CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210063Orig1s000

NON-CLINICAL 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

Application number:	210063
Supporting document/s:	16
Applicant's letter date:	02/19/2019
CDER stamp date:	02/19/2019
Product:	Fulvestrant injection, 250 mg/5 mL (50 mg/mL)
Indication (Form 356h):	Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
Submission Type:	505(b)(2)
Listed Drug (Form 356h):	Faslodex® (Fulvestrant) injection 250 mg/5 mL (50 mg/mL)
Applicant:	Teva Pharmaceuticals USA Inc Morris Corporate Center III 400 Interpace Parkway Parsippany, New Jersey
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
Reviewer:	Eias Zahalka, PhD, MBA
Supervisor:	Tiffany Ricks, PhD
Division Director:	John Leighton, PhD, DABT Julia Beaver, MD
Project Manager:	Mitchell Chan

Disclaimer

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or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 210063.

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1 Executive Summary

1.1 Introduction

Fulvestrant Injection is an estrogen receptor antagonist. On 12/28/2016, the Applicant submitted a 505(b)(2) application for a new formulation of fulvestrant compared to the listed drug, Faslodex® Injection. Teva Pharmaceuticals has developed a new formulation intended for the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The Applicant is relying on the listed drug (LD) product Faslodex® (fulvestrant) injection, for intramuscular use, 250 mg /5mL (50 mg/mL) of AstraZeneca Pharmaceuticals (NDA # 021344), which has been marketed in the US since 2002. The proposed Fulvestrant Injection strength, dosage form, and route of administration are similar to Faslodex Injection the LD, but several of the inactive ingredients are different (e.g. medium chain triglycerides [MCT] (b) (4) dehydrated alcohol (b) (4)

In support of the NDA application submitted on 12/28/2016, the Applicant conducted an *in vivo* bioequivalence study in healthy, adult, human female subjects (Study # ACT-15160) to establish the equivalence of the proposed formulation to that of the LD. For nonclinical support, the Applicant relied on the Agency's finding of safety and effectiveness for an LD (Faslodex®). In addition to reliance on the LD, the Applicant submitted two nonclinical study reports, in two species, and relied upon literature to support the safety of the proposed level of dehydrated alcohol and MCT in the drug product administered by the intramuscular route.

On 10/02/2017, the nonclinical reviewer (Eias Zahalka, PhD, MBA), concluded that the 12/28/2016 data submitted to the NDA qualified the proposed level of the impurity (b) (4) in the drug product but did not find the data to be adequate to qualify the excipient (MCT) in the drug product. The potential impact of the excipient MCT on local tissue toxicities, as it compares to the listed drug, was not adequately addressed. Subsequently, on 10/26/2017, a Complete Response Letter was sent to the Applicant by the FDA, followed by a Type A Meeting Preliminary Comments Correspondence on 03/02/2018 . In these communications, the Applicant was asked to provide an adequate justification/qualification for the safety of the proposed levels of MCT in the drug product administered by intramuscular injection. The FDA recommended that the Applicant should submit a final GLP nonclinical bridging toxicology study report in a single species comparing Teva's fulvestrant injection formulation to the listed drug product (Faslodex®) at a clinically relevant dose. Furthermore, the FDA stated that the nonclinical study should include assessment of local tissue effects (macro and microscopic) and toxicokinetics following repeated intramuscular injections.

On 02/19/2019, the Applicant submitted a Complete Response Amendment. The response included a final signed report from a GLP nonclinical bridging toxicology Study (G17058) comparing the toxicity and toxicokinetic profile of Teva's fulvestrant injection 250 mg/ 5 mL (50 mg/mL) and Faslodex® fulvestrant injection 250 mg/ 5 mL

(50 mg/mL) when administered as 3 intramuscular injections (on days 1, 15, and 29) to Wistar rats.

1.2 Brief Discussion of Nonclinical Findings

In the current submission, the Applicant conducted a nonclinical study in rats demonstrating that the toxicity (local tissue and systemic) profiles of Teva's fulvestrant injection 250 mg/ 5 mL (50 mg/mL) and Faslodex® fulvestrant injection 250 mg/ 5 mL (50 mg/mL) when administered as 3 intramuscular injections, were generally comparable.

The toxicokinetic profiles of both drugs (C_{max} and AUC) were comparable, while Tmax was reported at later timepoint for the LD (24 hours) as compared to Teva's fulvestrant formulation (3 to 7 hours), indicating that the Teva's fulvestrant formulation shows faster absorption than the LD.

Teva's fulvestrant formulation contains an excipient, MCT, that was not previously characterized when administered by the intramuscular route. The safety profile of the intramuscular administered MCT at the proposed clinical level was therefore characterized in a repeat-dose toxicology study in rats. In the submitted study, the Applicant compared Teva's fulvestrant formulation containing MCT to the listed drug. Both test articles showed comparable local and systemic toxicity profiles. Thus, the safety of the of the proposed levels of MCT in the drug product administered by intramuscular injection was considered qualified, and the potential impact of this excipient on local tissue toxicity, as it compares to the listed drug, was adequately addressed.

The current and previous data submitted to this NDA provide an adequate scientific bridge for reliance on the listed drug, Faslodex®, for the nonclinical requirements for approval as a 505(b)(2) NDA. Since FDA's previous finding of safety and efficacy is captured in the product labeling and includes findings inferred from fact of approval, no further nonclinical studies are needed to support the approval of Teva's fulvestrant injection.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data provided in response to the 10/26/2017 CR letter in the current submission by the Applicant was found to be adequate to address the safety concern of the excipient MCT contained in Teva's fulvestrant clinical formulation . As such, there are no issues from the Pharmacology/Toxicology discipline that would preclude approval of Teva's fulvestrant injection 250 mg/ 5 mL (50 mg/mL) for the proposed indications. The nonclinical discipline recommends approval of Teva's fulvestrant injection 250 mg/ 5 mL.

1.3.2 Additional Non Clinical Recommendations

None

2 Drug Information

2.1 Drug

Teva's fulvestrant injection, 250 mg/5 mL (50 mg/mL), is a clear colorless to yellow viscous liquid, supplied in sterile single-use prefilled syringe (PFS) for intramuscular injection, each containing 250 mg of Fulvestrant. Fulvestrant injection, 500 mg (250 mg/injection) will be administered intramuscularly into the buttocks (gluteal area) slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29; and once monthly thereafter.

Table 1: Qualitative and Quantitative Unit Composition including Function

Table 1: Qualitative and Quantitative Unit Composition including Function

Components of the drug product	mg/mL	mg/Pre-filled-Syringe	Function	Quality reference
Active Ingredient				
Fulvestrant, USP	50.0	250.0	Active substance	USP/NF current Edition / Manufacturer specification
Inactive Ingredients				
Dehydrated Alcohol, USP	100.0	500.0	(b) (4)	USP/NF current edition
Benzyl Alcohol, NF	100.0	500.0		USP/NF current edition
Castor Oil, USP	600.0	3000.0		USP/NF current edition
Medium Chain Triglycerides, NF	Q.S. to 1.0 mL	Q.S. to 5.0 [3] mL		USP/NF current edition
Nitrogen, NF [2]	Q.S.	Q.S.		USP/NF current edition

Q.S. – Quantity Sufficient.
Notes: (b)
[1] Overfill (4)% is applied.
(b) (4)
(b) (4)

(excerpted from Applicant's report)

3 Studies Submitted

3.1 Studies Reviewed

Study #	Study Title	Reviewed	
		Full	Summary
Pharmacokinetic			
G17058	Fulvestrant injection 250 mg/ 5 mL (50 mg/mL) and Faslodex® Fulvestrant injection 250 mg/ 5 mL (50 mg/mL): 30-day intramuscular toxicity study in Wistar rats with toxicokinetics	X	

3.2 Previous Reviews Referenced

Nonclinical review for NDA 210063, Eias Zahalka, PhD, MBA review signed on 10/02/2017

6 General Toxicology

Below is a review of the nonclinical study (rat) submitted by the Applicant on 02/19/2019, in response to the FDA CR, to support the safety of the proposed level of MCT in the proposed drug product to be administered by the intramuscular route.

