

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208524Orig1s000**

**MEDICAL REVIEW(S)**

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

**NDA** – 208524

**Name of drug** – Belviq XR (lorcaserin HCl) extended release tablets, 20 mg

**Sponsor** – Arena Pharmaceuticals, Inc.

**Date of Submission** – September 18, 2015

**PDUFA Goal Date** – July 18, 2016

**Medical Reviewer** – Julie Golden, M.D.

**BACKGROUND**

**Regulatory**

Belviq (lorcaserin HCl) was originally studied under IND 69888, and was approved in the U.S. June 27, 2012 under NDA 22529. Belviq is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m<sup>2</sup> or greater (obese), or
- 27 kg/m<sup>2</sup> or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)

The approved dose of the immediate release formulation of Belviq is 10 mg twice daily (BID).

PreIND 119664 meeting minutes (written responses only, WRO) were sent to the company April 18, 2014 to address their proposal for a bioavailability bridging approach in order to support approval of a 20 mg extended-release (XR) formulation for once daily (QD) dosing. FDA agreed that given the positive exposure–response for lorcaserin concentrations on weight loss, a pharmacokinetic bridging strategy was a reasonable approach. Specific guidance included a request an *in vitro* study to evaluate the effect of alcohol dose dumping. They were informed that other studies may be required and that labeling would be a review issue.

IND 119664 was opened August 30, 2014 to support the conduct of protocol APD356XR-101 (see review of this study below).

Pre-NDA meeting written responses (WRO) were sent to the sponsor July 13, 2015. FDA agreed that the sponsor could reference drug substance, nonclinical, and clinical information to NDA 22529. Furthermore, FDA agreed that integrated summaries of efficacy or safety were not required; however, the sponsor would need to justify that any PK differences would not impact efficacy or safety.

NDA 208524 was filed November 17, 2015. A 74-day filing letter was sent to the sponsor that included requests for quality information (regarding the dissolution method) and abuse potential information. Specifically, the controlled substances staff (CSS) noted that the information provided in the NDA to address the abuse potential was incomplete, and they asked for the following:

- *Provide full case report forms, where available, for each of the 117 cases mentioned in your summary.*
- *Provide an analysis of case reports in your safety database using the following search strategies: (1) cases identified using the SMQ Drug abuse and dependence; (2) cases in which an indication for the use of lorcaserin was provided but not related to weight loss; and (3) cases in which the indication for use of lorcaserin was missing, not reported, or unknown.*

### **Drug in study**

The chemical name of the drug substance (lorcaserin hydrochloride) is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate. The empirical formula is  $C_{11}H_{15}Cl_2N \cdot 0.5H_2O$ , and the molecular weight of the hemihydrate form is 241.16 g/mol.

The components of the lorcaserin HCl 20 mg extended release tablets are listed below:



## STUDY SUMMARIES

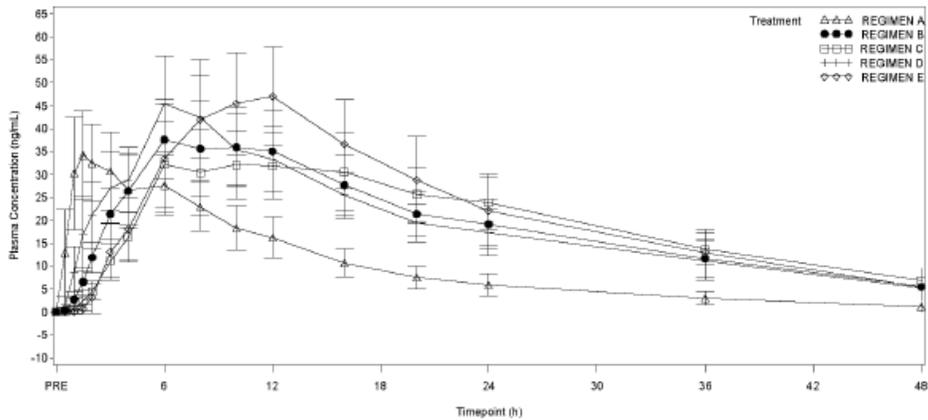
### APD356-031

This was a single-center (U.K.) open-label fixed sequence study in 12 healthy subjects to evaluate the pharmacokinetics of three 20 mg modified release prototype formulations of lorcaserin (medium [Regimen B], (b) (4) [Regimen C], and (b) (4) release [Regimen D]). A reference 10 mg IR formulation [Regimen A] was also included, as was a food effect (high fat breakfast) test [Regimen E].

Twelve subjects were enrolled and dosed in the study, and 11 subjects completed the study. Of these 11 subjects, 10 subjects received all 5 regimens. One subject (Subject 003) did not receive 1 regimen (Regimen D) due to requiring treatment for an AE (joint dislocation of finger) but received all of the remaining regimens and completed the study. One subject (Subject 010) was withdrawn from the study after dosing with Regimen B due to a Grade 3 AE (headache) and, therefore, did not receive Regimens C, D, and E.

