CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Supporting document/s:	Original submission and updates
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Product:	Phentermine ODT (Oral Disintegrating Tablet)
Indication:	Obesity
Applicant:	Citius Pharmaceuticals LLC
Review Division:	DMEP
Reviewer:	Mukesh Summan, PhD, DABT
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1 Executive Summary

1.1 Introduction

The proposed drug is a tablet of a drug substance listed for use in the United States. Phentermine was approved in 1959 for short term ("a few weeks") management of obesity as an adjunct to diet and exercise. Phentermine is indicated for use as an anorectic or appetite suppressant. The proposed formulation was designed to provide once daily oral dosing as an oral disintegrating tablet (ODT).

The new drug application was submitted in accordance with 21 U.S.C. 505(b)(2) and Citius Pharmaceuticals LLC, relied on publically available information, the approved product label for Adipex-P® (phentermine HCl) and FDA's previous findings of safety and efficacy to support the proposed use. The sponsor did not conduct a nonclinical development/animal toxicology program. A bridge between the reference listed drugs phentermine HCl 15 and 30 mg capsules (manufactured by Sandoz Pharmaceuticals) and Adipex-P® (manufactured by Gate Pharmaceuticals) and the new dosage form was provided by bioequivalence (BE) studies conducted in healthy volunteers and by chemical characterization of the drug substance, in lieu of conducting additional animal studies. Chemical analysis shows that impurities and degradants in the drug substance and drug product were not detected in the clinical batch with a specification at NMT (b) (4), and are appropriately qualified as per ICH Q3A and Q3B guidances. Genotoxicity and carcinogenicity studies have not been conducted for the referenced drug product or for the proposed ODT drug product; as a short-term treatment, an assessment of carcinogenicity is not required.

As phentermine ODT is a new dosage form of an already marketed product the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) is enacted, requiring that the sponsor propose a development plan for use of the drug product in the pediatric population. (b) (4)

(b) (4)

1.2 Brief Discussion of Nonclinical Findings

Nonclincial studies with the phentermine ODT drug product were not performed.

1.3 Recommendations

1.3.1 Approvability

Pharmacology and Toxicology recommends the approval of phentermine ODT for the proposed indication in adults.

1.3.2 Additional Non Clinical Recommendations

No pre- and postnatal developmental toxicity studies were conducted with phentermine ODT and thus there are no data on reproductive toxicity or neurotoxicity postnatally or in juvenile animals. Neurotoxic adverse events (e.g. agitation, anxiety or insomnia[1,2]) occur in a subset of obesity patients and healthy volunteers taking phentermine. (b) (4) [redacted]

(b) (4) [redacted] .

(b) (4) [redacted]

1.3.3 Labeling

For this 505(b)(2) application for which the sponsor did not conduct a nonclinical development/animal toxicology program, the language used in the label is identical to the reference listed drug label of Adipex-P®, with the likely exception of a change in the pregnancy section.

Nonclinical recommendations to be discussed for final labeling language:

8 USE IN SPECIFIC POPULATIONS, 8.1 Pregnancy

Pregnancy category X
The reference listed drug is currently labeled as 'Pregnancy Category C', citing a lack of reproductive toxicology studies in animals. However, there is concern of the potential for amphetamine-like vasoconstriction in the mother, the placenta or the fetus[3], and of the consequences of losing weight during pregnancy. Clinical considerations of the use of anorectics in pregnancy have raised discussion of changing the pregnancy category to 'X'. A contraindication in pregnancy would obviate the need for reproductive toxicology studies in animals.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)
1197-21-3 (HCl salt)
122-09-8 (free base)

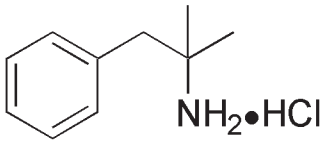
Generic Name
Phentermine HCl oral disintegrating tablet (ODT)

Code Name
(b) (4)

Chemical Name
Benzeneethanamine-α,α-dimethyl-hydrochloride α,α-dimethylphenetylamine hydrochloride.

Molecular Formula/Molecular Weight
$C_{10}H_{15}N{\bullet}HCl$ / 185.7 g/mol (free base 149.23 g/mol)

Structure or Biochemical Description



Pharmacologic Class
Sympathomimetic amine anorectic.

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 11-613 (Ionamin®).
NDA 88-023 (Adipex-P® generic capsule).
NDA 85-128 (Adipex-P® generic tablet).