6.1 Nonclinical Bridging Study in Rats

Study title: Fulvestrant injection 250 mg/ 5 mL (50 mg/mL) and Faslodex® Fulvestrant injection 250 mg/ 5 mL (50 mg/mL): 30-day intramuscular toxicity study in Wistar rats with toxicokinetics (Study # G17058)	
Study no.:	G17058
Objective:	To compare the toxicity and toxicokinetic profile of Teva's fulvestrant formulation versus the Listed Drug (LD), Faslodex®, when administered as 3 intramuscular injections (on days 1, 15, and 29) to Wistar rats.
Sponsor:	Teva Pharmaceutical Inc
Conducting laboratory and location:	(b) (4)
Experimental starting Date:	01 June, 2018
GLP compliance and QA statement:	Yes (OECD); Concentration and stability analysis of each formulation were not performed under GLP compliance. The Applicant stated: Exceptions to GLPs include the following study elements: • Dose concentration verification and stability testing of the ready to use formulations were performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA Good Manufacturing Practice (GMP) regulations. These exceptions are expected to have no impact on the integrity of the study since dose formulations analyses were performed under FDA GMP regulations.
Drug; Batch #:	Fulvestrant; Batch # 5AH501 Faslodex®; Batch # NV472

Methods:

<table>
<tr><td>Route/Frequency of dosing:</td><td>Intramuscular injection; on days 1, 15 and 29</td></tr>
<tr><td>Study Design:</td><td>Table 2: Study Design
<table>
<tr><th rowspan="2">Group No.</th><th rowspan="2">Treatment Groups</th><th rowspan="2">Colour of cage card</th><th rowspan="2">Concentration (mg/mL)</th><th rowspan="2">Dosage</th><th rowspan="2">Total Dose volume/ Rat*</th><th rowspan="2">No. of rats</th><th rowspan="2">Sex</th><th colspan="2">Rat numbers</th></tr>
<tr><th>From</th><th>To</th></tr>
<tr><td colspan="10">Toxicity Groups</td></tr>
<tr><td rowspan="2">G1</td><td rowspan="2">Control (Saline)</td><td rowspan="2">White</td><td rowspan="2">0</td><td rowspan="2">0 mg/rat</td><td rowspan="2">0.2 mL</td><td>10</td><td>M</td><td>Rv721</td><td>Rv730</td></tr>
<tr><td>10</td><td>F</td><td>Rv731</td><td>Rv740</td></tr>
<tr><td rowspan="2">G2</td><td rowspan="2">Teva's Formulation</td><td rowspan="2">Yellow</td><td rowspan="2">50</td><td rowspan="2">10 mg/rat</td><td rowspan="2">0.2 mL</td><td>10</td><td>M</td><td>Rv741</td><td>Rv750</td></tr>
<tr><td>10</td><td>F</td><td>Rv751</td><td>Rv760</td></tr>
<tr><td rowspan="2">G3</td><td rowspan="2">RLD Formulation (Faslodex®)</td><td rowspan="2">Pink</td><td rowspan="2">50</td><td rowspan="2">10 mg/rat</td><td rowspan="2">0.2 mL</td><td>10</td><td>M</td><td>Rv761</td><td>Rv770</td></tr>
<tr><td>10</td><td>F</td><td>Rv771</td><td>Rv780</td></tr>
<tr><td colspan="10">Toxicokinetic groups</td></tr>
<tr><td rowspan="2">G1TK</td><td rowspan="2">Control (Saline)</td><td rowspan="2">White</td><td rowspan="2">0</td><td rowspan="2">0 mg/rat</td><td rowspan="2">0.2 mL</td><td>6</td><td>M</td><td>Rv781</td><td>Rv786</td></tr>
<tr><td>6</td><td>F</td><td>Rv787</td><td>Rv792</td></tr>
<tr><td rowspan="2">G2TK</td><td rowspan="2">Teva's Formulation</td><td rowspan="2">Yellow</td><td rowspan="2">50</td><td rowspan="2">10 mg/rat</td><td rowspan="2">0.2 mL</td><td>6</td><td>M</td><td>Rv793</td><td>Rv798</td></tr>
<tr><td>6</td><td>F</td><td>Rv799</td><td>Rv804</td></tr>
<tr><td rowspan="2">G3TK</td><td rowspan="2">RLD Formulation (Faslodex®)</td><td rowspan="2">Pink</td><td rowspan="2">50</td><td rowspan="2">10 mg/rat</td><td rowspan="2">0.2 mL</td><td>6</td><td>M</td><td>Rv805</td><td>Rv810</td></tr>
<tr><td>6</td><td>F</td><td>Rv811</td><td>Rv816</td></tr>
</table>
M: Male; F: Female; *: 0.1 mL was administered to each quadriceps.

(excerpted from Applicant's report)</td></tr>
<tr><td>Dose Volume:</td><td>Total of 0.2 mL (0.1 mL each to the left and rights quadriceps muscles)</td></tr>
<tr><td>Formulation/Vehicle:</td><td>Fulvestrant (Fu); 0.9% w/v sodium chloride. The test formulation was used as received (ready to use).

Faslodex® (Fa); Administered as provided following the manufacturer's directions.</td></tr>
<tr><td>Species/Strain:</td><td>Wistar rats</td></tr>
<tr><td>Age:</td><td>6 – 7 weeks</td></tr>
<tr><td>Satellite groups/ unique design:</td><td>6/sex/group (toxicokinetics). Blood samples were collected on days 1 and 29. On days 7, 11, 15, 21 and 25 blood samples were collected from 3 rats/sex/group.

<u>Reviewer comment:</u>
Plasma samples were shipped from (b) (4) to (b) (4) for bioanalysis. The Applicant did not provide stability data for the plasma sample under the conditions of shipping (temperature and duration).</td></tr>
<tr><td>End points evaluated:</td><td>Animal sacrificed: the day after the last treatment- day 30 (main study).

Macro and microscopic evaluations: all tissue/organs, including injection sites, from all main study animals.

Table 3: Details of experimental design, treatment regime, clinical pathology investigations, sacrifice schedule and</td></tr>
</table>

	pathology schedule **TABLE 1. Details of experimental design, treatment regime, clinical pathology investigations, sacrifice schedule and pathology schedule**

Group	Dose (mg/rat)	No. of rats per group		Treatment days	TK sampling on days	Clinical pathology investigations (Day 30)			Sacrifice on day	Gross pathology	Organ weights	Histopathology
		M	F			Haematology & Coagulation	Clinical Chemistry	Urinalysis				
G1	0	10	10	1, 15 and 29	-	+	+	+	30	+	+	+
G2	10	10	10	1, 15 and 29	-	+	+	+	30	+	+	+
G3	10	10	10	1, 15 and 29	-	+	+	+	30	+	+	+
G1TK	0	6	6	1, 15 and 29	1, 7, 11, 15, 21, 25 and 29	-	-	-	31	-	-	-
G2TK	10	6	6	1, 15 and 29	1, 7, 11, 15, 21, 25 and 29	-	-	-	31	-	-	-
G3TK	10	6	6	1, 15 and 29	1, 7, 11, 15, 21, 25 and 29	-	-	-	31	-	-	-

+: Yes; -: No; M: Males; F: Females

(excerpted from Applicant's report)

Deviation from study protocol:	None of the deviations affected the integrity or interpretability of the study.

Results:

There were no mortalities, clinical signs, body weight changes, ophthalmoscopy findings reported in both treatment groups.

Table 4: Food Consumption (% of Control)

Sex	Males			Females		
Statistical comparison	**G2 vs G1**	**G3 vs G1**	**G2 vs G3**	**G2 vs G1**	**G3 vs G1**	**G2 vs G3**
Group	**G2**	**G3**	**G2**	**G2**	**G3**	**G2**
Dose (mg/rat)	**10**	**10**	**10**	**10**	**10**	**10**
No. of rats	**10**	**10**	**10**	**10**	**10**	**10**
Day 1-8	↓8%*	↓7%*	—	—	↓4%*	↑6%*
Day 8-15	—	—	—	—	—	—
Day 15-22	—	—	—	—	↓6%*	↑5%*
Day 22-29	—	↓10%*	—	—	↓12%*	↑8%*

G1: Control G2: Teva's formulation G3: RLD formulation
↓: Decrease
↑: Increase
—: Values were not considered statistically different
*: Statistically significant ($p<0.05$)

(excerpted from Applicant's report)

Hematology

Table 5: Hematology (% of Control)

Sex	Males			Females		
Group	**G2 vs G1**	**G3 vs G1**	**G2 vs G3**	**G2 vs G1**	**G3 vs G1**	**G2 vs G3**
Dose (mg/rat)	**10**	**10**	**10**	**10**	**10**	**10**
No. of rats	**10**	**10**	**10**	**10**	**10**	**10**
White Blood Corpuscles	↑13%	↑22%	↓8%	↑5%	↑5%	—
Neutrophils Absolute	↑6%	↑50%	↓29%	↑43%	↑35%	—
Lymphocytes Absolute	↑15%	↑12%	—	—	—	—
Monocytes Absolute	—	↑111%	↓45%	↑77%	↑43%	—
Eosinophils Absolute	—	↑78%	↓44%	—	—	—
Fibrinogen	↑25%	↑24%	—	↑59%	↑56%	—

↑: Increase ↓: Decrease G2: Teva's formulation G3: RLD formulation
—: Values are not considered statistically different.

