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NDA 28-169

1 OF 6

CD A20-169

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Co. Corres

Pharm./Tox
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— FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

AP Ltr

AE Ltr

05

NDA 20-169

SEP 19 1996

Corning Besselaar, Inc.
Attention: Carole Venetianer, R.N., M.S.
Manager, Regulatory Affairs and Biomedical Writing
210 Carnegie Center
Princeton, NJ 08540-6233

Dear Ms. Venetianer:

Please refer to your March 7, 1994, new drug application submitted on behalf of Hoechst Marion Roussel, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nilandron™ (nilutamide) Tablets, 50 mg.

We acknowledge receipt of your amendments dated February 26, March 15, April 11, August 7 and 14, and September 17 (telefacsimile) and 19 (telefacsimile), 1996, submitted in response to our second approvable letter dated February 22, 1996.

This new drug application provides for the use of Nilandron™ in combination with surgical castration for the treatment of Stage D₂ metastatic carcinoma of the prostate.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated August 14, 1996 (carton and container) and September 19, 1996 (package insert). Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on August 14, 1996 (carton and container), and September 19, 1996 (package insert). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

We note your commitment communicated in your September 17, 1996, submission to revise the tradename on the carton label, currently "Nilandron™," to "Nilandron™ (nilutamide) Tablets." We also agree to your request of September 17, 1996, to market the initial supply of Nilandron™ in cartons identical to the draft cartons submitted on August 14, 1996.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved NDA 20-169." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

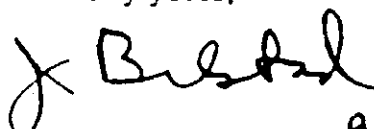
Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
(301) 827-4260

Sincerely yours,



James Bilstad, M.D.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

9/19/96

Name	Title	Signature	Date
Lana L. Pauls, M.P.H.	Chief, Project Management Staff	<i>Lana L. Pauls</i>	8/12/96
Jean Fourcroy, M.D., Ph.D.	Medical Officer	<i>Jean Fourcroy</i>	8/26/96
Xavier Ysern, Ph.D.	Review Chemist, HFD-510	<i>Xavier Ysern</i>	8/13/96
Stephen Moore, Ph.D.	Chemistry Team Leader, HFD-510	<i>H. Davies for S. Moore</i>	8/13/96
Helen Davies, Ph.D.	Chemistry Team Leader, HFD-580	<i>Helen W. Davies</i>	8/13/96
Yuan-yuan Chiu, Ph.D.	Director, Division of New Drug Chemistry II		
Jeri El-Hage, Ph.D.	Review Pharmacologist	<i>Jeri El-Hage</i>	8/12/96
Alexander Jordan, Ph.D.	Pharmacology Team Leader	<i>Alexander Jordan</i>	8/13/96
Lisa Rarick, M.D.	Acting Division Director	<i>Lisa Rarick</i>	8/27/96

cc:

Original NDA 20-169
 HFD-580/Div. files
 HFD-2/M. Lumpkin
 HFD-102/L. Ripper (with labeling)
 HFD-101/L. Carter (with labeling)
 HFD-820/Yuan Yuan Chiu
 DISTRICT OFFICE
 HF-2/Medwatch (with labeling)
 HFD-80 (with labeling)
 HFD-40/DDMAC (with labeling)
 HFD-613 (with labeling)
 HFD-735/(with labeling)
 HFD-021/J. Treacy (with labeling)
 HFD-510/XYsern, S. Moore (with labeling)
 HFD-580/J. Fourcroy, H. Davies, J. El-Hage, A. Jordan (with labeling)

drafted: LPauls/August 12, 1996/N20169AP.001

Concurrences see above

APPROVAL

FEB 22 1996

Coming Besselaar, Inc.
Attention: Carole Venetianer, R.N., M.S.
Manager, Regulatory Affairs and Biomedical Writing
210 Carnegie Center
Princeton, NJ 08540-6233

Dear Ms. Venetianer:

Please refer to the June 14, 1991, new drug application submitted on behalf of Roussel UCLAF, and your resubmission dated March 7, 1994, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nilandron® (nilutamide tablets).