Results are as follows:

**Figure 1. Mean ( $\pm$  SD) Lorcaserin Plasma Concentration vs Time Profiles, Study APD356-031**



Source: APD356-031 CSR, Figure 2

**Table 2. Geometric Mean (Geometric CV%) Values of Key Plasma Pharmacokinetic Parameters for Lorcaserin, Study APD356-031**

Regimen	A (10 mg)	B (20 mg)	C (20 mg)	D (20 mg)	E (20 mg)	C (20 mg)	E (20 mg)
Formulation	IR	MR prototype 1	MR prototype 2	MR prototype 3	MR prototype 2	MR prototype 2	MR prototype 2
Clear Ratio	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Fasted/Fed	Fasted	Fasted	Fasted	Fasted	High Fat Breakfast	Fasted	High Fat Breakfast
Population	PK Analysis Dataset 1 (n = 10)				PK Analysis Dataset 2 (n = 11)		
Tlag (h) <sup>a</sup>	0.00 (0.00–0.00)	0.50 (0.00–0.50)	1.00 (0.50–1.50)	0.00 (0.00–0.50)	1.50 (1.00–2.00)	1.00 (0.50–1.50)	1.50 (0.50–2.00)
Tmax (h) <sup>a</sup>	1.50 (1.00–6.00)	7.00 (6.00–12.00)	12.00 (8.00–23.53)	6.00 (6.00–8.00)	12.00 (6.00–20.00)	12.00 (6.00–23.53)	12.00 (6.00–20.00)
Cmax (ng/mL)	35.6 (31.9)	38.2 (29.2)	33.8 (29.0)	44.8 (25.0)	51.1 (22.6)	33.8 (27.4)	49.8 (23.1)
C12 (ng/mL)	16.4 (32.0)	34.0 (30.9)	31.4 (26.5)	32.5 (24.1)	46.7 (23.3)	31.0 (25.3)	45.9 (22.9)
C24 (ng/mL)	5.86 (43.6)	18.7 (32.1)	23.6 (26.6)	16.6 (32.6)	20.8 (39.9)	23.2 (26.0)	20.8 (37.7)
AUC(0-t) (ng.h/mL)	479 (30.7)	907 (27.1)	927 (24.7)	886 (23.0)	1020 (23.5)	916 (23.7)	1000 (22.9)
AUC(0-inf) (ng.h/mL)	568 (20.1) [n = 8]	909 (24.4) [n = 7]	978 (33.5) [n = 5]	887 (31.5) [n = 5]	1060 (25.3) [n = 8]	958 (30.3) [n = 6]	1040 (24.1) [n = 9]
T1/2el (h)	11.45 (19.6) [n = 8]	12.90 (23.1) [n = 7]	12.21 (14.4) [n = 5]	11.37 (17.8) [n = 5]	10.52 (15.3) [n = 8]	11.70 (16.6) [n = 6]	10.48 (14.4) [n = 9]
Frel (AUC(0-inf)) (%) <sup>b</sup>	NA	99.4 (5.5) [n = 7]	104.3 (7.3) [n = 5]	94.5 (10.0) [n = 5]	103.8 (14.9) [n = 8]	105.9 (7.6) [n = 6]	105.7 (14.9) [n = 9]
Fed/Fasted Frel (AUC(0-inf)) (%) <sup>c</sup>	NA	NA	NA	NA	NA	NA	98.5 (14.3) [n = 7]

NA: not applicable

<sup>a</sup> Median (range)

<sup>b</sup> relative bioavailability based on AUC(0-inf) for the test formulation (Regimen B, C, D or E) compared to the reference formulation (Regimen A) adjusted for dose differences

<sup>c</sup> relative bioavailability based on AUC(0-inf) for MR prototype 2 formulation under fed conditions (Regimen E) compared to under fasted conditions (Regimen C)

Source: APD356-031 CSR, Table 6

In the fasted state,  $C_{max}$  decreased in rank order for the (b) (4) medium and (b) (4) release formulations, with the  $C_{max}$  of the IR formulation in the fasted state falling between those of the (b) (4) and medium release formulations.

The AUC ratios were approximately 200%, which is expected given the total dose administered (10 mg IR, 20 mg MR).

In the fed state, the (b) (4) release formulation exhibited an elevated  $C_{max}$  compared to the fasted state. This difference (approximately 47%) was considered statistically significant; however, there was no suggestion of uncontrolled release of drug substance (i.e., ‘dose dumping’). There was no evidence of a food effect for  $AUC_{(0-inf)}$ .

The reference formulation and all test formulations of lorcaserin were well tolerated. No SAEs were reported during the study. The following is an enumeration of the adverse events. One patient was discontinued due to a severe headache.

**Table 3. Incidence of Adverse Events, Study APD356-031**

System Organ Class Preferred term	Regimen A (N = 12) n (%)	Regimen B (N = 12) n (%)	Regimen C (N = 11) n (%)	Regimen D (N = 10) n (%)	Regimen E (N = 11) n (%)	Overall (N = 12) n (%)
<b>Nervous System Disorders</b>	2 (16.7)	1 (8.3)	1 (9.1)	0	1 (9.1)	4 (33.3)
Headache	2 (16.7)	1 (8.3)	1 (9.1)	0	1 (9.1)	4 (33.3)
<b>Gastrointestinal Disorders</b>	1 (8.3)	0	1 (9.1)	0	1 (9.1)	3 (25.0)
Nausea	1 (8.3)	0	0	0	1 (9.1)	2 (16.7)
Abdominal distension	0	0	1 (9.1)	0	0	1 (8.3)
<b>Infections and Infestations</b>	0	1 (8.3)	0	1 (10.0)	0	2 (16.7)
Nasopharyngitis	0	1 (8.3)	0	1 (10.0)	0	2 (16.7)
<b>Injury, Poisoning and Procedural Complications</b>	0	1 (8.3)	1 (9.1)	0	0	2 (16.7)
Contusion	0	1 (8.3)	0	0	0	1 (8.3)
Joint dislocation	0	0	1 (9.1)	0	0	1 (8.3)
<b>Eye Disorders</b>	0	0	0	0	1 (9.1)	1 (8.3)
Eye pain	0	0	0	0	1 (9.1)	1 (8.3)
<b>General Disorders and Administration Site Conditions</b>	0	0	0	1 (10.0)	0	1 (8.3)
Catheter site related reaction	0	0	0	1 (10.0)	0	1 (8.3)
<b>Metabolism and Nutrition Disorders</b>	0	0	1 (9.1)	0	0	1 (8.3)
Decreased appetite	0	0	1 (9.1)	0	0	1 (8.3)