(excerpted from Applicant's report)

Clinical Chemistry

Table 6: Clinical Chemistry (% of Control)

Sex	Males			Females		
Group	G2 vs G1	G3 vs G1	G2 vs G3	G2 vs G1	G3 vs G1	G2 vs G3
Dose (mg/rat)	10	10	10	10	10	10
No. of rats	10	10	10	10	10	10
Aspartate Aminotransferase	↑115%	↑55%	↑39%	↑200%	↑178%	—
Alanine Aminotransferase	—	—	—	↑61%	↑62%	—

↑: Increase G1: Control G2: Teva's formulation G3: RLD formulation
—: Values are not considered statistically different
(excerpted from Applicant's report)

Additional findings that were considered treatment related by this reviewer.

Table 7: Additional Clinical Chemistry Findings (% of Control)

	Fulvestrant (Fu)	Faslodex® (Fa)	FU vs Fa
	male/female	male/female	male/female
T.Bil	--/--	37/--	--/--
Glob	5/--	13/--	--/7
A/G	--/--	12/16	11/17
Ca	7/11	12/13	--/--
ALP	--/39	--/--	18/--
Trig	--/30	--/37	--/--

--=no change

Urinalysis
Unremarkable

Gross Pathology

Table 8: Gross Pathology (incidence)

	Vehicle	Fulvestrant (Fu)	Faslodex® (Fa)
	male/female	male/female	male/female
Uterus-atrophy	--/--	--/9	--/6
Site of injection-focus, red	--/--	--/3	--/1

--=no change

Organ Weights

Table 9: Organ weight relative to body weight (% of Control)

	Fulvestrant (Fu)	Faslodex® (Fa)	FU vs Fa
	male/female	male/female	male/female
Thymus	23/--	14/--	--/--
Prostate	--/--	--/--	13/--

--=no change

Sex	Females		
Group	G2 vs G1	G3 vs G1	G2 vs G3
Dose (mg/rat)	10	10	10
No. of rats	10	10	10
Uterus/cervix – absolute weight	↓66%	↓55%	↓26%
– relative to Body weight	↓66%	↓54%	↓8%
– relative to Brain weight	↓65%	↓53%	↓25%

↓: Decrease G1: Control G2: Teva's formulation G3: RLD formulation

(excerpted from Applicant's report)

Histopathology

Adequate battery: Yes

Table 10: Histopathology (incidence and severity)

	Vehicle	Fulvestrant (Fu)	Faslodex® (Fa)
	male/female	male/female	male/female
Cervix atrophy - *marked*	0/0	0/10	0/10
Epididymis inflammation, chronic, unilateral focal, - *minimal*	0/0	1/0	0/0
Lung histiocytosis, alveolar, - *minimal*	0/0	2/0	0/0
inflammatory cell infiltrate, mixed cell - *minimal*	0/2	0/0	1/0
- *mild*	0/0	0/1	1/0
Mammary glands hypertrophy/hyperplasia - *minimal*	0/0	0/4	0/5
Ovaries cyst, follicular, unilateral/bilateral - *minimal*	0/0	0/6	0/3
- *mild*	0/0	0/4	0/6
Pancreas atrophy, lobular, focal - *minimal*	0/0	1/0	0/0
Inflammation, chronic, focal *mild*	0/0	0/1	0/0
Prostate inflammatory cell infiltrate, mononuclear cell - *minimal*	0/0	0/0	2/0
Nerve, Sciatic inflammatory cell infiltrate, mixed cell - *minimal*	0/0	0/2	0/0
- *mild*	0/0	0/0	0/1

Site of injection Inflammation, chronic			
- *minimal*	1/5	0/2	0/3
- *mild*	0/0	0/1	0/1
- *moderate*	0/0	0/3	2/0
- *marked*	0/0	0/0	0/1
inflammatory cell infiltrate, mixed/mononuclear cell			
- *minimal*	0/0	1/0	2/0
Uterus atrophy			
- *marked*	0/0	0/10	0/10
Vagina atrophy			
- *moderate*	0/0	0/2	0/1
- *marked*	0/0	0/8	0/9

-- = *no change*

Toxicokinetics

Fulvestrant

Table 11: Plasma Fulvestrant TK Parameters

Table 1: Composite Plasma Fulvestrant TK Parameters in Male and Female Rats Following IM Administration of 10 mg Fulvestrant as Teva Formulation on Days 1, 15, and 29 (G2TK)

Sex	Day	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-48} (ng•h/mL)	AUC_{0-t} (ng•h/mL)	t_{last} (h)	$t_{½}$[a] (h)	R_{obs}[b]
Female	1	74.6	7	2278	10605	336	350.8	NA
	29	101.5	3	4429	4429	48	NC	1.9
Male	1	38.6	7	1489	7785	336	306.7	NA
	29	68.4	3	2438	2438	48	NC	1.6

[a] Estimated value.
[b] R_{obs} = AUC_{0-48} on day 29 divided by AUC_{0-48} on day 1.
NA: Not applicable; NC: Not calculable.

Faslodex®

Table 12: Plasma Faslodex® TK Parameters

Table 2: Composite Plasma Fulvestrant TK Parameters in Male and Female Rats Following IM Administration of 10 mg Fulvestrant as RLD on Days 1, 15, and 29 (G3TK)

Sex	Day	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-48} (ng•h/mL)	AUC_{0-t} (ng•h/mL)	t_{last} (h)	$t_{½}$[a] (h)	R_{obs}[b]
Female	1	44.2	24	1774	9749	336	217.1	NA
	29	94.7	24	4065	4065	48	NC	2.3
Male	1	31.7	24	1314	7137	336	266.4	NA
	29	66.9	7	2886	2886	48	NC	2.2

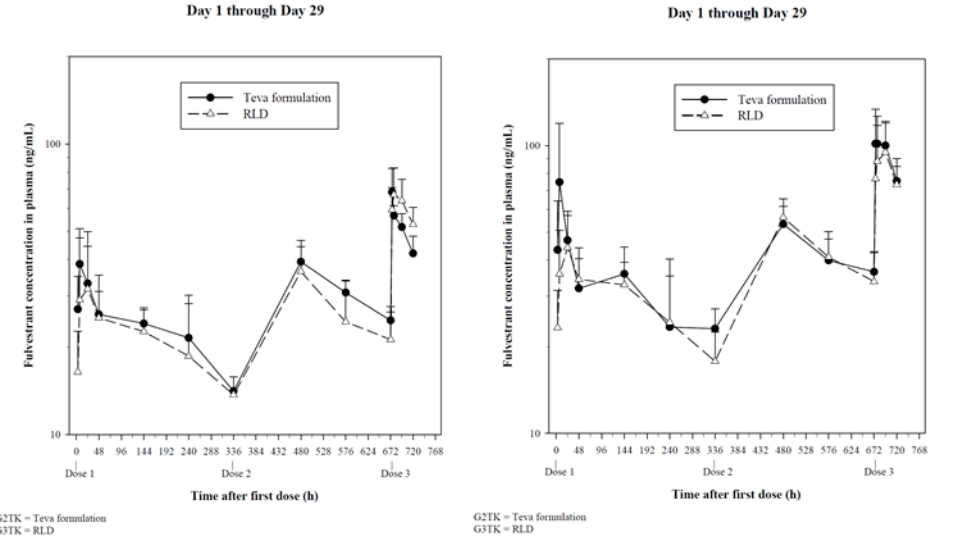
[a] Estimated value.
[b] R_{obs} = AUC_{0-48} on day 29 divided by AUC_{0-48} on day 1.
NA: Not applicable; NC: Not calculable.

