CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-344

Chemistry Review(s)

NDA 21-344
REVIEW # 1

FASLODEX (fulvestrant)
INJECTION
JOSEPHINE M. JEE
REVIEW CHEMIST
DIVISION OF ONCOLOGY
DRUG PRODUCTS
HFD-150/810
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Table of Contents

Chemistry NDA Review Data Sheet

1. NDA 21-344

2. REVIEW #: 1

3. REVIEW DATE: 16-JAN-2002

4. REVIEWER: JOSEPHINE M. JEE

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND [redacted]	06-DEC-1996

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (Vol. 1.1 – 1.10)	28-MAR-2001
Amendment [BC]	19-JUL-2001
Amendment] [SU]	20-JUL-2001
Amendment [BM]	09-AUG-2001
Amendment [BM]	28-AUG-2001
Amendment] [BS]	13-SEP-2001
Amendment [C]	18-OCT-2001
Amendment [BP	29-OCT-2001
Amendment [BC]	09-NOV-2001
Amendment [BL]	06-DEC-2001
Amendment [BP]	11-DEC-2001
Amendment]BP]	14-DEC-2001
Lab. Insert Rev.	06-MAR-2002

7. NAME & ADDRESS OF APPLICANT:

Name:
IPR Pharmaceuticals, Inc.

1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: FASLODEX™

b) Non-Proprietary Name (USAN): 7α-[9-[(4,4,5,5,5Pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol

c) Code Name/# (ONDC only): (ICI 182,780, ZD9238, fulvestrant)

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

FASLODEX (IM) Injection, 250 mg/5 mL, IPR Pharmaceuticals, Inc.

10. PHARMACOL. CATEGORY:

Antiestrogen (Treatment of Breast Cancer)

11. DOSAGE FORM:

Intramuscular Injection

12. STRENGTH/POTENCY:

250 mg/mL

13. ROUTE OF ADMINISTRATION:

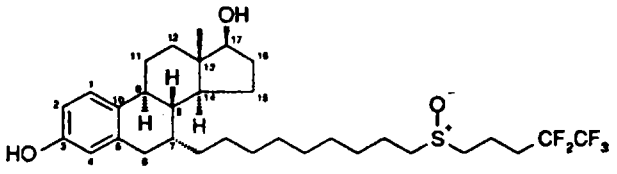
Intramuscular

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note21]:

N/A

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{32}H_{47}F_5O_3S$ **MW: 606.77**

7α-[9-[(4,4,5,5,5-Pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	1	Information Request Letter was sent to holder on 3/6/02	17-Jan-02	Need to provide tests and specs. For primary packaging materials
[redacted]	III	[redacted]	[redacted]	3	Adequate	28-Dec-2000	
[redacted]	III	[redacted]	[redacted]	3	Adequate	15-Jan-02	
[redacted]		[redacted]	[redacted]	3	Adequate	28-Mar-2000	
[redacted]	III	[redacted]	[redacted]	3	Adequate	28-Aug-2000	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	15-JAN-2002	Peiling Yang, Ph.D.
EES	Acceptable	10-JAN-2002	Melissa Garcia
Pharm/Tox	Acceptable	15-JAN-2002	Lilliam A. Rosario, Ph.D.
Biopharm	Acceptable	15-JAN-2002	Gene Williams, Ph.D.
LNC	not acceptable by OPDRA	15-JAN-2002	Nora Roselle, Pharm.D.
Methods Validation	pending		
OPDRA	**Does not recommend FASLODEX as TM	15-JAN-2002	Nora Roselle, PharmD
EA	Acceptable	18-JAN-2002	Josephine M. Jee
Microbiology	Acceptable	29-JAN-2002	David Hussong, Ph.D.

** **HFD-150** has decided not to follow OPDRA's recommendation.

The Chemistry Review for NDA 21-344

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

It is recommended that this application be approved. The PAI is acceptable by the Office of Compliance on Jan. 10, 2002. This application provided adequate CMC information. There are some minor administrative issues, such as providing the regulatory specifications of the fulvestrant drug substance and fulvestrant drug product for the stability studies; the reprocessing for both drug substance and drug product (commitment to notify the Agency), certificate of analyses from the suppliers of the container closures used in the drug product; and revision of the carton label, container label, and package insert. The regulatory specifications for both drug substance and drug product are on their stability data reports, but not as a cited document. Overall, these issues are minor, do not affect the safety or efficacy of FASLODEX and will be provided as postapproval agreements.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Approval is recommended from a CMC point of view. However, there is some information listed in Section A that needs to be provided as postapproval agreements.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

FASLODEX™ is a sterile, clear, colorless to yellow, viscous, oily solution for deep intramuscular (IM) injection in a 5 mL pre-filled syringe or two 2.5 mL pre-filled syringes (PFS) to deliver, as long acting (LA) injection. FASLODEX contains 50 mg per mL fulvestrant and is administered once a month. Fulvestrant drug substance is a white powder with a molecular weight of 606.77. Fulvestrant contains 6 asymmetric carbon atoms and stereogenic sulfoxide in the side chain.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used intramuscularly. The maximum recommended monthly dose is 250 mg and it is administered by a health practitioner. Based on supportive data of [redacted]-month long-term stability data, the requested [redacted] month expiration dating is acceptable.