Regimen A (Period 1): 10 mg lorcaserin IR tablet (reference) in a fasted state  
 Regimen B (Period 2): 20 mg lorcaserin MR prototype 1 tablet (test; medium release) in a fasted state  
 Regimen C (Period 3): 20 mg lorcaserin MR prototype 2 tablet (test; (b) (4) release) in a fasted state  
 Regimen D (Period 4): 20 mg lorcaserin MR prototype 3 tablet (test; (4) release) in a fasted state  
 Regimen E (Period 5): 20 mg lorcaserin MR prototype 2 tablet (test; release) in a fed state

Source: APD356-031 CSR, Table 11

The (b) (4) release prototype formulation was selected for further development.

### APD356XR-101

This was a two-way, two-sequence, randomized, crossover study to determine the pharmacokinetics and bioequivalence of single and multiple doses of Belviq XR and IR to 36 healthy males and females. Subjects were randomized to either IR/XR (Sequence 1) or XR/IR (Sequence 2).

A total of 36 subjects were randomized and dosed. Subjects #13 and #28 although missing a single time point, were included in the data analysis. Subject #34 left the study for personal reasons after Day 9. Data from this subject were incomplete and therefore not included in the PK analysis. Subject #7 was not included in the primary analysis. The sponsor described the rationale as follows (emphasis added):

- Lorcaserin concentration-time profiles for the IR treatment but not the XR treatment following single and multiple doses were dissimilar to the dosing population and also to the entire Phase 1 and population PK Phase 3 PK databases with the IR formulation. The concentration-time profile from the single day dosing period suggests that the second, hour 12 dose was either not taken or not absorbed; likewise, the PK profile for this subject indicated that doses were either not taken or were incompletely absorbed during the entire multi-dose IR regimen. It is routine practice at the clinical site to visually check if drug tablets/capsules are hidden under the tongue or in the buccal cavity. **Extensive review of the clinical personnel and dosing log could not rule out the possibility that subject #7 did take the medication as per protocol.** All plasma samples associated with subject #7 IR dosing were reanalyzed and

confirmed the original assay results. Comparison of subject #7 plasma concentration-time profiles after single or multiple doses of the XR formulation to all individuals dosed (Figure 3, panel B, n=35) suggests that absorption from the gastrointestinal tract of subject #7 was similar to the total dosing population. This subject was therefore not considered an “outlier” subject with respect to drug absorption from the XR tablet. The concentration-time profile for subject #7 suggested that the subject may not have swallowed the second IR tablet on Day 1. This is supported by evidence from the first IR single dose tablet that showed a “typical” lorcaserin concentration-time profile. These data on Day 1 further indicated that the subject was not an “outlier” absorber following IR tablet administration. However, during the multiple dose IR phase, all plasma lorcaserin concentrations for this subject were at or near the lower limit of assay detection. Therefore, the decision was made to exclude subject #7 from the primary PK analyses despite the failure to conclusively identify a reason for this subject’s highly disparate drug exposures during the IR but not the XR dosing sequences.

**Reviewer comment: The ultimate acceptability of the exclusion of subject #7 is deferred to clinical pharmacology reviewers; however, given that the impact affects the already approved IR, rather than the new XR formulation, it would seem reasonable to exclude this patient from the bioequivalence analyses.**

In summary, the following primary analyses excluded subjects #34 and #7.

**Table 4. Geometric Mean (% CV) of Lorcaserin PK Parameters after a Single Dose and Under Steady-State Conditions, Study APD356XR-101**

Parameter	Single Dose		Steady-State <sup>c</sup>	
	IR 10 mg b.i.d.	XR 20 mg q.d.	IR 10 mg b.i.d.	XR 20 mg q.d.
t <sub>1/2z</sub> <sup>a</sup> (hr)	11.8 (1.32)	13.6 (3.34)	11.9 (1.5)	11.8 (1.48)
t <sub>max</sub> <sup>b</sup> (hr)	3 (1.5, 4)	12 (6, 16)	1.5 (1, 3)	10 (6, 12)
AUC <sub>0-t</sub> (hr·ng/mL)	1212 (23.9)	1166 (27.3)	NA	NA
AUC <sub>0-∞</sub> (hr·ng/mL)	1240 (24.2)	1217 (27.9)	NA	NA
AUC <sub>0-24</sub> (hr·ng/mL)	754 (23.1)	633 (28.9)	1328 (26.5)	1235 (28.2)
C <sub>max</sub> (ng/mL)	52.3 (24.0)	38.8 (30.8)	80.1 (25.7)	73.9 (31.1)
C <sub>min,ss</sub> (ng/mL)	NA	NA	35.2 (25.8)	29.9 (37.1)
C <sub>24</sub> (ng/mL)	27.7 (24.2)	23.6 (27.4)	39.2 (27.8)	34.6 (32.4)
C <sub>av,ss</sub> (ng/mL)	NA	NA	55.3 (26.5)	51.5 (28.2)
V <sub>z</sub> /F (L)	229 (23.1)	265 (26.7)	216 (26.0)	231 (25.8)
CL/F (L/hr)	13.5 (25.2)	13.9 (27.9)	12.7 (26.5)	13.7 (28.2)
Fluctuation <sup>d</sup>	NA	NA	0.800 (19.6)	0.824 (25.4)
Swing <sup>e</sup>	NA	NA	1.26 (26.5)	1.42 (46.4)