(excerpted from Applicant's report)

Figure 1: Plasma Concentration versus Time Profile (Teva Formulation versus LD)

Figure 3: Comparison of the Composite Mean (+SD) Plasma Concentration-versus-time Profiles for Fulvestrant in Male Rats Following IM Administration of 10 mg Fulvestrant as the Teva Formulation or the RLD on Days 1, 15, and (G2TK versus G3TK) (Continued)

Figure 4: Comparison of the Composite Mean (+SD) Plasma Concentration-versus-time Profiles for Fulvestrant in Female Rats Following IM Administration of 10 mg Fulvestrant as the Teva Formulation or the RLD on Days 1, 15, and 29 (G2TK versus G3TK) (Continued)



(excerpted from Applicant's report)

- Comparable systemic exposure (C_{max} and AUC) was reported between Fulvestrant and the LD formulation Faslodex®.
- Systemic exposure was higher in females than males in both formulations after single and repeat dosing.
- T_{max} was reported at later timepoint for the LD (24 hours) compared to the Fulvestrant formulation (3 to 7 hours).
- $T_{1/2}$ for Fulvestrant was longer on Day 1 in females (38%) and males (13%) than the LD.

Formulation Analysis

Concentration and stability analysis of each formulation were not provided by the Applicant.

The following IR was sent to the Applicant:

In study No G17058, concentration and stability analysis of each formulation (Fulvestrant and Faslodex®) were not provided (21 CFR Part 58.113). Accordingly, provide the concentration and stability analysis of each formulation used in study G17058, or indicate where in the submitted NDA such information is located. Provide the requested information by June 12, 2019.

Applicant responded on 6/11/2019.

Teva's Response:

Details for the Test Item (Teva's proposed product, 50 mg/mL, lot 5AH501) and Reference Item (Reference Product Faslodex Injection, manufactured by AstraZeneca) including concentration are contained in Section 9.1 of the Tox Report G17058, submitted previously in the Complete Response Amendment dated February 19, 2019. Neither the Test Item nor the Reference Item was mixed with a carrier prior to use.

As stated in Section 9.1 of the study report previously submitted, Test and Reference Items were provided preformulated by the Sponsor as 5 mL syringes at 50 mg/mL. No formulation preparation was required as the test and reference formulations were used as received (ready-to-use).

The Test Item used in the study (lot 5AH501) is the same lot of drug product used for the stability batch and details presented in Module 3. We refer the reviewer to the Executed Batch Record (submitted previously in Module 3.2.R, which contains the formulation) and Release and Stability Data (up to 36 months) submitted in Modules 3.2.P.5.4 and 3.2.P.8.3, respectively.

The Appendix 10 of the previously submitted report for Study G17058 includes the following documents:

- CoA of Teva's Fulvestrant Injection 250 mg/5 mL (50 mg/mL), batch 5AH501, (Section ii of Appendix 10) that was issued on May 2018, before the study initiation.
- CoA of Teva's Fulvestrant injection 250 mg/5mL (50 mg/mL), batch 5AH501, after reanalysis (Section vii of Appendix 10) that was issued after the study completion, on September 2018, in order to confirm that no changes occurred in the DP during the study.
- CoA of the Listed Drug (Reference Product) Faslodex, batch NV472, issued on May 2018, before the study initiation, within its shelf life, expiry date being 01/2021 (Section i of Appendix 10).

QA Statements for these analyses are also included (Appendix 10 Section iii and Section viii, respectively). Further stability testing of the Reference Item was not determined during the course of study G17058.

(excerpted from Applicant's report)

Reviewer comment, given that the dose concentration verification and stability of the formulations were performed in compliance with the GMP regulations and the test articles were not formulated at the testing site and were used as received, the Applicant response is acceptable. Thus, there are no additional nonclinical issues.

Conclusion

Comparable systemic exposure and toxicity profiles were reported between Fulvestrant and the LD formulation Faslodex®. Thus, the excipient MCT contained in Teva's Fulvestrant formulation at the clinical level was qualified, and this study supports reliance on this listed drug (Faslodex®).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EIAS A ZAHALKA
07/31/2019 12:40:13 PM

TIFFANY RICKS
07/31/2019 12:45:16 PM

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

Application number:	**210063**
Supporting document/s:	**1, 8**
Applicant's letter date:	**12/28/2016**
CDER stamp date:	**12/28/2016**
Product:	**Fulvestrant Injection**
Indication:	**Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy**
Submission Type:	**505(b)(2)**
Listed Drug (Form 356h):	**Faslodex (fulvestrant) injection**
Applicant:	**Teva Pharmaceuticals USA Inc. Parsippany, New Jersey**
Review Division:	**Division of Hematology Oncology Toxicology (Division of Oncology Products 1)**
Reviewer:	**Eias Zahalka, PhD, MBA**
Supervisor:	**Todd Palmby, PhD**
Division Director:	**John Leighton, PhD, DABT Julia Beaver, MD (DOP1-Acting)**
Project Manager:	**Sakar Wahby**

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 210063 are owned by Teva Pharmaceuticals USA Inc. or are data for which Teva Pharmaceuticals USA Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 210063 that Teva Pharmaceuticals USA Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 210063.

1. Introduction

Fulvestrant Injection is an estrogen receptor antagonist. This 505(b)(2) submission is for a new formulation of fulvestrant compared to the listed drug, Faslodex Injection. Teva Pharmaceuticals has developed a new formulation intended for the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The Applicant is relying onthe listed drug (LD) product Faslodex (fulvestrant) injection, for intramuscular use, 250 mg /5mL (50 mg/mL) of AstraZeneca Pharmaceuticals (NDA # 021344), which has been marketed in the US since 2002. The proposed Fulvestrant Injection strength, dosage form, and route of administration are similar to Faslodex Injection the LD, but several of the inactive ingredients are different (medium chain triglycerides (b) (4) (b) (4) dehydrated alcohol (b) (4)). In support of this NDA application, the Applicant conducted an *in vivo* bioequivalence study in healthy, adult, human female subjects (Study # ACT-15160) to establish the equivalence of the proposed formulation to that of the LD. For nonclinical support, the Applicant relied on the Agency's finding of safety and effectiveness for an LD (Faslodex). In addition to reliance on the LD, the Applicant submitted two reports of nonclinical studies in two species, and relied upon literature to support the safety of an inactive ingredient, medium chain triglycerides (MCT), which was used in the formulation of the drug product (Fulvestrant Injection).

1.2 Brief Discussion of Nonclinical Findings

The CMC review team requested input from the pharmacology/toxicology discipline in regard to the acceptance criterion level of the impurity (b) (4) ((b) (4) ppm), and to qualify the inactive ingredient (medium chain triglycerides [MCT]) used in the formulation of the drug product. Additionally, the team was asked to qualify the potential leachable (b) (4) levels in the drug product.

Impurity, (b) (4) The proposed level of (b) (4) ppm ((b) (4) %) for the impurity (b) (4) in the drug product is lower than the ICHQ3B(R2) qualification threshold. As such, this impurity is acceptable at the proposed specification level and presents no concern.

Excipient, MCT: The Applicant submitted two nonclinical studies in two species to support the safety of the proposed level of MCT in the drug product administered by the intramuscular route. The studies were not adequate to qualify the excipient. The study reports did not list MCT as a component of the formulation/vehicle administered to the animals in both studies. The Applicant stated in the cover letter submitted with these reports that the formulations administered in these rat and rabbit studies did contain MCT, but no amounts were provided making qualification of the specific levels contained in the clinical formulation impossible. The Applicant also provided no explanation for why the study reports did not list MCT as a component of the vehicle used in those studies or why the Certificates of Analysis did not report MCT levels. As such, the potential safety concern in regard to MCT local tissue effects was not addressed.

Leachable (b) (4) A leachables study was conducted by the Applicant using pre-filled syringes of the drug product fulvestrant injection 250 mg/5 ml. The syringes were stored at 2-8°C for 12 months from the manufacturing date. The syringe plunger used contained (b) (4) so the Applicant tested if any of the (b) (4) will potentially leach to the drug product. (b) (4) was not detected in the drug product after 12 months of testing. A limit of quantitation (LoQ) for (b) (4) in the drug product was set at (b) (4) µg/5 ml syringe for the leachables test, which was acceptable by the pharmacology/toxicology team. (b) (4) may have been present in the drug product at a maximum amount of (b) (4) µg/5 ml syringe which contains 250 mg of fulvestrant based on this LoQ. This level is below the qualification threshold of 0.2% for drug product impurities, as established by ICH Q3B.
As such, the (b) (4) that might leach into the drug product presents a minimal safety concern for the patients, based on the information provided by the Applicant. The proposed indication for this 505(b)(2) application for the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy falls within the scope of the International Council on Harmonization (ICH) S9 Guidance for Nonclinical Evaluation for Anticancer Pharmaceuticals. If additional indications are pursued for this product in the future, the applicability of ICH S9 should be re-evaluated at that time to determine if the potential level of (b) (4) is still acceptable.