We acknowledge receipt of your amendments dated April 13, May 24, August 15, and December 13, 1995, and February 20, 1996 (telefacsimile) submitted in response to our approvable letter dated March 7, 1995. The bioavailability/pharmacokinetic study results submitted December 13 have been accepted as correspondence but have not yet been reviewed.

We have completed the review of this application as submitted with the draft labeling dated December 13, 1995. Based on the clinical data submitted, the application may be approved for the treatment of post-orchietomy prostate cancer patients, but not of chemically castrated patients.

Before the application may be approved, however, it will be necessary for you to submit the following information:

Environmental Assessment (EA)

1. In regard to the facility, the references to the Drug Master File (which is confidential and not available to the public) are not sufficient. Our Guidance for Industry for the Submission of an Environmental Assessment, November 1995, allows foreign facilities to self-certify compliance with emission requirements and environmental laws to fulfill the EA requirements for manufacturing facilities. The responsible official should certify that the manufacturing facility is:
 - a. in compliance with all local and national environmental laws;
 - b. in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
 - c. is not expected to affect compliance with all emission requirements or compliance with environmental laws once approval is granted and the subsequent increase in production at the facility ensues.

The statement should be signed and dated by the responsible official, and if not in English, a certified English translation should be provided. This self-certification from

should be included in the non-confidential EA since you have identified as a contract manufacturer.

2. Section 6.1 of the confidential environmental assessment (page 63) cites an "optimistic forecast" for production as being between tablets annually. This is consistent with the figure cited in Section 4.2 of both the confidential and non-confidential versions of the assessment (pages 8 and 350, respectively). Section 6.1 of the non-confidential assessment, however, states that the fifth year production should not exceed tablets. This discrepancy in annual production volumes should be corrected. In addition, the MEEC, which is calculated from the market projection, should be revised if is the actual market projection.

Please note that market projections and MEEC are considered confidential business information and need not be included in the non-confidential EA.

3. The method of disposal in the United States of returned or expired drug product must be addressed specifically and/or it should be clarified if these goods are returned to France for destruction. If destroyed in the United States, the specific information should include the:
 - a. method of destruction (e.g., incineration, landfill);
 - b. identification of current facility used for destruction;
 - c. facility license/permit number;
 - d. license/permit issuing agent; and
 - e. license/permit expiration dates (if appropriate).

The method of destruction (e.g., incineration, landfill), whether it occurs in the United States or France, should be included in the non-confidential EA.

4. The MSDS for nilutamide, included on pages 267-271 of the confidential EA, should be included in the non-confidential EA. In addition, please provide a statement indicating that FDA may attach the MSDS to the non-confidential EA.

It is not necessary to provide a complete revision of the confidential and non-confidential EA to address these deficiencies. You may provide replacement pages and/or addendums to the EA's which FDA will incorporate into the EA.

Please note, *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* is available from the Division of Communications Management, HFD-210, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD 20855, 301-594-1012; FAX on Demand, 1-800-342-2722, Document # 0803; or via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.VDA.GOV).

Biopharmaceutics

To help in the development of a reasonable dissolution method for nilutamide, our March 7, 1995, approvable letter requested that you test dissolution in a more physiologic medium (i.e., simulated intestinal fluid) using the batches/lots that were used in the NDA's clinical and pharmacokinetic studies. In your submission dated August 15, 1995, you provided dissolution data in simulated intestinal fluid, but the batches were past the NDA's accepted expiration date. Therefore, the utility of these data is questionable. For this reason, the dissolution method provided originally, with a modification of the specification from Q % to Q % in minutes (see below), should be used on an interim basis. In addition, we request you submit a Phase 4 commitment for the timely submission of dissolution profiles (up to min) on three batches (12 tablets per batch) in simulated intestinal fluid on batches that are within the expiration date. These data should allow a determination of whether, in fact, a method using simulated intestinal fluid is more appropriate for this product.