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DMF: (b) (4) for phentermine manufacture, held by (b) (4)
DMF: (b) (4) for peppermint flavor (as an excipient) used in the drug product, held by (b) (4)

2.3 Drug Formulation

The sponsor proposes to manufacture three strengths (15, 30 and 37.5mg) of the phentermine oral disintegrating tablets (ODT) with the following composition (sponsor's table):

Table 1. Composition of Phentermine ODT Drug Product.

Components	Phentermine HCl 15 mg strength	Phentermine HCl 30 mg strength	Phentermine HCl 37.5 mg strength
	mg/tablet		
Phentermine HCl	15.00*	30.00*	37.50*
Mannitol powder (b) (4) (b) (4)	(b) (4)		
Citric Acid powder			
Povidone CL (b) (4)			
Povidone K 30 (b) (4)			
Sucralose			
Magnesium Stearate			
Peppermint flavour			
Talc			
Sodium Lauryl Sulfate			
Mannitol pregranulated (b) (4)			
FD&C Blue # 1 lake (b) (4)			
FD&C Yellow # 5 lake (b) (4)			

(b) (4)

2.4 Comments on Novel Excipients

Each compendial excipient to be used in the proposed commercial drug product meets the requirements of the respective USP or NF monograph. The non-compendial excipients are as follows:

Table 2. Composition of Phentermine ODT Drug Product Excipients

Excipient	Phentermine HCl 15 mg strength	Phentermine HCl 30 mg strength	Phentermine HCl 37.5 mg strength
Non-USP			
FD&C Blue # 1 lake (b) (4)	•	–	•
FD&C Yellow # 5 lake (b) (4)	•	•	–
Peppermint flavour	•	•	•

The color additives FD&C Blue #1 lake and FD&C Yellow #5 lake are certified by the FDA. The sponsor has provided reference to DMF (b) (4) for the peppermint flavor. Peppermint flavor is identified as an inactive ingredient in approved drug products in the FDA inactive ingredient database, and is also GRAS listed.

2.5 Comments on Impurities/Degradants of Concern

Degradants

Degradants found in the phentermine ODT formulation from forced degradation studies are described below (sponsor's table). Unidentified degradants were not detected in the phentermine ODT formulation.

Table 3. Unidentified Degradants From Forced Degradation Studies.

Impurity	Raw Result (%)	Reported Result (%) Reporting Threshold	Total Daily Intake (TDI) of Degradation Product (rounded result in µg	Action	
				Identification Threshold 0.2% exceeded	Qualification Threshold 200 µg TDI exceeded (b) (4)

Impurities

Phentermine ODT has the following impurities and specifications (sponsor tables):

Table 4. Impurities of Phentermine ODT Drug Product (a) and Specification (b).

(a)

Impurity Structure	Impurity Formation
(b) (4)	

(b)

Impurity	Specification
(b) (4)	

All impurities are within the ICH Q3A identification and qualification thresholds and the impurities were not identified in the drug product for the clinical batch (sponsor's table):

Table 5. Impurities of Phentermine ODT Clinical Batch Drug Product.

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Phentermine ODT is intended as a short term (a few weeks) use as an adjunct for the treatment of obesity and weight management for patients with an initial body mass index ≥30 kg/m^2, or ≥27 kg/m^2 with one or more risk factors (e.g. diabetes, dyslipidemia or hypertension). The recommended daily dose is one tablet administered (b) (4)

2.7 Regulatory Background

Phentermine as a resin was first approved by the FDA in 1959. In 1962, Congress amended the 1938 FD&C act to give the FDA the authority to regulate medicines for efficacy in addition to safety. All drugs approved between 1938 and 1962 on the basis of safety alone, now required an assessment of efficacy under the Drug Efficacy and Study Implementation (DESI) process; which was initiated in the late 1960's. In 1973 phentermine hydrochloride (HCl), an amphetamine congener, was reviewed under the DESI process and deemed efficacious for a short term ("a few weeks") treatment of obesity. Since 1973 many generic versions of phentermine HCl have been approved by the Agency.

On March 13th 2007, Citius Pharmaceuticals LLC, submitted a pre-IND for an orally disintegrating tablet (ODT) formulation of phentermine HCl to the Division of Metabolism and Endocrinology Products (DMEP).

3 Studies Submitted

3.1 Studies Reviewed

This is a 505(b)(2) submission. The sponsor is referencing the Agency's previous findings of safety and efficacy for the reference listed drug of Adipex-P® (NDA 88-023) to support the new formulation of phentermine ODT.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

No original pharmacology studies were submitted or conducted for the new dosage form of phentermine. Information on phentermine are contained in the label of the reference listed product. The summary of the available information on phentermine ODT is derived from the drug label and published literature.

