CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20753

CHEMISTRY REVIEW(S)

A. Staton

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

OCT 1 4 1999

NDA #: 20-753 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 10/8/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original (Vol.	Dec. 18, 1998	Dec. 21, 1998	Dec. 28, 1998
N/C	Jun. 4, 1999	Jun. 7, 1999	Jun. 8, 1999
NBL	Jun. 14, 1999	Jun. 16, 1999	Jun. 21, 1999
N (BC)	Jul. 12, 1999	Jul. 13, 1999	Jul. 14, 1999
BL	Aug. 11, 1999	Aug. 12, 1999	Aug. 18, 1999
BL	Oct. 11, 1999	Oct. 12, 1999	Oct. 13, 1999

NAME & ADDRESS OF APPLICANT: Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

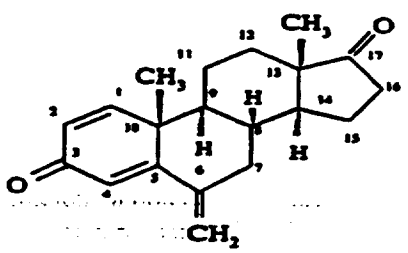
DRUG PRODUCT NAME

Proprietary:	AROMASIN® Tablets (Exemestane Tablets)
Nonproprietary/USAN:	androsta-1,4-diene-3,17-dione-6-methylene
Code Name/#:	FCE 24304, PNU-155971
Chem.Type/Ther.Class:	
CAS:	107868-30-4
CAS Name:	6-methylenandrosta-1,4-diene-3,17-dione
Patent Info:	US Patents – 4,808,616 and 4,904,650, exp. 7/7/2006

PHARMACOL. CATEGORY/INDICATION: Irreversible, steroidal aromatase inactivator

DOSAGE FORM:	Tablets
STRENGTHS:	25 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	X Rx ___

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



RELATED DOCUMENTS:

Related Doc. #	Holder/Applicant	Subject Status
IND	Pharmacia & Upjohn	

SUPPORTING DOCUMENTS:

TYPE / No.	SUBJECT	HOLDER/SPONSOR	STATUS	REVIEW DATE
DMF Type III			Adequate by M. Shih	6/23/98
DMF Type III			Adequate by A. Langowski	9/11/98
DMF Type III			Adequate by C. Bertha	3/17/99
DMF TYPE III			Adequate by Ravi S. Haranparanhalli	5/12/99
DMF Type III			Adequate by M. Ortwerth	6/1/4/99
DMF Type III			Adequate by James Vidra	9/1/99
DMF Type I			Adequate	8/10/99
DMF Type I			Adequate	8/10/99
DMF Type I			Adequate	9/27/99
DMF	Pharmacia & Upjohn		Adequate	9/28/99
DMF			Adequate by the Div. Of Colors	4/14/70
DMF			Adequate by M.E. Ysern	6/30/98
DMF Type III			Adequate by R. Seevers	3/98
DMF Type III			Adequate by R. Trimmer	9/28/99
DMF			Adequate by P. Dietze	7/7/95 – No change since.

CONSULTS:

Consult Type	Status	Comments
Trademark - Lab. & Nomenclature	Acceptable	O.K. on 1/19/99 by D. Boring
Carton Label Design – OPDRA	Acceptable	10/1/1999 by C. Holquist
Container Labels - DDMAC	Acceptable	10/8/99 by Jean-Ah Choi

REMARKS/COMMENTS:

Patent Information and Certification, see Vol. 3.1, Attachment 7.
U.S. Patents nos. 4,808,616 and 4,904,650 which currently expire July 7, 2006 and are subject to extension.
See below for additional comments.

CONCLUSIONS & RECOMMENDATIONS:

This application can be considered Approvable from a CMC point of view only if the remaining deficiencies can be addressed satisfactorily. The CMC deficiencies are listed in the List of Chemistry deficiencies and comments.