USP Apparatus II (Paddle), 50 rpm
900 mL water at 37°C
Q % in min

Labeling**Package Insert**

3. **Clinical Studies** subsection

WARNINGS section

DOSAGE AND ADMINISTRATION section

Carton and Container Labels

Safety Update

A safety update as provided for by 21 CFR 314.50(d)(5)(vi)(b) must be submitted.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolism and Endocrine Drug Products and two copies of both the promotional material and the package insert, directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Lana L. Pauls, M.P.H.
Project Manager
Telephone: (301) 443-3510

Sincerely yours,

 2/22/16

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE

Name	Title	Date	Signature
Enid Galliers	Chief, Project Management Staff	2/2/96	Galliers
Jean Fourcroy, M.D., Ph.D.	Medical Officer	2/6	J. Fourcroy
Lisa Rarick, M.D.	Acting Deputy Director II	2/7	L. Rarick
Xavier Ysern, Ph.D.	Chemist		
Stephen Moore, Ph.D.	Acting Supervisory Chemist II	2/2/96	Stephen Moore
Yuan-Yuan Chiu, Ph.D.	Director, Division of New Drug Chemistry II	2/7/96	Yuan-Yuan Chiu
Jeri El-Hage, Ph.D.	Pharmacologist	2/5/96	Jeri El-Hage
Alexander Jordan, Ph.D.	Supervisory Pharmacologist	2/5/96	Alex Jordan
Solomon Sobel, M.D.	Division Director	2/7/96	Sobel

cc:

Original NDA

DISTRICT OFFICE

HF-2/MEDWATCH

HFD-2/MLumpkin

HFD-009/JTreacy/KReedy

HFD-510

HFD-510/JFourcroy/LRarick/XYsern/SMoore/YYChiu/JElHage/AJordan

HFD-80

HFD-102/LRipper

HFD-538

HFD-735/DBarash

HFD-510/LPauls/02.02.96/N20169AE.002

Revisions per LRipper & JBilstad/2.22.96

Concurrences: (see above)

APPROVABLE

MAR - 7 1995

G.H. Besselaar Associates
Attention: James Burns, Jr., Ph.D.
Senior Vice President, Regulatory Affairs
210 Carnegie Center
Princeton, NJ 08540-6681

Dear Dr. Burns:

Please refer to the June 14, 1991, new drug application submitted on behalf of Roussel UCLAF, and your resubmission dated March 7, 1994, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nilandron® (nilutamide tablets).

We acknowledge receipt of your amendments dated September 4 and December 6, 1991; January 21, March 4, April 23, and August 18, 1992; April 5, 1993; March 28, April 27, July 1 and 12, August 2, 8, and 22, September 2 and 27, October 14 and 24, November 11, and December 5, 1994; and January 18, 20, 25, and 27(2), 1995.

We have completed the review of this application as submitted with the draft labeling dated February 24, 1994. Based on the clinical data submitted, the application may be approved for the treatment of post-orchietomy patients only, and not for patients who have been chemically castrated. We have concluded that the evidence for efficacy in Study #606, in which patients were treated concurrently with nilutamide and leuprolide, is not adequate to support an indication for the use of nilutamide with leuprolide. In contradistinction to Study #908, there was no significant increase in the time of progression. The distinctly favorable findings in regard to the time of death that were seen in Study #908 were not seen in Study #606. Furthermore, we do not accept utilizing a retrospective surrogate endpoint that uses a low baseline alkaline phosphatase and a 3-month normalization of PSA values as a means for establishing efficacy in Study #606.

Before the application may be approved, it will be necessary for you to submit the following information:

Biopharmaceutics:

1. A pharmacokinetic/bioavailability study should be conducted to assess the effect of food on this tablet and to support the labeling recommendation that Nilandron be administered prior to breakfast with a glassful of water. This study should include at least twelve healthy subjects and utilize a standard high-fat breakfast. Please contact Dr. Albert Chen in the Division of Biopharmaceutics for further information regarding the study design.
2. Between-study analyses should be conducted relating nilutamide plasma levels with efficacy and safety parameters. For example, is the difference in the

number of patients who reported impaired adaptation to darkness and were receiving nilutamide in conjunction with either surgical or chemical castration (13% vs. 56%) related to differences in drug plasma levels?

3. The following dissolution method/specification should be implemented:

USP Apparatus II (Paddle), 50 rpm
900 mL USP pH 7.5 simulated intestinal fluid (SIF) without enzymes
at 37°C
Q = % in min

Before this method is finalized, however, dissolution profiles (up to min) must be provided for the biobatches (12 tablets per batch) used in the pharmacokinetic studies as well as the batches used in the two pivotal clinical studies (Nos. FF/86/908/01 and GHBA 606).