Phentermine is a contraction for "**phen**yl-**ter**tiary-butyla**mine"** and is a sympathomimetic amine in the β-phenethylamine family. It is a congener of amphetamine, lacking an α-hydrogen due to methylation at the α-carbon. Phentermine stimulates norepinephrine (NE) release with approximately 6-fold lower potency than *d*-amphetamine. Compared to amphetamine, phentermine only slightly stimulates dopamine release (10-fold lower) due to greater selectivity for NE release compared to dopamine stimulation[4]. Phentermine seems to have a minor effect on pre-synaptic serotonin (5-HT) release and reuptake, which are significantly lower than its effect on NE stimulation[4].

Despite the available information on neurotransmitter effects, it is not clear which mechanisms contribute directly to weight loss. Weight loss seems to occur due to a combination of anorectic (decreased food consumption), thermogenic (increased metabolic activity), and drug-induced increased physical activity [5, 6, 7].

Pharmacologic effects of amphetamine and sympathomimetics, coupled with mechanistic research on phentermine, provide insight into potential convergence of multiple pathways contributing to weight loss. Acute inhibition of food intake may be due to activation of hypothalamic β-adrenergic and dopamine receptors. Dopamine release in rodents *in vivo* seems to be involved in the anorectic response of phentermine (and amphetamine), however, the clinical relevance is unclear and no dopamine effect was seen in baboons by PET scan[8]. Phentermine has no apparent effects on α-adrenergic, serotonergic, or cholinergic receptors[9]. Modulation of various peptides involved in appetite and energy use has been postulated but no studies have been conducted with

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phentermine. For example, neuropeptide Y (NPY) is antagonistically active in the perifornical hypothalamus and affects the amphetamine-mediated dopamine modulation and subsequent hypothalamic-mediated weight loss in rodents[10]. The cocaine- and amphetamine-regulated transcript (CART) encodes secreted neurotransmitter peptides and is expressed in hypothalamic regions involved in energy regulation[11]. Changes in leptin homeostasis may also play a role in weight loss because sympathetic nervous system activation and β-adrenergic stimulation decrease leptin expression, thereby decreasing the leptin-mediated control of food intake[12]. There is also some evidence that amphetamine may increase cholecystokinin (CCK), which transiently inhibits food intake, by decreasing gastric emptying and intestinal motility[13].

4.2 Secondary Pharmacology

No secondary pharmacology or drug-drug interaction (DDI) studies were submitted. Secondary pharmacology and DDI information for phentermine is based on a review of the published literature. Phentermine has been investigated for potential treatment of drug abuse and nonclinical effects showed attenuation of cocaine abuse in rhesus monkey and cocaine-induced dopamine release in rats[14, 15]. Phentermine has also been investigated for potential increased cognitive and motor function after sleep deprivation.

4.3 Safety Pharmacology

No safety pharmacology studies were submitted. Safety pharmacology information for phentermine is based on a review of the published literature.

Clinical adverse events and side effects for phentermine are listed on the label for approved drug(s) and are consistent with class related side effects of sympathomimetics, including: cardiovascular (palpitations, tachycardia, increased blood pressure); CNS (overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, and rare psychotic episodes); gastrointestinal (dry mouth, unpleasant taste, diarrhea, constipation, “other gastrointestinal disturbances”); allergic (urticaria); and endocrine (impotence, changes in libido). Primary pulmonary hypertension and/or regurgitant cardiac valvular disease are also listed on the phentermine label and will be discussed in more detail below.

The potential for phentermine abuse has been studied because amphetamine and derivatives are known drugs of abuse (e.g., ‘speed’ and ‘crystal meth’) and neural food reward center activation is thought to provoke a similar potential for abuse. There is some nonclinical evidence of self-administration of phentermine for stimulant effects but data from non-human primates showed a 5-fold lower “reinforcing potency” of phentermine as an anorectic compared to amphetamine[16]. Dopamine activation in the nucleus accumbens is associated with drug abuse potential and amphetamine has a dopaminergic effect[17]. As noted previously, phentermine has lower potency and efficacy compared to amphetamine for receptor activation (NE and dopamine release and reuptake) and anorectic and behavioral effects[18].