COMMENT BY REBECCA H. WOOD, Ph.D. on 10/14/99:
An Approval letter with CMC commitments to respond promptly to the chemistry comments (p. 23) would be acceptable.

cc:
Org. NDA 20-753
HFD-150/Division File
HFD-150/JJee/10-8-99
HFD-150/Jjee/10-14-99
HFD-150/Rwood/10-14-99
HFD-150/AStaten
HFD-150/DPease
R/D Init by: ____ /S/ 10-14-99

/S/ 10/14/99
Josephine M. Jee, Review Chemist

filename: nda20753 II.doc

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

Labeling Review

NDA:	20-753
Product:	Exemestane Tablets
Applicant:	Pharmacia & Upjohn Co.
Date of Submission:	12/18/98, and 8/12/99 e-mail from Mr. Patrick Guinn, CSO
Stamp Date:	12/21/98
Date of Review:	9/17/99
Material Reviewed:	Package Insert Labeling

Labeling

1. **DESCRIPTION:**
   - i. The molecular formula $C_{20}H_{24}O_2$ in the labeling is identical as the one listed in the USP Dictionary of USAN and International Drug Names.
   - ii. The molecular weight of exemestane submitted in the labeling insert is 296.41, this is consistent with USAN.
   - iii. The chemical name, 6-methylenandrosta-1,4-diene-3,17-dione is identical with the USP Dictionary of USAN and International Drug Names.
   - iv. The description of the active ingredient is consistent with the description provided in the application..
   - v. The list of inactive ingredients are consistent with the components and composition statement with the exception of Methyl-p-hydroxybenzoate. This ingredient is listed as Methylparaben, NF and the official name in the current USP/NF is Methylparaben, NF.
2. **HOW SUPPLIED:**
   The description of the tablets is satisfactory.
   The applicant should provide the NDC codes for both blister packs, 15-tablet and 30-tablet.

/S/ 9/17/99

Josephine M. Jee
Review Chemist, DNDC I

cc: NDA 20-753
HFD-150/Division File
HFD-150/JJee
HFD-150/RWood
HFD-150/ASTATEN
F/T byJJee/9/17/99
R/D by:
File:20753lab.doc

/S/ 9-20-99

JAN 29 1999

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls
45-Day Meeting CMC Summary

NDA #: 20-753 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 1/29/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	Dec. 18, 1999	Dec. 21, 1999	Dec. 28, 1999

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7000 Portage Road
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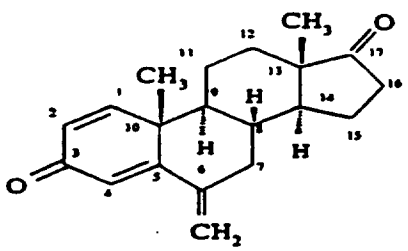

DRUG SUBSTANCE

Specifications for appearance, identification, particle size, specific optical orientation, water, sulfated ash, heavy metals, residual solvents, related substances and assay. Assay is by [ ] and the specification is [ ] %. The analytical method for related substances is [ ]

DRUG PRODUCT

The to be-marketed formulation a 25 mg tablet (formulation) manufactured in batches of [ ] units information on the batches and formulations used in the various clinical trials is presented in the .... submission on pages ... The manufacturing process consists of [ ]

NDA 20-855, Rev # 1

Three types of packaging are submitted: 30 tablet in HPDE bottles, and 30-blister packs.

Full term stability data of 24 months has been submitted for 1 lot of blister packs. In addition, actual batch records and a method validation package was submitted.

LABELING

Pharmacia submitted a list of information to be part of the bottle and blister labels on Vol. 2 pp 43 – 46. The applicant needs to submit samples of the labels.

CONSULTS NEEDED:

EER's for Pharmacia &Upjohn SpA. was submitted on Jan. 26, 1999.

/S/

Josephine M. Jee, Review Chemist, HFD-150

cc: Orig NDA 20-753
Div File
HFD-150 / Master / JJcc