Environmental Assessment:

1. The environmental assessment document will be releasable under the Freedom of Information Act; therefore, confidential data and information that were pertinent to the environmental review of the proposed action must be submitted separately as a confidential section. However, this information must be summarized in the environmental assessment document to the extent possible. In addition, the appropriate information from must be included in the environmental assessment document.
2. The environmental assessment document omits Sections 7 through 11, citing an exemption under 21 CFR 25.31a(b)(3). However, no information is provided in Section 4 to justify the exemption. The environmental assessment document should be treated as a stand-alone document; therefore, the brief description of the requested approval and need for action should contain sufficient information on the use of nilutamide to justify the requested exemption.
3. Section 4 (description of the proposed action) should be revised as follows:
 - a. The document should contain a brief description of the requested approval and of the need for action.
 - b. The complete address should be included for the subcontractor
 - c. The environments at, and surrounding, each facility should be described in sufficient detail to allow evaluation of the environmental impact of the proposed action, i.e., urban, suburban, rural.

- d. The document should include a description of the expected locations of use of the drug product.
 - e. The identity, location, and permit numbers should be included for any facilities involved with the recycling and/or disposal of wastes from manufacturing, formulation, and packaging activities.
- 4. Section 5 (identification of chemical substances) should be revised to include a physical description of the drug substance as well as identification of the impurities.
- 5. Section 6 (introduction of substances into the environment) should be revised as follows:
 - a. Each chemical that is anticipated to be in the effluent, waste, or emission from each process step should be identified. In addition, an anticipated concentration should be provided.
 - b. A table should be included showing the estimates for production levels for five years.
 - c. The description of environmental controls at Compiègne should be expanded to include dust emissions from the tableting process.
 - d. The efficiency of each emission control step should be included for all facilities.
 - e. Section 6.3 should reference the inspection report for Compiègne.
 - f. The document should include sufficient information for each facility to allow confirmation of the statement that approval of the proposed action will have no adverse effect on compliance with existing permits.
 - g. The document should provide an estimate of the maximum yearly market volume of the drug product and a calculation of Estimated Expected Emitted Concentration.
 - h. The document should describe the method of disposal of returned or expired drug product.
- 6. Section 14 (references) should be revised to include the citations for all material referred to and used in the preparation of the environmental assessment.

Labeling:

DESCRIPTION section

CLINICAL PHARMACOLOGY section

9

INDICATIONS and USAGE section

CONTRAINDICATIONS section

WARNINGS section

PRECAUTIONS section

- c. The subsection **Laboratory Tests**, should be revised to read:

- g. The entire Pregnancy subsection should be revised to read:

This drug is not indicated for use in women or children."

- h. A new subsection entitled "Animal pharmacology and toxicology " should be added to the end of this section. This new subsection should read as follows:

ADVERSE REACTIONS section

CARTON and CONTAINER LABELS

All carton and container labels must be submitted.

In addition, a safety update as provided for by 21 CFR 314.50(d)(5)(vi)(b) must be submitted.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolism and Endocrine Drug Products and two copies of both the promotional material and the package insert, directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

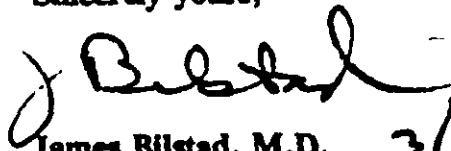
Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
Telephone: (301) 443-3510

Sincerely yours,

 3/7/95

James Bilstad, M.D.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Name	Title	Date	Signature
Enid Galliers	SCSO	3/7/95	Enid Galliers
Jean Fourcroy, M.D., Ph.D.	Medical Officer	3/7/95	Jean Fourcroy
G. Alexander Fleming, M.D.	Supervisory Medical Officer	3/7/95	G. Alexander Fleming
Xavier Ysern, Ph.D.	Chemist	3/7/95	Xavier Ysern
Yuan-yuan Chiu, Ph.D.	Supervisory Chemist	3/7/95	Yuan-yuan Chiu
Jeri El-Hage, Ph.D.	Pharmacologist	3/7/95	Jeri El-Hage
Alexander Jordan, Ph.D.	Supervisory Pharmacologist	3/8/95	Alexander Jordan
Solomon Sobel, M.D.	Division Director	3/7/95	Solomon Sobel

cc:

Original NDA

DISTRICT OFFICE

HF-2/MEDWATCH

HFD-2/MLumpkin

HFD-009/JTreacy/KReedy

HFD-510

HFD-510/JFourcroy/AFleming/XYsern/YYChiu/JElHage/AJordan

HFD-80

HFD-500

HFD-638

HFD-735/DBarash

HFD-510/LPauls/02.07.95, 03.07.95/N20169AE.001

Revisions 03.07.95

Concurrences: (see above)

APPROVABLE

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NILUTAMIDE

PATENT INFORMATION

1.	ACTIVE INGREDIENT	NILUTAMIDE
2.	STRENGTHS	50 mg.
3.	TRADE NAME	ANANDRON TABLETS
4.	DOSAGE FORM, ROUTE OF ADMINISTRATION	TABLET, ORAL
5.	APPLICANT FIRM NAME	ROUSSEL UCLAF
6.	APPLICABLE PATENT NUMBERS AND EXPIRATION DATE OF EACH	USP 4,097,578 expiring 27 June 1995 (Nilutamide alone) USP 4,472,382 expiring 18 September 2001 (Nilutamide with LHRH agonist)

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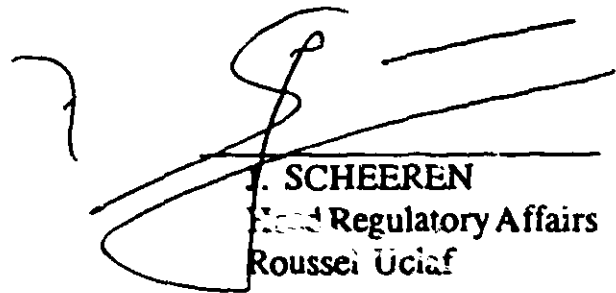
CERTIFICATION STATEMENT
as requested by
Generic Drug Enforcement Act of 1992

I certify that Roussel Uclaf did not and will not use in any capacity the services of any individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with New Drug Application 20-169, Anandron (nilutamide tablets).

To the best of my knowledge, I am not aware of any relevant convictions of any affiliated persons responsible for the development or submission of the application.



A. Ulmann MD
Head Endocrinology Domaine
Roussel Uclaf



J. SCHEEREN
Head Regulatory Affairs
Roussel Uclaf

Feb. 12 / 94
Date

2/02/94
Date

102 et 111, Route de Noisy - B.P. N° 9 - 93230 Romainville
Tél. + 33 (1) 49 91 49 91 Tlx. ROUSS A 235 477 F
SIRET 542 008 081 00052 00045 CCP 2012 37 5
Ad. télég. Roussel Uclaf Romainville

*Roussel-Uclaf, Société Anonyme à Directeur et Conseil de Surveillance
au capital de 534 666 000 F - R.C.S. Paris B 542 008 081
Siège social: 35, Boulevard des Invalides 75007 Paris*

CERTIFICATION STATEMENT
as requested by the
Generic Drug Enforcement Act of 1992

On behalf of G. H. Besselaar Associates ("Besselaar"), acting as agent for Roussel-UCLAF, I hereby certify that Besselaar did not and will not use in any capacity the services of any individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with New Drug Application 20-169, Anandron (nilutamide tablets).

To the best of my knowledge, I am not aware of any relevant convictions of any affiliated persons responsible for the development or submission of the application.



J. P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

4 March 1994
Date

DIVISION DIRECTOR MEMO

4/16 1996

NDA: 20-169 Nilandron (Nilutamide) tablets

Sponsor: Corning Besselaar, Inc
Princeton, NJ

Date of Memo: August 27, 1996

This sponsor has addressed all outstanding issues raised in our approvable letters of March 15, 1995 and February 22, 1996.

The group leader memo of February 1, 1996 summarizes the February 1995 Advisory Committee recommendations as well as the Medical Officer Review and labeling comments.

The current submission includes proposed labeling (August 14, 1996) which addresses the outstanding labeling comments. The proposed labeling is satisfactory. In terms of the clinical sections, two items previously suggested have been modified in the sponsor's draft label.