<sup>a</sup> Mean (sd)

<sup>b</sup> Median (minimum, maximum)

<sup>c</sup> Steady-state achieved after 5 consecutive days of dosing (Figure 5)

<sup>d</sup> Fluctuation: (C<sub>max,ss</sub>-C<sub>min,ss</sub>)/C<sub>av,ss</sub>

<sup>e</sup> Swing: (C<sub>max,ss</sub>-C<sub>min,ss</sub>)/C<sub>min,ss</sub>

Source: APD356XR-101 CSR, Table 7

The following tables present the ratios of population geometric means with the 90% confidence intervals (CI) for lorcaserin HCl 20 mg XR QD and 10 mg IR BID single-dose (Table 5) and at steady-state (Table 6). After the single dose, bioequivalence was demonstrated for AUC. The 90% CI of the GMR of  $C_{max}$  was outside the bioequivalence limits following the single dose treatments. However, the steady-state  $C_{max}$  and  $AUC_{0-24}$  were within the bioequivalence limits following multiple dose treatments.

**Table 5. 90% CI on the Geometric Mean Ratio of Lorcaserin PK Parameters following a Single Dose of Lorcaserin HCl 20 mg XR QD and 10 mg IR BID, Study APD356XR-101**

Parameter	N <sup>a</sup>	Geometric Mean		G.M. Ratio <sup>d</sup>	90% CI <sup>e</sup>
		Test <sup>b</sup>	Reference <sup>c</sup>		
AUC <sub>0-∞</sub> (hr·ng/mL)	34	1219	1235	0.987	(0.948, 1.028)
AUC <sub>0-t</sub> (hr·ng/mL)	34	1169	1207	0.968	(0.931, 1.007)
C <sub>max</sub> (ng/mL)	34	39.0	52.2	0.748	(0.705, 0.793) <sup>f</sup>

CI=confidence interval; GM=geometric mean

<sup>a</sup> N=34; excludes subjects #7 and #34

<sup>b</sup> Test = 20 mg XR q.d.

<sup>c</sup> Reference = 10 mg IR b.i.d.

<sup>d</sup> G.M. Ratio = Geometric mean of the test/reference ratio

<sup>e</sup> 90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

<sup>f</sup> Did not meet BE.

Source: APD356XR-101 CSR, Table 8

**Table 6. 90% CI on the Geometric Mean Ratio of Lorcaserin PK Parameters following Multiple Doses of Lorcaserin HCl 20 mg XR QD and 10 mg IR BID, Study APD356XR-101**

Parameter	N <sup>a</sup>	Geometric Mean		G.M. Ratio <sup>d</sup>	90% CI <sup>e</sup>
		Test <sup>b</sup>	Reference <sup>c</sup>		
AUC <sub>0-24,ss</sub> (hr·ng/mL)	34	1234	1324	0.932	(0.891, 0.975)
C <sub>max,ss</sub> (ng/mL)	34	73.8	79.9	0.924	(0.876, 0.975)

<sup>a</sup> N=34, excludes subjects #7 and #34

<sup>b</sup> Test = 20 mg XR q.d.

<sup>c</sup> Reference = 10 mg IR b.i.d.

<sup>d</sup> G.M. Ratio = Geometric mean of the test/reference ratio

<sup>e</sup> 90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

Source: APD356XR-101 CSR, Table 9

All 36 subjects received study medication and were included in the safety evaluation. A total of 84 TEAEs were reported by 28 (77.8%) subjects following administration of lorcaserin HCl: 33 AEs were reported by 18 (50.0%) during Treatment A (IR), 32 AEs were reported by 17 (48.6%) subjects during Treatment B (XR), and 19 AEs were reported by 10 (27.8%) subjects during the Day 10–14 washout period. The majority of these AEs were reported as mild in severity and considered related to study drug. None of these AEs resulted in study termination. There were no deaths or SAEs.

**Table 7. Summary of Treatment-Emergent Adverse Events in > 1 Subject, Study APD356XR-101**

Category	Treatment A (IR) (N=36)	Treatment B (XR) (N=35)	Washout (Days 10-14) (N=36)	All (N=36)
<b>Number (%) of Subjects Reporting TEAEs</b>	<b>18 (50.0%)</b>	<b>17 (48.5%)</b>	<b>10 (27.8%)</b>	<b>28 (77.8%)</b>
<b>Gastrointestinal disorders</b>				
Abdominal pain	1 (2.8%)	1 (2.9%)	1 (2.8%)	3 (8.3%)
Constipation	3 (8.3%)	1 (2.9%)	0 (0.0%)	4 (11.1%)
Nausea	2 (5.6%)	1 (2.9%)	3 (8.3%)	6 (16.7%)
<b>General disorders and administration site conditions</b>				
Fatigue	0 (0.0%)	2 (5.7%)	0 (0.0%)	2 (5.6%)
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	0 (0.0%)	1 (2.9%)	1 (2.8%)	2 (5.6%)
<b>Musculoskeletal and connective tissue disorders</b>				
Flank pain	1 (2.8%)	1 (2.9%)	0 (0.0%)	2 (5.6%)
<b>Nervous system disorders</b>				
Dizziness	1 (2.8%)	3 (8.6%)	4 (11.1%)	6 (16.7%)
Headache	16 (44.4%)	7 (20.0%)	4 (11.1%)	19 (52.8%)
Presyncope	0 (0.0%)	1 (2.9%)	1 (2.8%)	2 (5.6%)
Somnolence	0 (0.0%)	3 (8.6%)	0 (0.0%)	3 (8.3%)

Note: If a subject experienced the same event more than once during a treatment period, the first occurrence was tabulated. MedDRA version 17.0 was used as the adverse event coding dictionary.