1.3 Recommendations

1.3.1 Approvability:

The Pharmacology/Toxicology discipline does not recommend approval

1.3.2 Additional Non clinical Recommendations

The following nonclinical deficiency will be included in the Complete Response Letter for this application:

The safety of the proposed level of the medium chain triglycerides (MCT) excipient in the drug product to be administered by intramuscular injection was not adequately justified. The potential impact of this excipient on local tissue toxicities as it compares to the listed drug was not adequately addressed. You may not rely on information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries to justify a safe level of an excipient. MCT were not listed as a component of the vehicle or in the Certificate of Analysis in the reports for the rat and rabbit toxicology studies conducted with fulvestrant intramuscular injection and submitted to your NDA. The levels and fatty acid composition of the MCT administered to rats and rabbits in your fulvestrant injection studies were not provided. Therefore, these studies were inadequate to assess the safety of intramuscular injection of the proposed levels of MCT present in your to be marketed Fulvestrant Injection drug product. Provide an adequate justification for the safety of the proposed levels of MCT in your drug product administered by

intramuscular injection. We recommend that you submit a final report from a GLP nonclinical bridging toxicology study in a single species comparing your Fulvestrant Injection formulation to the listed drug product (Faslodex) at a clinically relevant dose. This study should include assessment of local tissue effects (macro and microscopic) and toxicokinetics following repeated intramuscular injections.

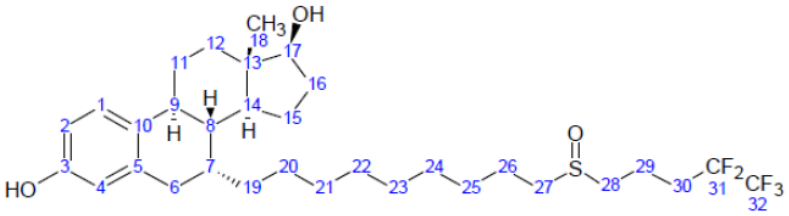
2. Drug Information

2.1 Drug

Name: Fulvestrant

Molecular Formula/Molecular Weight: $C_{32}H_{47}F_5O_3S$/606.77

Structure or Biochemical Description:



(excerpted from Applicant's report)

Pharmacologic Class: Estrogen receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

None

2.3 Drug Formulation

Fulvestrant Injection, 250 mg/5 mL (50 mg/mL), is a clear colorless to yellow viscous liquid, supplied in sterile single-use prefilled syringe (PFS) for intramuscular injection, each containing 250 mg of Fulvenstrant. Fulvestrant Injection, 500 mg (250 mg/injection) will be administered intramuscularly into the buttocks (gluteal area) slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29; and once monthly thereafter.

Table 1: Qualitative and Quantitative Unit Composition including Function

Components of the drug product	mg/mL	mg/Pre-filled-Syringe	Function	Quality reference
Active Ingredient				
Fulvestrant, USP	50.0	250.0	Active substance	USP/NF current Edition / Manufacturer specification
Inactive Ingredients				
Dehydrated Alcohol, USP	100.0	500.0	(b) (4)	USP/NF current edition
Benzyl Alcohol, NF	100.0	500.0		USP/NF current edition
Castor Oil, USP	600.0	3000.0		USP/NF current edition
Medium Chain Triglycerides, NF	Q.S. to 1.0 mL	Q.S. to 5.0 [(1)] mL		USP/NF current edition
Nitrogen, NF [(2)]	Q.S.	Q.S.		USP/NF current edition

Q.S. – Quantity Sufficient.
Notes: (b) (4)
[1] Overfill (b) (4)% is applied.
(b) (4)
(b) (4)

(excerpted from Applicant's report)

2.4 Comments on Novel Excipients

There were no novel excipients used in the formulation of the drug product. However, there are no approved products for IM injection containing Medium Chain Triglyceride (MCT). The CMC review team requested input from the Pharmacology/Toxicology discipline in regard to the acceptance criterion level of the excipient in the drug product.

Medium chain triglyceride (MCT) is an inactive ingredient that was used in the Fulvestrant injection formulation for the intramuscular route of administration. MCT was not used as an excipient in the listed drug (LD) product formulation (Faslodex). The justification for the proposed level and specification for MCT for the intramuscular route of administration provided by the Applicant in the original submission (12/28/2016) was not sufficient. The Applicant referenced summary level data from animal studies (e.g. Kracht, 1961, 1962, 1963) to support the characterization of the potential local effects of intramuscular injection of MCT in patients at the proposed level. The cited papers by Kracht were not available in published form. As such, they can't be used to qualify MCT at the proposed level and route.

An Information Request (IR) was sent by the FDA to the Applicant on June 22, 2017 stating:

"Your justification for the proposed level and specification for medium chain triglycerides (MCT) is not adequate. Summary level data from animal studies referred to in your NDA submission (e.g. Kracht, 1961, 1962, 1963; study data are unpublished) are not

sufficient to characterize potential local effects of intramuscular injection of MCT in patients at the proposed level. Submit an adequate data based justification to support the safety of the proposed level of MCT in your drug product administered by the intramuscular route. This may include literature reports of relevant studies that contain sufficient data providing a safety assessment for the proposed level of MCT in your drug product. If sufficient data are not available in published literature, this justification may include a full report from an appropriate repeat-dose study in animals assessing local tissue effects of your drug product or MCT following intramuscular injection."

On June 30, 2017, in response to the FDA IR, the Applicant submitted reports for two nonclinical studies (rat and rabbit) to support of the safety of MCT in the proposed drug product, intended for intramuscular administration. The data from these nonclinical studies are owned by the Applicant.

- Fulvestrant injection: 28-day intramuscular toxicity study in female Sprague-Dawley rats (Study # G9860).
- Fulvestrant injection: Repeated dose (2 cycles) intramuscular toxicity study in female New Zealand White rabbits (Study # G9861).

Upon review of the nonclinical studies (see below, section 6), they were not sufficient to support the safety of the proposed level of MCT in the proposed drug product administered by the intramuscular route. The presence or level of MCT in the formulation administered to the animals in both studies was not reported in the study reports. The Applicant stated in the cover letter submitted with these reports that the formulations administered in these rat and rabbit studies did contain MCT, but no amounts were provided making qualification of the specific levels contained in the clinical formulation impossible. There was no discussion of the fatty acid composition of the MCT claimed to be administered to rats and rabbits and if it was similar to the MCT present in the Fulvestrant Injection drug product. The Applicant also provided no explanation for why the study reports did not list MCT as a component of the vehicle used in those studies or why the Certificates of Analysis did not report MCT levels. The only listed excipients in the Certificate of Analysis (C of A) were ethanol and benzyl alcohol. As such, the potential safety concern in regard to MCT local tissue effects was not addressed.

In addition, in the cover letter from June 30, 2017, the Applicant provided a summary of the nonclinical findings from the LD product (Faslodex) NDA nonclinical summary review published by the FDA. The nonclinical Faslodex studies were used to compare the histopathology findings in the LD drug product at the injection site to the rat and rabbit findings from the fulvestrant injection studies. Reliance on published nonclinical NDA discipline reviews to provide data necessary for approval is not acceptable for a 505(b)(2), unless the Applicant obtains the right of reference.

Additionally, the Applicant referenced products that were approved in the European Union and Canada (Depixol injection [flupentixol decanoate] and Clopixol injection [Zuclopenthixol decanoate]). Non-US labeling or non-US regulatory authority

assessments may not be relied upon to support a 505(b)(2), as they are neither FDA's findings of safety and efficacy for a listed drug, nor are they published literature.

In conclusion, the nonclinical studies, and the other information submitted to the NDA, were insufficient to support the safety of the MCT excipient used in the formulation of Fulvestrant Injection intended for the intramuscular route of administration.

2.5 Comments on Impurities/Degradants of Concern

The CMC review team requested input from the pharmacology/toxicology discipline in regard to the acceptance criterion level of the impurity, (b) (4), in the drug product ((b) (4) ppm).