In the "Clinical Studies" section the sponsor has not included the third paragraph previously requested to read:

Recommendation

Because the indication section clearly reads that the product is approved in combination with surgical castration, the added discussion in the clinical studies section is not required at this time.

Members of the Division will be meeting in September in order to assess the labeling (and its consistency) of all approved anti-androgens. At that time we will further address and make recommendations regarding the presentation of clinical studies and results in the labeling of this class of products.

A further labeling change requested involved wording in the section in "Warnings"/"Hepatitis".

As per our previous letter, we requested that the second paragraph of this section read "...".

The sponsor has proposed that this section read

Recommendation

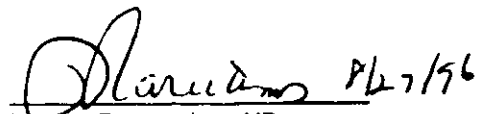
After similar discussions with the sponsor of another of the approved anti-androgens, we have previously accepted this compromise wording (see flutamide approved labeling).

During our anticipated Divisional meeting and labeling review (see above) we will again discuss the most appropriate warning statement and implement the conclusion across all approved drugs in this class.

CONCLUSION:

As per the previous action and the Advisory Committee recommendations, we anticipate approval of this NDA.

Labeling revisions have been incorporated and are acceptable.



Lisa Rarick, MD

Acting Director

Division of Reproductive and Urologic Drug Products, HFD-580

cc:

NDA 20169

HFD-580/Rarick/Fourcroy\\wpfiles/20169.2

ORIGINAL

March 5, 1995

Memorandum

From : Solomon Sobel M.D. Director, Division of Metabolism and Endocrine Drug Products

To: NDA file 20 -169 Nilutamide

Subject: Reappraisal after Advisory Committee meeting

I recommend that we approve nilutamide for post orchiectomy patients and not for patients who have been

This would reflect the conditions of the study in which a significant result for a primary endpoint was reached. Similarly, when we approved flutamide we approved it only for use with leuprolide which was the drug used to induce castration in the pivotal (and only) study .

The evidence in 908 is significant in regard to delaying progression. There is evidence that there is a trend towards prolonging survival especially for prostatic cancer related causes. In 908 the median time to death due to prostate cancer is 36 months in the nilutamide group (median survival has not been reached) and 27.5 in the placebo group where median survival has been reached.

Median time to death due to any cause is 28.3, nilutamide vs. 23.2 placebo. For all causes median survival has been reached for both groups.

(Dr. Ed Nevius informed me that Mary Johnson a statistician working as a consultant to Roussell-Uclaf faxed the following material to him. The data were an update past the 12/31/92 cutoff presented at the Advisory Committee. She said that this material was also sent to FDA in a recent submission. The update showed a p-value for cancer survival of .0416 and an overall survival of .1293. These were, however, evaluable patient results. A table Dr. Johnson provided showed the results for the "all patients" analysis to be .0135 for cancer survival and .0586 for overall survival.)

These data are substantial in regard to survival for the use of nilutamide in post-orchietomy patients.

Although the Division rejects the retrospective analysis employing baseline alkaline phosphatase and 3 month response in respect to PSA there is some favorable support from 606:

cancer pain at 6 months $p=.065$

performance status at 6 months $p=.025$

bone scan uptake .002 at 6mos, .091 at 18 months and .066 at endpoint

primary tumor volume .033 at endpoint.

number of patients who achieved a complete of partial regression during the study 54% vs. 43% $p=0.02$

Conclusion:

I have reevaluated my position in respect to the approvability of nilutamide.

However, the approvable letter must indicate that we are limiting the indication to use in post-orchietomy patients and that we do not accept the information given in the present labeling in respect to the utility of baseline alkaline phosphatase and PSA response in choosing patients for treatment.

Solomon Sobel

conferred
2/7/96
jsobel

Memorandum

February 13, 1995

To the File: NDA 20-169 Anandron (nilutamide)

From: Solomon Sobel M.D., Director, Division of Metabolism and *Sobel*
Endocrine Drug Products

Subject: Non-approvability of the NDA

Background:

a pre-NDA meeting was held with the sponsor in November of 1990 at which time FDA discussed the discordant results of the 2 primary studies, 908 and 606. The company decided to submit the NDA with proposed labeling for only surgically castrated patients (relying on 908).