A: 1 day treatment with lorcaserin HCl 10 mg IR b.i.d → 3-day washout → 5 days treatment with lorcaserin HCl 10 mg IR b.i.d.

B: 1 day treatment with lorcaserin HCl 20 mg XR q.d. → 3-day washout → 5 days treatment with lorcaserin HCl 20 mg XR q.d.

Source: APD356XR-101 CSR, Table 18

***Reviewer comment: It is noted that more AEs of somnolence and fatigue were reported with the XR as compared to IR or washout periods. No conclusions can be drawn from this limited, short-term trial.***

There were no clinically significant changes in laboratory parameters (hematology, chemistry, urinalysis, or coagulation) or ECG during this study. Although some subjects showed sporadic out of normal range laboratory or vital sign values after study drug administration, none was reported as an AE.

### **APD356XR-102**

This study was a two-way, two-sequence, randomized, balanced, cross-over study to determine the relative bioavailability of single and multiple doses of lorcaserin HCl 20 mg XR in the fed (high-fat) and fasted state.

- Treatment A (fasted state): consisted of a single day of treatment with lorcaserin HCl 20 mg XR q.d. in the *fasted* state, followed by a washout period of 3 days, then followed by 5 days of treatment with lorcaserin HCl 20 mg XR q.d. in the *fasted* state.

- Treatment B (fed state): consisted of a single day of treatment with lorcaserin HCl 20 mg XR q.d. in the *fed* state, followed by a washout period of 3 days, then followed by 5 days of treatment with lorcaserin HCl 20 mg XR q.d. in the *fed* state.
- There was an inpatient washout period of 5 days between treatments.
- Treatments A and B were administered in one of 2 sequences of 18 subjects each.

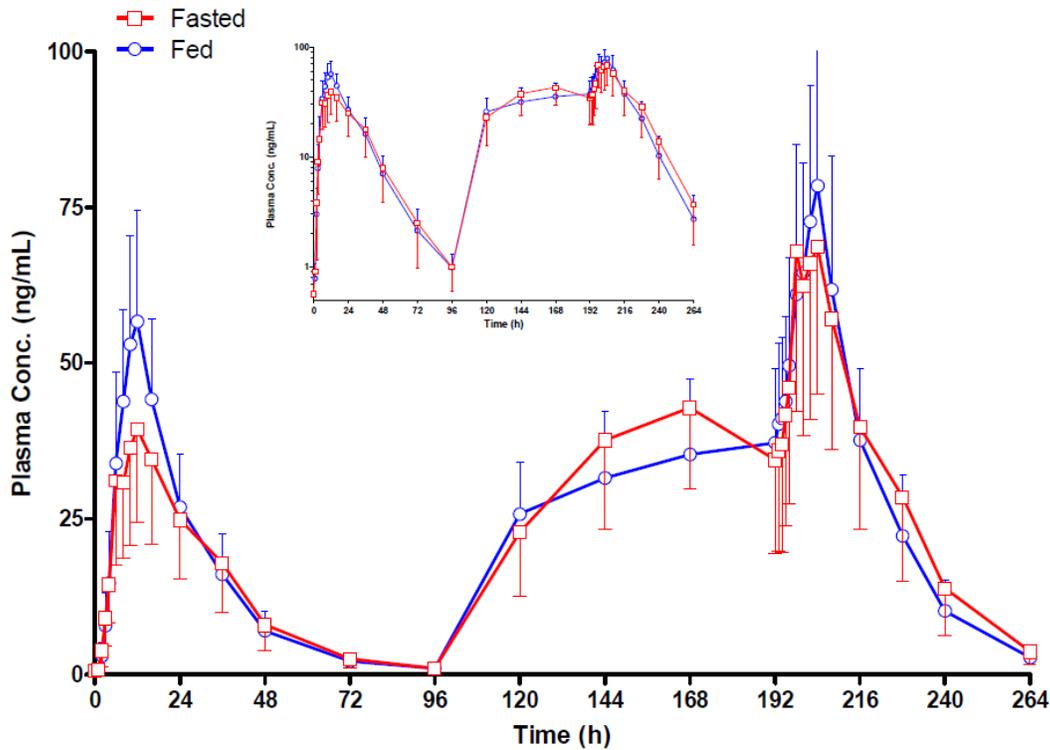
**Sequence 1:** Treatment A (fasted) → Treatment B (fed)

**Sequence 2:** Treatment B (fed) → Treatment A (fasted)

A total of 36 subjects were enrolled and completed the study, and were included in the pharmacokinetic analysis.