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Serious potential cardiovascular toxicity by association from phentermine use, was identified in the 1990s based on adverse events from clinical use of combination fenfluramine and phentermine for weight loss. The Adipex-P® label lists warnings for primary pulmonary hypertension (PPH) and valvular heart disease (VHD) from phentermine use. While the Adipex-P® label notes that PPH and valvular heart disease have not been definitively linked to phentermine use, the warnings note the following (emphasis included in label):

> **Primary Pulmonary Hypertension (PPH) – a rare, frequently fatal disease of the lungs – has been reported to occur in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine. The possibility of an association between PPH and the use of phentermine alone cannot be ruled out; there have been rare cases of PPH in patients who reportedly have taken phentermine alone….**
>
> **Valvular Heart Disease: Serious regurgitant cardiac valvular disease, primarily affecting the mitral, aortic and/or tricuspid valves, has been reported in otherwise healthy persons who had taken a combination of phentermine with fenfluramine or dexfenfluramine for weight loss. The etiology of these valuopathies has not been established and their course in individuals after the drugs are stopped are unknown. The possibility of an association between valvular heart disease and the use of phentermine alone cannot be ruled out; there have been rare cases of valvular heart disease in patients who reportedly have taken phentermine alone.**

In a human single dose study with phentermine HCl tablets (salt or resin), a transient increase in systolic and diastolic blood pressure was observed, but was less than that observed for amphetamine. No alterations were observed for heart rate and in the ECG[19]. In the published literature an analysis of clinical data has shown that phentermine monotherapy is not associated with cardiac valvuopathy[20].

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME/Toxicokinetics

No new nonclinical pharmacokinetic/ADME/Toxicokinetic studies were conducted for this 505(b)(2) submission.

6 General Toxicology

6.1 Single-Dose Toxicity

No new nonclinical toxicology studies were conducted for this 505(b)(2) submission. Toxicology information for phentermine is based on a review of the published literature. The acute oral toxicity of phentermine HCl was determined in SD rats and Webster mice. The LD_{50} values were 151 and 124 mg/kg in the rats and mice, respectively[21]. In rabbits the acute intravenous LD_{50} of phentermine HCl was 15-20 mg/kg[22]. In male

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albino mice, a single i.p. administration of phentermine HCl caused hyperactivity, convulsions and “ataxic running and jumping” and resulted in a LD_{50} of 71.4 mg/kg [23].

Rats administered phentermine orally at 2.5 or 5 mg/kg showed a dose-dependent increase in motor activity. In anesthetized dogs phentermine at 0.5 mg/kg administered intravenously showed a mean increase in blood pressure of 64.5 mm (Hg)[21].

6.2 Repeat-Dose Toxicity

No new nonclinical repeat dose toxicology studies were conducted for this 505(b)(2) submission.

7 Genetic Toxicology

No new genetic toxicology studies were conducted for this 505(b)(2) submission. The genetic toxicity of phentermine ODT has not been assessed.

8 Carcinogenicity

No new carcinogenicity studies were conducted for this 505(b)(2) submission. Carcinogenicity in rodents or other species has not been assessed for phentermine ODT.

9 Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies were conducted for this 505(b)(2) submission.

In the published literature chlorphentermine or phentermine at 30 mg/kg, respectively, were administered subcutaneously to pregnant rats (n= 8-10) from gestation day (GD) 16 to GD 20. The dams were allowed to deliver at GD 21 and the neonates monitored for 24 hours prior to necropsy. In the dams phentermine did not alter body weight gain compared to pair-fed controls. In addition, there were also no differences in mortality, body weight, crown-rump length, liver or lung to body weight ratios or developmental abnormalities in the phentermine treated neonates compared to pair-fed control neonates[24].

In contrast, chlorphentermine decreased pup survival, growth and produced pulmonary phospholipidosis in both the dams and pups[24].

10 Special Toxicology Studies

None.

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11 Integrated Summary and Safety Evaluation

This is a 505(b)(2) application for a new dosage form of phentermine as an oral disintegrating tablet (ODT) for the treatment of obesity and weight management. This 505(b)2 application relies primarily on the Agency findings of safety and efficacy as reflected in the approved product label for Adipex-P® (phentermine HCl). The sponsor did not submit nonclinical studies or conduct a nonclinical program for phentermine ODT. A bridge between the approved product and the new dosage form was established by bioequivalence studies conducted in healthy volunteers, in lieu of conducting additional nonclinical studies.

Phentermine is only indicated for short term treatment of obesity ("a few weeks") and was originally approved as a phentermine resin in 1959 prior to the current nonclinical regulatory guidelines and practices. Phentermine went through the Drug Efficacy Study Implementation (DESI) process as the amphetamine congener, phentermine HCl in 1973 and was deemed safe and efficacious for the indicated weight loss.