The NDA was submitted in June of 1991 and FDA refused to file the application citing the need for 2 adequate and well controlled studies. (Only 908 showed a positive significant result for one of the primary endpoints, i.e., time to progression. There was a non significant trend for overall survival in respect to prostate cancer deaths but not for overall mortality).

In December of 1991 the sponsor presented additional efficacy analyses to define (retrospectively) subgroups of patients who might derive benefit from nilutamide in conjunction with medical or surgical castration.

The subgroup for which the sponsor seeks an indication are those patients who at the initiation of treatment have a low or minimally elevated alkaline phosphatase and then on subsequent observation at 3 months of treatment normalize their PSA values.

There are three areas of concern which have arisen during the review of this NDA:

- a. The preclinical toxicology
- b. the adverse reaction profile in the clinical studies.
- c. the non-replicability of the pivotal studies, the retrospective approach to attempt to achieve replication, and the probable lack of the achieving of the 2 study requirement for approval.

CSD

A comparison of toxicities in 3 species yields the following information:

	anemia	liver	kidney	lung
RAT:				
nilutamide	+	+	+	+
flutamide	+	+	+	-
DOG:				
nilutamide	+	+	+	-
flutamide	+	+	-	-
MAN:				
nilutamide	-	+	?	+
flutamide	+	+	-	-

In dogs, the best animal model for flutamide and nilutamide metabolism, lethality occurred at AUCs at equal or greater than 8 times the maximum human exposure with flutamide but at only 0.1 to 1 times the human exposure with nilutamide.

In respect to clinical adverse reactions the following is noteworthy:

Study	incidence of interstitial pneumonitis	incidence of nausea and vomiting	incidence of visual disturbances
908	1/225 (0.4%)	25/225 (11%)	64/225 (28%)
606	7/209 (1.8%)	64/209 (31%)	138/209 (66%)

The mean plasma levels were higher in study 606 than in 908. In Japanese men (Study 1108) where plasma levels were highest, the incidence of pneumonitis was 17%.

Study 606 failed to replicate the finding of a significant difference to the time of progression which was noted in study in 908.

In an attempt to explain this lack of replication, the sponsor showed that the baseline characteristics of patients in Study 606 were different than those in Study 908. Patients in 606 were considerably healthier than those in 908 at baseline.

Noteworthy were the baseline alkaline phosphatase levels; 41% of patients in 908 as compared to 23% of patients in 606 had levels more than two times the upper limit of normal.

The sponsor claimed that if one were to limit the analysis to patients who had achieved a response as measured by a less than 4 ng/ml level of PSA at 3 months, and in addition had had, at baseline, an alkaline phosphatase level of less than twice normal then both studies would show that nilutamide was significantly effective in achieving the normalization of PSA. Thus, by using this surrogate measure of PSA normalization both studies (908 and 606) could be used in support of efficacy and thus meet our two study requirement.

It is to be noted that in neither study was there a demonstration of an improvement of mortality findings. (although when one limits the life table analysis to deaths from prostatic cancer alone there was a near statistically significant trend to improved mortality findings with nilutamide in study 908) Thus, the concession we have made in some instances in the past in regard to accepting one study when the sponsor had performed a large study which had demonstrated an improvement in mortality would not be applicable here. (Indeed our approval of flutamide rested on one study; however, for that drug, a mortality advantage was demonstrated).

We have carefully considered the arguments of the sponsor. (please refer to Dr. Huberman's statistical consultation).

I believe that the sponsor has not shown that normalization of PSA with nilutamide use is equivalent (especially in respect to results on mortality) to a spontaneous normalization after castration.

In 606, 88% of evaluable patients with PSA measurements responded in the nilutamide group and 71% responded in the placebo group (statistically significant).

Among responders approximately 60% died on either treatment arm.

In 908, 76% of evaluable patients with PSA measurements responded in the nilutamide group and 50% in the placebo group. (statistically significant).

Among responders 40% of the placebo patients died while 50% of the nilutamide patients died. This latter result favoring placebo may lead one to believe that the normalization of PSA (responder) may come at too high a price. Either, the responder status as induced by nilutamide is spurious and does not represent true tumor regression or the toxicity of nilutamide overwhelms any benefit of regression.