Co-administration with a high fat meal did not alter  $t_{max}$  either after a single dose or under steady-state conditions. After a single dose, mean  $C_{max}$  increased approximately 46% after a standard high fat meal. Mean AUC values, while higher with food, achieved bioequivalence with respect to  $AUC_{0-inf}$ . Under steady-state dosing conditions, bioequivalence in both the  $C_{max}$  and  $AUC_{0-24}$  parameters was achieved, and similarity in  $t_{max}$  values was confirmed between fed and fasted conditions.

**Figure 2. Mean (SD) Lorcaserin Plasma Concentration-Time Profiles, Sequential Single and Multiple Dosing of Lorcaserin HCl XR 20 mg to Steady-State (Inset: Semi-Log Plot), Study APD356XR-102**



Source: APD356XR-102 CSR, Figure 1

**Table 8. Geometric Mean (% CV) for Lorcaserin PK Parameters after a Single Dose or Under Steady-State Conditions, Study APD356XR-102**

Parameter <sup>a, d</sup>	Single Dose		Steady-State	
	fasted	fed	fasted	fed
AUC <sub>0-24</sub> (hr·ng/mL)	611 (42.9)	808 (27.7)	1216 (40.4)	1318 (29.5)
AUC <sub>0-∞</sub> (hr·ng/mL)	1141 (48.6)	1332 (28.6)	NA	NA
AUC <sub>0-t</sub> (hr·ng/mL)	1097 (48.1)	1294 (28.0)	NA	NA
C <sub>av,ss</sub> (ng/mL)	NA	NA	50.7 (40.4)	54.9 (29.5)
C <sub>max</sub> (ng/mL)	38.5 (39.4)	56.1 (31.8)	69.5 (38.4)	78.7 (30.9)
C <sub>min,ss</sub> (ng/mL)	NA	NA	28.9 (54.9)	NA
t <sub>1/2z</sub> (hr) <sup>b</sup>	13.0 (2.44)	12.4 (2.35)	12.4 (1.94)	12.0 (1.68)
t <sub>max</sub> (hr) <sup>c</sup>	12 (6, 24)	12 (8, 16)	10 (6, 12)	12 (4, 16)

NA = not applicable

<sup>a</sup> healthy volunteer subjects, n = 36/treatment

<sup>b</sup> mean (SD)

<sup>c</sup> median (minimum, maximum)

<sup>d</sup> numbers rounded to 3 significant figures

Source: APD356XR-102 CSR, Table 6

**Table 9. Bioequivalence Determination between Fed and Fasted States after Single Dose Lorcaserin HCl XR 20 mg**

Parameter	N	Geometric Mean		G.M. Ratio <sup>c</sup>	90% CI <sup>d</sup>
		Test <sup>a</sup>	Reference <sup>b</sup>		
AUC <sub>0-∞</sub> (hr·ng/mL)	36	1332	1141	1.167	(1.092, 1.247)
AUC <sub>0-t</sub> (hr·ng/mL)	36	1294	1097	1.179	(1.103, 1.260) <sup>e</sup>
C <sub>max</sub> (ng/mL)	36	56.1	38.5	1.459	(1.345, 1.581) <sup>e</sup>

<sup>a</sup> Test = 20 mg XR q.d. in the fed state (n=36)

<sup>b</sup> Reference = 20 mg XR q.d. in the fasted state (n=36)

<sup>c</sup> G.M. Ratio = Geometric mean of the test/reference ratio

<sup>d</sup> 90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

<sup>e</sup> BE not achieved; BE boundaries 0.800, 1.250

Source: APD356XR-102, Table 7

**Table 10. Bioequivalence Determination between Fed and Fasted States after Multiple Dose Lorcaserin HCl XR 20 mg QD**

Parameter	N	Geometric Mean		G.M. Ratio <sup>c</sup>	90% CI <sup>d</sup>
		Test <sup>a</sup>	Reference <sup>b</sup>		
AUC <sub>0-24</sub> (hr·ng/mL)	36	1318	1216	1.084	(1.027, 1.145)
C <sub>max,ss</sub> (ng/mL)	36	78.7	69.5	1.134	(1.071, 1.199)

<sup>a</sup> Test = 20 mg XR q.d. in the fed state

<sup>b</sup> Reference = 20 mg XR q.d. in the fasted state

<sup>c</sup> G.M. Ratio = Geometric mean of the test/reference ratio

<sup>d</sup> 90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio

Source: APD356XR-102, Table 8

The sponsor concludes that lorcaserin HCl XR can be administered without regard to food.

***Reviewer comment: Dr. Singh notes that although C<sub>max</sub> increases in the fed state after a single dose, importantly bioequivalence was established for both C<sub>max</sub> and AUC at steady state. Furthermore, she points out that the higher C<sub>max</sub> that was observed with single dose of lorcaserin 20 mg XR in the fed state was similar to that observed with the IR formulation in study APD356XR-101 in the fasted state. She recommends that lorcaserin XR can therefore be administered without regard to food. I agree with this recommendation.***

All 36 subjects received study medication and were included in the safety evaluation. A total of 66 AEs were reported by 22 (61.1%) of subjects following administration of lorcaserin HCl: AEs were reported by 13 (36.1%) subjects during Treatment A (fasted), 21 AEs were reported by 13 (36.1%) subjects during Treatment B (fed), and 15 AEs were reported by 10 (27.8%) subjects during the Day 10–14 washout period. All but one of the AEs were reported as mild in intensity (the one moderate AE was ‘skin irritation’). There were no SAEs and no AEs that resulted in study termination. Headache, nausea, and constipation were the most commonly reported preferred terms in the study.