- Maximum Daily Dose (MDD) of Fulvestrant Injection is 500 mg/day as two 5 mL injections (250 mg/injection) to each buttocks.
- Per ICH Q3B(R2), limits for a Drug Product impurity/degradant with a MDD ranging between (b) (4) mg to (b) (4) g is (b) (4)%, or (b) (4) mg TDI, whichever is lower.
- (b) (4)% of 500 mg (MDD) = (b) (4)mg

The Applicant proposed impurity level of (b) (4) ppm (b) (4)) of 500 mg (MDD) = (b) (4)mg, which is lower than ICHQ3B(R2) qualification threshold of (b) (4)% ((b) (4) mg) or (b) (4) mg TDI (whichever is lower). As such the proposed level of this impurity is acceptable and presents no concern.

Extractables and Leachables

Fulvestrant Injection, supplied in a single-use prefilled syringe for intramuscular injection, each containing 250 mg of fulvestrant. The syringe plunger used contained (b) (4) so the Applicant tested if any of (b) (4) would potentially leach to the drug product. An limit of quantitation (LoQ) for (b) (4) in the drug product was set at (b) (4) µg/5 ml syringe by the Applicant. The CMC review team requested input from the pharmacology/toxicology discipline in regard to the acceptance of the limit of quantitation used for the leachable, (b) (4) in the drug product.

A leachables study was performed by the Applicant using 100 pre-filled syringes of the product fulvestrant injection 250 mg/5 ml. The syringes were stored at 2-8°C for 12 months from the manufacturing date.

(b) (4) was not detected in the drug product after 12 months of testing.

(b) (4) present in the drug product at levels (b) (4) the LoQ of (b) (4) µg of (b) (4)/syringe/(b) (4) µg fulvestrant would result in a leachable level of approximately (b) (4). For the maximum daily dose of 500 mg as two 5 ml injections, (b) (4)/day/(b) (4) µg fulvestrant would result in an leachable level of approximately (b) (4), which is below the qualification threshold of 0.2% (ICH Q3B).

Conclusion: An LoQ of (b) (4) µg/5 ml syringe for (b) (4) used by the Applicant in the conducted of leachables test is acceptable. (b) (4) at a maximum amount of (b) (4) µg/5 ml syringe that might leach into the drug product and would not have been detected in the leachables test presents minimal safety concern for the patients, based on the information provided by the Applicant. This level is acceptable for the proposed indication for this 505(b)(2) application.

3. Studies Submitted

3.1 Studies Reviewed

(original studies not previously reviewed)

Study #	Study Title	Reviewed	
		Yes	No
G9860	Fulvestrant injection: 28-day intramuscular toxicity study in female Sprague-Dawley rats	X	
G9861	Fulvestrant injection: repeated dose (2 cycles) intramuscular toxicity study in female New Zealand White rabbits	X	

4. Pharmacology

No new studies were submitted

5. Pharmacokinetics/ADME/Toxicokinetics

No new studies were submitted

6. General Toxicology

Below is a review of the nonclinical studies (rat and rabbit) submitted by the Applicant on June 30, 2017, in response to the FDA IR, to support the safety of the proposed level of MCT in the proposed drug product to be administered by an intramuscular route.

Study Title: Fulvestrant injection: 28-day intramuscular toxicity study in female Sprague-Dawley rats	
Study no.:	G9860
Objectives:	To assess the systemic toxic potential of 'Fulvestrant injection' when administered as Intramuscular injections twice (on Days 1 and 14).
Testing Facility:	(b) (4)
Study initiation day:	23 July, 2014
GLP compliance/QA statement:	Yes (OECD)
Drug and lot #:	Fulvestrant injection; Lots # FVS-07-004 and FVS-07-006. Certificate of Analysis: (b) (4) ANALYTICAL SAMPLE TEST REPORT Name of product :- Fulvestrant injection Sample ID :- Fulvestrant injection-Initial B.No :- FVS-07-004 Strength :- 50mg/mL Exp date :- Not applicable Analysis start date :- 01/07/14

S. No	TEST	RELEASE SPECIFICATION	RESULT
1.	Assay of Fulvestrant	(b) (4)	103.7%
2.	Assay of Ethanol		99.6%
3.	Assay of Benzyl alcohol		104.2%
4.	Related substance by HPLC 1. Sulfone impurity 2. Any other unknown impurity 3. Total impurities		0.122% 0.045% 0.49%

(b) (4)

ANALYTICAL SAMPLE TEST REPORT

Name of product :- Fulvestrant injection
Sample ID :- Fulvestrant injection-Initial
B.No :- FVS-07-006
Strength :- 50mg/mL
Exp date :- Not applicable
Analysis start date :- 01/07/14

S. No	TEST	RELEASE SPECIFICATION	RESULT
1.	Assay of Fulvestrant	(b) (4)	100.1%
2.	Assay of Ethanol		102.2%
3.	Assay of Benzyl alcohol		101.8%
4.	Related substance by HPLC 1. Sulfone impurity 2. Any other unknown impurity 3. Total impurities		0.117% 0.037% 0.52%

(excerpted from Applicant's report)

Vehicle: Placebo for Fulvestrant injection (Batch # FVS-07-026)

APPENDIX 7. Certificate of Analysis

(b) (4)

ANALYTICAL SAMPLE TEST REPORT

Name of product :- Fulvestrant injection
Sample ID :- Fulvestrant injection-Placebo
B.No :- FVS-07-026
Strength :- Not applicable
Exp date :- Not applicable
Analysis start date :- 22/07/14

S. No	TEST	RELEASE SPECIFICATION	RESULT
1.	Density	Report the results	0.93956g/cm^3
2.	Viscosity	Report the results	39.6mpa.S
3.	Assay of Ethanol	(b) (4)	97.9%
4.	Assay of Benzyl alcohol		105.2%

(excerpted from Applicant's report)

Key Study Findings:

- The Certificate of Analysis (C of A) for the formulation/vehicle did not list MCT as one of the excipient. The C of A listed ethanol and benzyl alcohol as the only

excipients. As such, this study report was not sufficient to characterize the MCT local tissue effects of intramuscular injection.

- NOAEL was 15 mg/kg for both lots, based on the hisopathology data.
- There were fulvestrant injection-related hematological findings reported (RBC, hemoglobin, hematocrit, MCH, reticulocytes, white blood cells and lymphocytes).
- fulvestrant injection-related microscopic findings were reported in the ovaries, uterus and vagina.
- Similar macroscopic effects were reported in the vehicle group and treatment groups in the lung and the injection site, indicating, that the effect may be mediated by the vehicle.

Methods:

Doses/ Number/Sex/Group:	
Route:	Intramuscular injection
Frequency:	On days 1 and 14
Sex/Species/Strain:	Female Sprague-Dawley rats
Age:	6-7 weeks
Endpoints evaluated:	Mortalities, clinical signs, injection site, body weight, food consumption, ophthalmology, hematology, coagulation, chemistry, urinalysis, organ weights, macroscopic and microscopic evaluations.

Group No.	Group	Colour of cage card	Dose (mg/kg)	Conentration of the test item (mg/mL)	Dose Volume (mL/kg)	No. of Rats	Sex	Rat Numbers	
								From	To
G1	Vehicle Control	White	0	0	0.3	6	F	Rp8061	Rp8066
G2	Low Dose	Yellow	5	50	0.1	6	F	Rp8067	Rp8072
G3	Mid Dose	Green	10	50	0.2	6	F	Rp8073	Rp8078
G4	High Dose	Pink	15	50	0.3	6	F	Rp8079	Rp8084
G5	Low Dose	Yellow with stripes	5	50	0.1	6	F	Rp8221	Rp8226
G6	Mid Dose	Green with stripes	10	50	0.2	6	F	Rp8227	Rp8232
G7	High Dose	Pink with stripes	15	50	0.3	6	F	Rp8233	Rp8238

F: Female

(excerpted from Applicant's report)

Results:

Mortalities

There were no mortalities reported.

Clinical Observations and local Reaction at the Site of Injection

Unremarkable.

Body Weight and food consumption

Unremarkable.

Ophthalmology

Unremarkable.

Hematology and Coagulation

Hematology (% change from control)

Sex	Female					
Test item	FVS-07-004			FVS-07-006		
Group	G2	G3	G4	G5	G6	G7
Dosage (mg/kg)	5	10	15	5	10	15
No. of rats	6	6	6	6	6	6
RBC	—	—	—	↑(6)	↑(4)	↑(6)
Hemoglobin	—	↑(3)	—	—	—	↑(4)
Hct	—	↑(4)	↑(4)	↑(5)	—	↑(5)
MCH	—	—	—	↓(3)	—	—
Reticulocytes A	—	—	—	—	↓(27)	↓(28)
Reticulocytes %	—	—	—	↓(26)	↓(30)	↓(32)
WBC	—	—	—	—	—	↓(29)
Lymphocytes A	—	—	—	—	—	↓(29)

↑: Significant Increased ↓: Significant Decreased —: No Change
Values in parenthesis indicate percentage change, When compared to concurrent control

(excerpted from Applicant's report)

Clinical Chemistry and Urinalysis

Unremarkable.