C. Basis for Approvability or Not-Approval Recommendation

FASLODEX has an acceptable GMP inspection. From a CMC perspective, AstraZeneca provided information to support the adequacy of fulvestrant drug substance and drug product. The physical and chemical characteristics, impurity profile, and the stability for fulvestrant drug substance are adequately demonstrated in this application. The HPLC method provided for an acceptable separation of fulvestrant from its impurities and degradants. The [redacted] method is capable of separating solvents that may be potential organic solvent impurities. The validation of HPLC and [redacted] methods demonstrated the ruggedness and specificity of these methods. They also provided acceptable validation and justification for the remaining analytical methods used in the determination of fulvestrant drug substance and drug product.

III. Administrative

A. Reviewer's Signature [redacted]

B. Endorsement Block

Josephine Jee/Date: 18-JAN-2002
Josephine Jee/ Rev. 10-APR-2002
Josephine Jee/ Rev. 16-APR-2002
Richard Lostritto/Date:
Amy Baird/Date

C. CC Block

Orig. NDA 21-344
HFD-150/Division File
HFD-150/JJee
HFD-150/ABaird
HFD-150/RLostritto
HFD-810/JSimmons

Redacted 53

pages of trade

secret and/or

confidential

commercial

information

B. Environmental Assessment Or Claim Of Categorical Exclusion
Vol. 1.5, section "Environmental Assessment", p.1
IPR Pharmaceutical states they have no knowledge of any exceptional circumstances exist that would require additional controls to be imposed on the use of FASLODEX in order to protect the environment..
IPR Pharmaceuticals requests that NDA 21-344 for FASLODEX be qualified for a categorical exclusion based on Sec. 25.31(a) and (b) wherein the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb).

Evaluation: **Adequate.**

III. List Of Deficiencies To Be Communicated

We have the following comments regarding fulvestrant drug substance:

1. **The proposed specification for [redacted] assay is [redacted]% w/w and the total organic impurities is [redacted]%. The applicant should provide information on additional impurities or degradants that may contribute to the remaining [redacted]%.**

2. **The proposed assay specification for [redacted], is [redacted]% w/w and the total organic impurities is specified as [redacted]% w/w maximum. Please provide any impurities or degradants in [redacted] that may contribute to the remaining [redacted] w/w.**

3. **The proposed assay specifications for [redacted] range from [redacted]% w/w. [redacted] is listed as an impurity at [redacted]% w/w maximum. Please provide information on degradants or impurity that may contribute to the remaining [redacted] %.**

4. **The proposed assay specifications for [redacted] assay range from [redacted]. This specification is rather broad it should be tightened to better reflect actual batch data.**

5. **The proposed specifications for [redacted] assay is specified as [redacted]%. The applicant should provide the impurities that may contribute to the remaining [redacted]%.**

6. **Please revise the drug substance specification for water content, [redacted] specific optical rotation, microbial content, and endotoxins to reference appropriate USP/NF methods.**

7. **The limit for [redacted] should be lowered to NMT [redacted]% since it was not detected in any batches of fulvestrant drug substance studied.**

8. **Please submit adequate documentation on the [redacted] bags which indicates that it complies with 21 CFR. Please describe further, the materials of construction for the [redacted] lid used for bulk packaging of fulvestrant drug substance and acceptance criteria, to support use of these materials.**

9. **Please provide the stability regulatory specification and tests for fulvestrant drug substance.**

10. **Please revise the specification for identification test to the IR absorption spectrum**

of fulvestrant sample compares with that obtained from the Fulvestrant Reference Standard.

11. **Please revise the Fulvestrant Reference Standard specification for water content, specific optical rotation, microbial content, and endotoxins to reference appropriate USP/NF methods.**

12. **Please include tests and limits for Total Organic Impurities in the Specifications for Fulvestrant Reference Standard.**

13. **Please provide a commitment that no will be performed without notification to the Agency.**

We have the following comments for Faslodex Injection:

1. **We have reviewed Drug Master File (DMF) submitted by Vetter GmbH & Co. KG and identified several comments. The nature of these comments will be communicated to the DMF holder separately.**

2. **Please include tests for optical clarity, viscosity, extractables and free fatty acid content in the specifications for fulvestrant drug product as they are provided in the stability study of fulvestrant drug product.**

3. **Please provide the complete regulatory specifications for the stability study of FASLODEX Injection.**

4. **Please provide the chemical resistance test and results for the Type I glass components (syringe barrel) as per current USP <661>.**

5. **Given the solvent power of the drug product vehicle, please provide results for a one-time characterization of extractables from the rubber container-closure components into the formulation**

6. **Please provide the test results for syringe barrel, rubber plunger and rubber tip-cap as per tests and specifications listed in Vol. 1.5, Container Closure Section of this application.**

7. **Please submit certificate of analyses from the suppliers of container closure for batches of drug product submitted in this application.**

8. **Please provide a commitment that no Faslodex Injection will be performed without notification to the Agency.**

Chemistry Assessment Section

NDA 21-344 Review #1 FASLODEX (fulvestrant) Injection

We recommend the following revisions to the Carton Label (2.5 mL and 5 mL) and Syringe Label:

1. **Please revise the list of inactive ingredients in the Carton Label and list as: Alcohol, USP; Benzyl Alcohol, NF; Benzyl Benzoate, USP; and Castor Oil, USP.**

2. **Please include the following statement on the Syringe Label: RX only.**

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

/s/

Josephine Jee
4/17/02 05:03:56 PM
CHEMIST

Richard Lostritto
4/22/02 01:32:45 PM
CHEMIST