**Table 11. Summary of Adverse Events, Study APD356XR-102**

System Organ Class	Preferred Term	Treatment A (Fasted) (N=36)	Treatment B (Fed) (N=36)	Washout (Days 10-14) (N=36)	All (N=36)
<b>Blood and lymphatic system disorders</b>					
	Lymphadenopathy	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
<b>Gastrointestinal disorders</b>					
	Abdominal distension	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
	Abdominal pain	3 (8.3%)	0 (0.0%)	0 (0.0%)	3 (8.3%)
	Constipation	2 (5.6%)	1 (2.8%)	1 (2.8%)	4 (11.1%)
	Diarrhoea	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
	Nausea	4 (11.1%)	1 (2.8%)	1 (2.8%)	5 (13.9%)
	Vomiting	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
<b>General disorders and administration site conditions</b>					
	Fatigue	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
<b>Infections and infestations</b>					
	Conjunctivitis	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
	Folliculitis	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
	Vaginal infection	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
	Vulvovaginal mycotic infection	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
<b>Metabolism and nutrition disorders</b>					
	Decreased appetite	2 (5.6%)	1 (2.8%)	1 (2.8%)	4 (11.1%)
<b>Musculoskeletal and connective tissue disorders</b>					
	Back pain	1 (2.8%)	1 (2.8%)	1 (2.8%)	3 (8.3%)
	Myofascial pain syndrome	1 (2.8%)	1 (2.8%)	0 (0.0%)	2 (5.6%)
	Pain in extremity	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
<b>Nervous system disorders</b>					
	Dizziness	1 (2.8%)	1 (2.8%)	0 (0.0%)	2 (5.6%)
	Headache	5 (13.9%)	7 (19.4%)	1 (2.8%)	12 (33.3%)
	Myoclonus	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
	Somnolence	1 (2.8%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
<b>Psychiatric disorders</b>					
	Abnormal dreams	0 (0.0%)	1 (2.8%)	2 (5.6%)	2 (5.6%)
	Agitation	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
	Anxiety	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
	Euphoric mood	1 (2.8%)	1 (2.8%)	0 (0.0%)	2 (5.6%)
<b>Psychiatric disorders</b>					
	Irritability	1 (2.8%)	0 (0.0%)	1 (2.8%)	2 (5.6%)
<b>Renal and urinary disorders</b>					
	Pollakiuria	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
<b>Reproductive system and breast disorders</b>					
	Dysmenorrhoea	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
<b>Skin and subcutaneous tissue disorders</b>					
	Acne	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
	Rash	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)

System Organ Class	Preferred Term	Treatment A (Fasted) (N=36)	Treatment B (Fed) (N=36)	Washout (Days 10-14) (N=36)	All (N=36)
	Skin irritation	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
<b>Vascular disorders</b>					
	Flushing	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
	Hot flush	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)

If a subject experienced the same event more than once during a treatment period, the first occurrence was tabulated  
A = 1 day treatment lorcaserin HCL 20 mg XR qd in fasted state -> 3-day wash-out -> 5 days treatment lorcaserin HCL 20 mg XR qd in fasted state  
B = 1 day treatment lorcaserin HCL 20 mg XR qd in fed state -> 3-day wash-out -> 5 days treatment lorcaserin HCL 20 mg XR qd in fed state

Source: APD356XR-102, Table 8

There were no clinically significant changes in laboratory parameters (hematology, chemistry, urinalysis, or coagulation) or ECG during this study. Although some subjects showed sporadic out of normal range laboratory values after study drug administration, none were reported as AEs.

### CONTROLLED SUBSTANCES

A search of the lorcaserin safety database was performed for reports received from 27 June 2012 (U.S. approval) through 30 Sep 2015 coded to the MedDRA SMQ of Drug Abuse and Dependence. These reports include all spontaneous adverse events recorded in patients receiving Belviq therapy, serious adverse events reported from the lorcaserin clinical trials, solicited adverse events, and nonserious adverse events of special interest (e.g., euphoria) recorded from the ongoing cardiovascular outcomes trial.

The search revealed a total of 14 reports describing 15 events; 10 spontaneous reports and 4 clinical trial reports with the following distribution of AEs:

**Table 12. AEs for Belviq in SMQ Drug Abuse and Dependence**

Preferred Terms (PT)	Clinical Study Adverse Events	Spontaneous Adverse Events
Accidental overdose	3	0
Drug Screen positive	0	2
Drug withdrawal syndrome	0	2
Intentional overdose	0	1
Intentional product misuse	0	1
Overdose	1	1
Withdrawal syndrome	0	4

Source: Clinical Information Amendment, NDA 208524, serial no. 0006

There were a total of six reports of withdrawal syndrome/drug withdrawal, all of which were nonserious and from spontaneous sources. Four of the six reports of overdose were accidental and did not suggest an attempt to abuse lorcaserin. One of the accidental overdose reports from the CVOT involved an accidental overdose of opiates and benzodiazepines and not an overdose of lorcaserin.

One of the two reports of intentional overdose describes a situation where the patient reported she was not sure she could afford to stay on Belviq for a long period of time, so she increased the dosage of Belviq to 20 mg BID for “better and faster results”.