Organ Weights

Organ Weights (% change from control)

Test item	FVS-07-004			FVS-07-006		
Group	G2	G3	G4	G5	G6	G7
Dosage (mg/kg)	5	10	15	5	10	15
No. of rats	6	6	6	6	6	6
Spleen						
–Absolute	—	—	—	↓(15)	—	↓(18)
–relative to Bwt	—	—	—	↓(13)	—	↓(16)
– relative to Brain wt.	—	—	—	—	—	↓(16)
Thymus						
–Absolute	—	—	—	—	—	↑(26)
–relative to Bwt	↑(27)	↑(34)	↑(36)	↑(27)	↑(27)	↑(30)
– relative to Brain wt.	—	—	—	—	—	↑(30)
Uterus with cervix						
–Absolute	↓(60)	↓(62)	↓(66)	↓(61)	↓(62)	↓(70)
–relative to Bwt	↓(59)	↓(60)	↓(64)	↓(59)	↓(61)	↓(69)
– relative to Brain wt.	↓(60)	↓(61)	↓(65)	↓(60)	↓(61)	↓(69)

↑: Significant Increased ↓: Significant Decreased —: No Change
Values in parenthesis indicate percentage change, When compared to concurrent control

(excerpted from Applicant's report)

Additional findings potentially drug-related (Relative to bodyweight)

Dose (mg/kg)	Females					
	% change from control					
	Lot # FVS-07-004			Lot # FVS-07-006		
	5	10	15	5	10	15
No. of animals	6	6	6	6	6	6
Ovaries	--	--	--	--	--	-21

-- = no remarkable change

Microscopic Findings

- In the lung and the injection site, similar effects were reported in the vehicle and treatment groups, indicating that the effect may be vehicle-mediated. The Applicant stated that the "*changes at the injection site were commonly located in the adipose tissue adjacent to the muscle fiber. The cystic space(s) were empty spaces of different sizes surrounded by thin fibrous connective tissue wall and it was surrounded by inflammatory changes. In addition, individual muscle fiber degeneration/ disintegration and connective tissue proliferation was also observed in the area of chronic inflammation*."

	No. of animals affected						
Lot #	**FVS-07-004**				**FVS-07-006**		
Dose (mg/kg)	**0**	**5**	**10**	**15**	**5**	**10**	**15**
No. examined	6	6	6	6	6	6	6
Treatment-related Findings:							
INJECTION SITE							
Chronic inflammation with cystic space(s)	4	2	3	0	3	5	2
– *minimal*	0	1	2	2	1	0	1
– *mild*	0	0	0	1	0	0	2
– *moderate*							
Chronic dermatitis, focal	1	0	0	0	0	0	0
– *mild*							
LUNG							
Inflammatory focus(i)	2	0	0	2	0	0	5
– *minimal*	2	0	0	2	0	0	0
– *mild*	1	0	0	1	0	0	0
– *moderate*	0	0	0	0	0	0	1
– *severe*							
OVARIES							
Retention of enlarged corpora lutea	0	2	1	3	1	2	0
Decreased corpus luteum	0	1	3	1	2	0	5
Follicular cyst(s)	0	2	1	0	1	0	2
UTERUS WITH CERVIX							
Dilatation							
– *minimal*	1	0	0	0	0	0	0
– *mild*	1	0	0	0	0	0	0
Atrophy	0	1	1	0	3	4	1
– *minimal*	0	2	3	6	2	2	5
– *mild*							
VAGINA							
Atrophy	0	2	2	1	2	4	2
– *minimal*	0	2	1	5	2	2	4
– *mild*							
Cyst	0	0	1	0	0	0	0
– *present*							

	No. of animals affected						
Lot #	**FVS-07-004**				**FVS-07-006**		
Dose (mg/kg)	**0**	**5**	**10**	**15**	**5**	**10**	**15**
No. examined	6	6	6	6	6	6	6
Treatment-related Findings:							

Study Title: Fulvestrant injection: repeated dose (2 cycles) intramuscular toxicity study in female New Zealand White rabbits	
Study no.:	G9861
Objectives:	To assess the systemic toxic potential of 'Fulvestrant injection' when administered as Intramuscular injections twice (on Days 1 and 15).
Testing Facility:	(b) (4)
Study initiation day:	12 August, 2014
GLP compliance/QA statement:	Yes (OECD)
Drug and lot #:	Fulvestrant injection; Lots # FVS-07-004 and FVS-07-006 <u>Certificate of Analysis:</u>

(b) (4)

ANALYTICAL SAMPLE TEST REPORT

Name of product :- Fulvestrant injection
Sample ID :- Fulvestrant injection-Initial
B.No :- FVS-07-004
Strength :- 50mg/mL
Exp date :- Not applicable
Analysis start date :- 01/07/14

S. No	TEST	RELEASE SPECIFICATION	RESULT
1.	Assay of Fulvestrant	(b) (4)	103.7%
2.	Assay of Ethanol		99.6%
3.	Assay of Benzyl alcohol		104.2%
4.	Related substance by HPLC 1. Sulfone impurity 2. Any other unknown impurity 3. Total impurities		0.122% 0.045% 0.49%

	No. of animals affected						
Lot #	**FVS-07-004**				**FVS-07-006**		
Dose (mg/kg)	**0**	**5**	**10**	**15**	**5**	**10**	**15**
No. examined	6	6	6	6	6	6	6
Treatment-related Fi							

(b) (4)

ANALYTICAL SAMPLE TEST REPORT

Name of product :- Fulvestrant injection
Sample ID :- Fulvestrant injection-Initial
B.No :- FVS-07-006
Strength :- 50mg/mL
Exp date :- Not applicable
Analysis start date :- 01/07/14

S. No	TEST	RELEASE SPECIFICATION	RESU
1.	Assay of Fulvestrant	(b) (4)	100.
2.	Assay of Ethanol		102.
3.	Assay of Benzyl alcohol		101.
4.	Related substance by HPLC 1. Sulfone impurity 2. Any other unknown impurity 3. Total impurities		0.11 0.03 0.5

(excerpted from Applicant's report)

APPEARS THIS WAY ON ORIGINAL

	No. of animals affected						
Lot #	**FVS-07-004**				**FVS-07-006**		
Dose (mg/kg)	**0**	**5**	**10**	**15**	**5**	**10**	**15**
No. examined	6	6	6	6	6	6	6
Treatment-related Findings:							

Vehicle: Placebo for Fulvestrant injection (Batch # FVS-07-026)

APPENDIX 7. Certificate of Analysis

(b) (4)

ANALYTICAL SAMPLE TEST REPORT

Name of product :- Fulvestrant injection
Sample ID :- Fulvestrant injection-Placebo
B.No :- FVS-07-026
Strength :- Not applicable
Exp date :- Not applicable
Analysis start date :- 22/07/14

S. No	TEST	RELEASE SPECIFICATION	RES
1.	Density	Report the results	0.9395
2.	Viscosity	Report the results	39.6r
3.	Assay of Ethanol	(b) (4)	97.
4.	Assay of Benzyl alcohol		105

(excerpted from Applicant's report)

APPEARS THIS WAY ON ORIGINAL

Key Study Findings:

- The Certificate of Analysis (C of A) for the formulation/vehicle did not list MCT as one of the excipients. The C of A listed ethanol and benzyl alcohol as the only excipients. As such, this study report was not sufficient to characterize the MCT local tissue effects of intramuscular injection.
- The NOAEL was 15 mg/kg for both lots, based on clinical pathology and macro-microscopic findings.
- There were fulvestrant injection-related hematological (reticulocytes, white blood cells, lymphocytes, neutrophil and PLT) and clinical chemistry (ALT, AST, glucose, blood urea nitrogen, total bilirubin and total cholesterol) findings reported.
- There were fulvestrant injection-related microscopic findings reported at the injection site, liver, kidneys, mammary glands, ovaries, oviducts, uterus and vagina.

