injection were not defined in (b)(4) SOP PS-104, paper and electronic source records revealed that samples injected prior to the analytical run were usually eight calibration standards, one blank, and one low QC sample processed with the actual run. No study samples were used as pre-injection samples and pre-injections did not occur in every analytical run; only 33.3% of the analytical runs in study 1809PB and 42.9% of the analytical runs in study 18089D had pre-injection samples. Moreover, audit trails of the pre-injection and analytical runs were maintained by (b)(4) and were examined during the inspection. DSI found that selection or changes to automatic integration parameters did not bias run acceptance. Thus, the above observation should not impact study outcomes.

(b)(4) acknowledged the findings. Since the completion of studies 1809PB and 18089D, an SOP for selection of pre-injection samples was implemented, in which samples independent of the study batch are prepared for pre-injection and instrument stabilization.

2. Failure to document all aspects of study conduct.

Specifically, documentation for individual calibrator and Quality Control (QC) sets used in phentermine studies 1809PB and 18089D during sample processing was not maintained. QC samples were not identified and tracked along with samples from studies 1809PB and 18089D.

(b)(4) acknowledged the observation. Since August 2010, individual calibrators and QCs are identified and tracked along with study samples.

Conclusions:

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

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Page 5 - NDA 202-088, (b) (4) (phentermine hydrochloride)
orally-disintegrating tablet, 15 mg, 30 mg, (b) (4)

Abhijit Raha, Ph.D.

Arindam Dasgupta, Ph.D.

Final Classification:

**Worldwide Clinical Trials Drug Development Solutions (formerly
CEDRA Clinical Research LLC), San Antonio, TX - VAI**

(b) (4)
- VAI

CC:

CDER DSI PM TRACK
OC/DSI/Haidar/Ball/Raha/Dasgupta/Yau/Dejernett
SW-FO/DAL-DO/INV/SNA-TX/Joel.martinez@fda.hhs.gov
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CDER/OCP/DCPII/Sahajwalla/Zadezensky
Draft: AR, AD 6/6/11
Edit: MFS 6/6/11
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/s/

ABHIJIT RAHA
06/06/2011

ARINDAM DASGUPTA
06/06/2011

MICHAEL F SKELLY
06/06/2011
On behalf of Martin K. Yau, Ph.D.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: A drug use study conducted annually for 3 years after product launch.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>09/30/2011</u>
	Study/Clinical trial Completion Date:	<u>NA</u>
	Final Report Submission Date:	<u>12/03/2014</u>
Other:	Interim Report Submission Dates:	<u>12/03/2012</u>
		<u>12/03/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The assessment of drug utilization of this phentermine formulation requires its availability in the marketplace.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Phentermine is currently approved for short-term use (a few weeks), although there are reports of off-label use. Its long-term safety and efficacy when taken as monotherapy is unknown. A comprehensive assessment of drug utilization will help inform the safety of the drug, in particular, abuse potential.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

Which regulation?

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor will be required to conduct a nationally representative (or nationally projected) study of annual phentermine ODT use data that provides: 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. Most analyses should be stratified by age, then age and gender, as appropriate. Results should be submitted annually, with each updated report including annual and cumulative data since launch of phentermine ODT, for a period of 3 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: A clinical trial to assess the effect of mild, moderate and severe renal impairment and end stage renal disease (ESRD) on the pharmacokinetics of phentermine.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/13/2012
Study/Clinical trial Completion Date: 01/31/2014
Final Report Submission Date: 06/30/2014
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The sponsor mentions in the product background information, that about 30% of phentermine is excreted unchanged in urine and that the excretion is highly variable and dependent on urinary pH. Literature information (published by Delbeke & Debackere *Arzneim-Forsch* **36**:134-7 (1986)) reports cumulative urinary excretion of phentermine under uncontrolled urinary pH conditions to be between 63% to 85%.

Increases in exposure due to renal impairment are likely considering the urinary excretion of phentermine and dose adjustment is likely to be necessary for safe and effective use in patients with renal impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The required clinical trial would provide an estimate of exposure changes in patients with decreased renal function. The required clinical trial would provide information that form the basis for dosage adjustment in patients with renal impairment.

Exposure response relationships for safety and efficacy have not been established. Increased exposures thus, bear the potential risk of increased cardiovascular, central nervous system or gastrointestinal adverse events.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

Which regulation?

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial to assess the effect of mild, moderate and severe renal impairment and end stage renal disease (ESRD) on the pharmacokinetics of phentermine. Approximately equal numbers of patients from the following groups should be recruited:

Normal renal function (estimated Creatinine Clearance ≥ 90 mL/min),
Mild renal impairment (estimated Creatinine Clearance 60-89 mL/min),
Moderate renal impairment (estimated Creatinine Clearance 30-59 mL/min),
Severe renal impairment (estimated Creatinine Clearance 15-29 mL/min) and
ESRD (estimated Creatinine Clearance ≤ 15 mL/min).

The number of patients enrolled in the study should be sufficient to detect PK differences large enough to warrant dosage adjustments. The renal function groups should be comparable to each other with respect to age, gender, and weight.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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-
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 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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-
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-

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PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

AMY G EGAN
06/08/2011