Pharmacology
Phentermine is centrally acting sympathomimetic amine and weight loss seems to occur due to a combination of anorectic (decreased food consumption), thermogenic (increased metabolic activity) and drug-induced increased physical activity.

Safety Pharmacology
No safety pharmacology studies were submitted by the sponsor. General phentermine toxicity is consistent with the class-related effects of sympathomimetics including cardiovascular (palpitations, tachycardia, increased blood pressure), CNS (overstimulation, restlessness, insomnia, euphoria) and gastrointestinal (dry mouth) effects.

Toxicology
No new nonclinical toxicology studies were conducted for this 505(b)(2) submission and the sponsor relied on public literature and the FDA's prior safety determination for the listed phentermine indication.

Potential for phentermine-induced primary pulmonary hypertension (PPH) and valvular heart disease (VHD) in the lung and heart is a concern due to the clinical use of a combination of fenfluramine and phentermine ('fen-phen') for obesity treatment. The published literature reveals no evidence to implicate phentermine in PPH or VHD and cites the involvement and interaction of fenfluramine with the 5-HT_{2b} receptor as the cause of VHD and this has led to the removal of fenfluramine from the market[25,26].

Based on single dose studies in the published literature phentermine primarily caused CNS (hyperactivity, convulsions and increased motor activity) effects in rodents and hemodynamic (increased blood pressure) effects in the dog.

Genetic Toxicology
Genetic toxicity was not assessed for phentermine ODT.

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Carcinogenicity and Reproductive and Developmental Toxicology
Carcinogenicity and reproductive and developmental toxicology was not assessed for phentermine ODT.

In the published literature limited treatment of pregnant rats with phentermine revealed no developmental abnormalities. As phentermine ODT is a new dosage form of an already marketed product, it is subject to PREA and a complete development program in children is needed to confirm safety and efficacy in the pediatric population. (b) (4)

As there are potential fetal risks (vasoconstriction in the mother, placenta or fetus) and no clinical benefits of using phentermine ODT in pregnancy, and in concurrence with the maternal health team, Pregnancy category X is warranted.

12 References

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/s/

MUKESH SUMMAN
04/12/2011

TODD M BOURCIER
04/12/2011
I concur. Pharm/tox supports approval.
Recommendations are made for the pediatric plan

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202088 **Applicant: Citius Pharmaceuticals, LLC** **Stamp Date: August 17th 2010**

Drug Name: Phentermine HCl NDA Type: 505(b)2
ODT/ (b) (4)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not Applicable. Preclinical data are appropriately referenced.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not Applicable. Preclinical data are appropriately referenced.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not Applicable. Preclinical data are appropriately referenced.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not Applicable. Preclinical data are appropriately referenced.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not Applicable. Preclinical data are appropriately referenced.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not Applicable. Preclinical data are appropriately referenced.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not Applicable. Preclinical data are appropriately referenced.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	Sponsor has not submitted labeling.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			Not Applicable. Preclinical data are appropriately referenced.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not Applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

Background

NDA 202088 is a 505(b)2 for the (b) (4) drug product which is phentermine hydrochloride oral disintegrating tablet (ODT) formulated at 15, 30 and 37.5 mg.

From the CMC review of the drug substance (IND 76, 477), impurities for the phentermine hydrochloride ODT have been structurally identified and are not more than (b) (4); with the exception of one unknown impurity which is at (b) (4) and are thus appropriately qualified as per ICH Q3 guidelines. For the drug product most of the excipients are USP listed and are present in the inactive ingredient database except for the peppermint flavoring which is non-USP.

With reference to IND 76,477 (SDN5, 03.12.2008) the Pharm Tox reviewer determined that the preclinical data for ODT phentermine were appropriately referenced for the proposed 505(b)(2) submission (Pharm Tox review submitted into DARRTs 12.18.2008).

For NDA 202088 the sponsor has submitted a single volume (module 4, volume 1.9) for pharmacology and toxicology review. With reference to this volume, nonclinical studies were not submitted by the sponsor based on a Division advice letter for IND 76,477 (06.01.2007) which deemed the phentermine hydrochloride ODT toxicological characterization adequate, with the appropriate bridge being provided by comparative CMC information to the reference listed product.

Information requested for the 74-Day Letter: None

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

External comment to sponsor: None.

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/s/

MUKESH SUMMAN
10/12/2010

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10/12/2010
NDA fileable for pharm/tox