Methods:

Doses/ Number/Sex/Group:

Group No.	Group	Dose (mg/kg)	Concent-ration of the test item (mg/mL)	Dose Volume (mL/kg)	No. of Rabbits	Sex	Rabbit Numbers	
							From	To
G1	Vehicle Control	0	0	0.3	3	F	RBa581	RBa583
G2	Low Dose	5	50	0.1	3	F	RBa584	RBa586
G3	Mid Dose	10	50	0.2	3	F	RBa587	RBa589
G4	High Dose	15	50	0.3	3	F	RBa590	RBa592
G5	Low Dose	5	50	0.1	3	F	RBa593	RBa595
G6	Mid Dose	10	50	0.2	3	F	RBa596	RBa598
G7	High Dose	15	50	0.3	3	F	RBa599	RBa601

F: Female
(excerpted from Applicant's report)

Route: Intramuscular injection; injected slowly into the quadriceps muscle of the right and left femur.

Frequency: On days 1 and 15

Sex/Species/Strain: Female New Zealand White Rabbits

Age: 5-6 months

Endpoints evaluated: Mortalities, clinical signs, injection site, body weight, food consumption, ophthalmology, hematology, coagulation, chemistry, organ weights, macroscopic and microscopic evaluations.

Results:

Mortalities
There were no mortalities reported.

Clinical Observations and local Reaction at the Site of Injection
Unremarkable.

Body Weight and food consumption
Unremarkable.

Ophthalmology
Unremarkable.

Hematology and Coagulation

Hematology (% change from control)

Sex	Females			Females		
Test item	FVS-07-004			FVS-07-006		
Group	G2	G3	G4	G5	G6	G7
Dosage (mg/kg)	5	10	15	5	10	15
No. of rabbits	3	3	3	3	3	3
Reticulocytes A	↓(22)#	↑(10)#	—	—	↓(38)	↓(41)
Reticulocytes %	↓(21)#	↑(19)#	—	—	↓(42)	↓(41)
WBC	—	↓(14)#	—	↓(22)	—	—
Neutrophil A	—	↓(25)#	—	—	↓(38)#	—
Lymphocytes A	—	—	—	↓(25)	—	—
PLT	↓(16)#	↓(23)#	↓(24)#	—	↓(27)	—

↑: Significant increase ↓: Significant decrease; —: No significant change
#: Apparent change not statistically significant
Values in parenthesis indicate change in percentage, when compared to vehicle control animals

(excerpted from Applicant's report)

Clinical Chemistry

Clinical Chemistry (% change from control)

Sex	Females			Females		
Test item	FVS-07-004			FVS-07-006		
Group	G2	G3	G4	G5	G6	G7
Dosage (mg/kg)	5	10	15	5	10	15
No. of rabbits	3	3	3	3	3	3
Glu	↓(11)	↓(18)	—	—	↓(12)#	—
BUN	↑(42)	—	↑(30)	—	↑(20)	—
AST	—	↓(53)#	↑(209)#	↑(46)#	↓(28)#	↑(59)#
ALT	—	—	↑(137)#	↑(60)#	—	↑(42)#
T. Bil	—	↓(50)	↓(47)	—	—	↓(28)#
T. Chol	—	↓(30)#	↓(37)#	↓(42)	↓(38)	↓(40)

↑: Significant increase ↓: Significant decrease; —: No significant change
#: Apparent change not statistically significant
Values in parenthesis indicate change in percentage, when compared to vehicle control animals

(excerpted from Applicant's report)

Macroscopic Findings

Unremarkable.

Organ Weights

Organ Weights (% change from control)

Sex	Females			Females		
Test item	FVS-07-004			FVS-07-006		
Group	G2	G3	G4	G5	G6	G7
Dosage (mg/kg)	5	10	15	5	10	15
No. of rabbits	3	3	3	3	3	3
Adrenals						
–Absolute	↑(66)#	↑(31)#	↑(22)#	↑(27)#	↑(34)#	↑(44)#
–Relative to Bwt	↑(58)#	↑(28)#	↑(21)#	↑(27)#	↑(39)#	↑(40)#
–Relative to brain wt	↑(43)#	↑(30)#	↑(21)#	↑(29)#	↑(38)#	↑(42)#
Brain						
–Absolute	↑(14)	—	—	—	—	—
Heart						
–Absolute	↑(14)#	—	↑(21)#	—	—	—
–Relative to Bwt	—	—	↑(18)#	—	—	—
–Relative to brain wt	—	—	↑(21)#	—	—	—
Ovaries						
–Absolute	—	↓(22)#	↑(23)#	—	—	↑(31)#
–Relative to Bwt	↓(11)#	↓(25)#	↑ (23)#	—	—	↑(27)#
–Relative to brain wt	↓(16)#	↓(20)#	↓(25)#			↑(31)#
Spleen						
–Absolute	↓(18)#	↑(36)#	↓(16)#	↓(28)#	↓(25)#	↑(24)#
–Relative to Bwt	↓(19)#	↑(33)#	↓(17)#	↓(27)#	↓(22)#	↑(18)#
–Relative to brain wt	↓(28)#	↑(34)#	↓(17)#	↓(26)#	↓(24)#	↑(23)#
Thyroid with parathyroid						
–Absolute	↑(56)#	↑(35)#	↑(43)#	↑(35)#	↑(18)#	—
–Relative to Bwt	↑(52)#	↑(32)#	↑(41)#	↑(34)#	↑(23)#	—
–Relative to brain wt	↑(38)#	↑(35)#	↑(43)#	↑(37)#	↑(21)#	
Uterus with cervix						
–Absolute	↓(59)	↓(52)	↓(36)	↓(37)#	↓(41)	↓(59)
–Relative to Bwt	↓(61)	↓(53)	↓(37)	↓(38)#	↓(40)	↓(60)
–Relative to brain wt	↓(64)	↓(51)	↓(35)	↓(35)#	↓(39)#	↓(59)

↑: Significant increase ↓: Significant decrease; —: No significant change
#: Apparent change not statistically significant
Values in parenthesis indicate change in percentage, when compared to vehicle control animals

(excerpted from Applicant's report)

Microscopic Findings

	No. of animals affected						
Lot #	**Lot FVS-07-004**				**Lot FVS-07-006**		
Dose (mg/kg)	**0**	**5**	**10**	**15**	**5**	**10**	**15**
No. examined	3	3	3	3	3	3	3
Treatment-related Findings:							
INJECTION SITE							
Chronic inflammation – *Minimal*	1	1	2	2	0	0	1
Leukocytic infiltration, dermal – *minimal*	0	0	0	2	0	0	0
Chronic inflammation with c stic space (s) – *mild*	0	0	0	0	0	1	0
KIDNEYS							

	No. of animals affected						
Lot #	**Lot FVS-07-004**				**Lot FVS-07-006**		
Dose (mg/kg)	**0**	**5**	**10**	**15**	**5**	**10**	**15**
No. examined	3	3	3	3	3	3	3
Treatment-related Findings:							
Basophilic tubules	0	0	0	0	0	0	2
– *minimal*	0	0	0	0	0	0	1
– *mild*							
Inflammatory focus	0	0	0	0	0	0	1
– *minimal*	0	0	0	0	0	0	1
– *mild*							
Mononuclear cell infiltration							
– *minimal*	1	0	0	0	0	0	3
Dilated tubules, multi focal	0	0	0	1	0	0	2
LIVER							
Necrosis, focal							
– *minimal*	0	0	0	0	0	0	1
Bile duct inflammation	0	0	0	2	0	0	0
– *minimal*	0	0	0	0	0	0	2
– *mild*							
Mononuclear cell infiltration							
– *minimal*	0	0	0	1	0	0	2
– *mild*	0	0	0	0	0	0	1
MAMMARY GLANDS							
Atrophy							
– *mild*	0	0	0	3	0	0	2
OVARIES							
Mineralization							
– *minimal*	1	1	0	2	1	1	1
Luteal cyct(s)	0	0	0	1	0	0	1
Follicular cyst(s)	0	0	0	2	1	0	2
Corpus luteum present	0	0	0	1	0	0	1
Interstitial cell atrophy	0	0	0	0	0	0	1
Hemocyst(s)	0	2	2	3	2	1	3
OVIDUCTS							
Atrophy	0	1	2	2	0	3	1
– *mild*							
UTERUS WITH CERVIX							
Atrophy	0	2	3	2	2	2	3
– *mild*	0	1	0	0	0	0	0
– *moderate*							
VAGINA							
Atrophy	0	3	2	0	1	3	3
– *mild*							

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/s/

EIAS A ZAHALKA
10/02/2017

TODD R PALMBY
10/02/2017