The second report of intentional overdose (PT: Intentional Product Misuse) was a serious report from a consumer in the US. The patient’s mother indicated the patient’s three brothers found her daughter screaming with a few empty boxes of Belviq samples of eight tablets each. Her daughter was hospitalized and subsequently diagnosed with acute psychosis described as not being able to detect reality, moods ranging from being unresponsive to verbal stimuli (Belviq “killed her feelings”) to episodes of aggression, not being able to concentrate, not wanting to go anywhere, and people had to be careful of what was said around her otherwise she would “flip out.” The acute psychosis was considered by the reporter to have caused persistent/significant disability/incapacity. Belviq was discontinued. A blood test showed trace amounts of Ativan (lorazepam) and opioids [Norco (hydrocodone bitartrate/acetaminophen)] for sleep and pain, respectively. No medical history or psychiatric history was reported. The patient is employed at a clinic as a non-clinical staff member; this is believed to be where she obtained the samples of Belviq. Ativan and Norco were also discontinued. The acute psychosis improved.

## **AUDITS**

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection, given that OSIS recently inspected the clinical site and the inspectional outcome from the inspection was classified as No Action Indicated (NAI).

***Reviewer comment: I have no concerns with this recommendation.***

## **CMC**

No CMC deficiencies were identified. The CMC review noted that commercial formulation was used in the *in vitro* alcohol dose-dumping study, which found no dose-dumping issue.

## **PHARMACOLOGY/TOXICOLOGY**

No new pharmacology/toxicology data were provided in the NDA.

## **FINANCIAL DISCLOSURE**

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

## **LABELING**

The sponsor has requested changes to sections 6 (eye disorders) and 14 (DEXA). FDA agreed to those changes in a previous labeling supplement for Belviq IR (for a PLLR conversion). Aside from the labeling changes related to dosage change to 20 mg QD that will be addressed separately in discussions with other disciplines (e.g., clinical pharmacology and chemistry), the changes related to the aforementioned labeling supplement, i.e., PLLR and hypersensitivity (sections 4 and 6), will also be made with this NDA for consistency with NDA 22529/Belviq IR labeling.

## **PROPRIETARY NAME**

Division of Medication Error Prevention and Analysis (DMEPA) reviewed “Belviq XR” from a promotional and safety perspective and determined that the name is acceptable.

***Reviewer comment: I have no concerns with this recommendation.***

## **PEDIATRIC STUDY REQUIREMENTS**

The division agreed with the iPSP at the time of IND submission, which cross-references the studies being conducted under NDA 22529 (PK studies in patients aged 12-17 years and 7-11 years) as well as proposes using the XR formulation in the 52-week safety and efficacy study in the 12-17 year old age group. The acceptability of this approach is pending the review of the XR formulation in adults (current NDA), and given the approval recommendation, seems appropriate. The dose/formulation for the safety and efficacy study in 7-11 year olds is still to be determined.

In the current NDA, the sponsor has provided a request for waiver for ages 0-6 years. This request should be granted as it is unlikely that lorcaserin would be prescribed to a substantial number of patients in this age group and pharmacotherapy in general for excess body weight has not been shown superior to behavioral and lifestyle interventions in children in this age group.

The sponsor has requested a deferral for ages 7-11 years and 12-17 years. This request should be granted as Belviq XR will be ready for approval in adults before the pediatric studies are complete.

## **RECOMMENDATION**

I recommend approval of Belviq XR at a dosing regimen of 20 mg QD based on bioequivalence to Belviq IR at a dosing regimen of 10 mg BID.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JULIE K GOLDEN  
06/30/2016

JAMES P SMITH  
06/30/2016

## CLINICAL FILING CHECKLIST FOR NDA

**NDA Number: 208524**

**Applicant: Arena  
Pharmaceuticals, Inc.**

**Stamp Date: 18 Sept 2015**

**Drug Name: Belviq XR  
(lorcaserin HCl)**

**NDA Type: Standard**

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
<b>LABELING</b>					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm</a> )	x			
<b>SUMMARIES</b>					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?			x	No new clinical trial data were submitted; summary of clinical safety describes safety in the BA/BE studies
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	No new clinical trial data were submitted; summary of clinical efficacy references NDA 22529
10.	Has the applicant submitted a benefit-risk analysis for the product?	x			Section 2.5.6 in the clinical overview
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
<b>505(b)(2) Applications</b>					
12.	If appropriate, what is the relied upon listed drug(s)?				
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?				
14.	Describe the scientific bridge (e.g., BA/BE studies)				
<b>DOSAGE</b>					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g.,			x	

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
	appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:				
<b>EFFICACY</b>					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			x	
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
<b>SAFETY</b>					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			x	
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dosage (or dosage range) believed to be efficacious?			x	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
25.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	x			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	

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

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

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
<b>OTHER STUDIES</b>					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			iPSP agreement 17 Sep 2015
<b>PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE</b>					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see <a href="http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm">http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm</a> )?	x			See NDA 22529 SDN 487 (submitted as part of pending labeling supplement)
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		x		Response to IR re abuse potential was submitted 21 Oct 2015; however, according to the controlled substances staff, more data are needed (e.g., CRFs). Defer to CSS re: information to be requested in 74-d letter.
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	BA/BE studies APD356XR-101 and -102 conducted in U.S.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
37.	Are all datasets to support the critical safety analyses available and complete?	x			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
<b>CASE REPORT FORMS</b>					

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		x		See info needed for CSS review, above
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			Studies APD356-031, APD356XR-101, and APD356XR-102 all include a statement in the respective study reports

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?    yes**

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

N/A

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

None.

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Reviewing Medical Officer Date

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Clinical Team Leader Date

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JULIE K GOLDEN  
11/06/2015

JAMES P SMITH  
11/06/2015