Thus, we have difficulty in according "surrogate status" to PSA response.

Conclusion:

Based on the concerns and problems discussed above, I recommend non-approval of this application.

Solomon Sobel



SUPERVISORY MEDICAL OFFICER NDA REVIEW

NDA: 20-169 Nilandron (Nilutamide) tablets

FEB - 1 1996

Sponsor: GH Besselaar, NJ for
Roussel UCLAF, France

Submission date: December 13, 1995

Date of Review: February 1, 1996

Date of MO review: Initial draft: Jan 28, 1995
Revised: Feb 9, 1995
Modifications: Jan 31, 1996

This application includes the GH Besselaar response to the approvable letter dated 7 March 1995 for NDA 20-169. The approvable letter outlined specific actions required prior to approval.

In order to generate a clinical recommendation at this time I have carefully examined the original Medical Officer report (Feb. 1995), with reference to the sponsor's original NDA submission as needed. I have recommended extensive clarifications, corrections and modifications of the Feb. 1995 medical officer review. I have also noted the Jan. 1996 Medical Officer review of the resubmission.

The original NDA issues were presented at an Advisory Committee meeting on Feb 24, 1995. At that time the expert committee responded to the prepared questions as follows:

1. Do the studies (908 and 606) described provide adequate evidence of effectiveness in the intended patient population to support approval?

Yes--6 (2. reluctantly; 2. because study 908 is convincing and sufficient, though 606 is not)

No--1

2. Is the demonstrated efficacy in regard to progression sufficient to balance the animal toxicology results and the clinical adverse reaction profile of the drug?

Yes--6 (2. barely; 2. human toxicity seems rare)

No--1

Suggestions for further study from the Committee members:

- Undertake a Phase IV surveillance for toxicities.
- Include a quality of life assessment in the trials.
- Label the Indication for minimal disease because it seems more successful at the early stage.

After extensive internal discussion of the three main areas of concern-- including the adverse preclinical toxicology profiles, the adverse reaction profile in human studies and the non-replicability of the pivotal studies--the Agency proceeded with an "approvable" action and letter dated Mar 7, 1995.

The resubmission, as well as the original NDA relied on several small studies intended to evaluate pharmacokinetics, preliminary safety parameters and dose finding issues. Two larger trials were submitted to support the safety and efficacy of this product for use in the treatment of metastatic prostate cancer (stage D₂).

As was previously concluded, trial "908" did support the efficacy of this product in lengthening the time to death in Stage D₂ prostatic cancer patients who had undergone surgical castration. Trial "606" was not persuasive in convincing readers of the effectiveness in subjects treated concurrently with leuprolide. Thus the approvable action was for use of this product in the treatment of post-orchietomy patients only, and not for patients who have been chemically castrated.

The current submission includes proposed labeling which attempts to address the outstanding labeling changes requested in the March, 1995 letter. In terms of the clinical discussion, the proposed labeling is satisfactory but should be revised as follows:

CLINICAL PHARMACOLOGY

Mechanism of Action

Please revise last sentence to include the word

Clinical Studies

This section should include a short discussion of the second clinical trial as previously suggested. Thus, a third paragraph should be added which reads:

WARNINGS

Hepatitis

As per our previous letter, this section should read "

We also recommend a third paragraph to read:

The medical officer review of a recent adverse reaction report also recommends inclusion of a description of a newly submitted serious adverse event which involved elevated hepatic enzyme levels and death after use in a 65 year old man being treated for benign prostatic hyperplasia. Although not fully discussed in the MO review, it appears that this subject had no concomitant illness, drug use, or explanation for his hepatotoxicity and death other than nilutamide use. Thus, I concur with the MO recommendation to include a mention of this case in the warnings section under "hepatitis". For example the following sentence could be added:

PRECAUTIONS

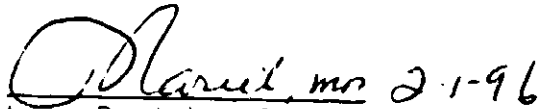
Drug Interactions

I agree with the sponsor's proposal to leave this section as "Drug Interactions". The hepatic enzyme level discussion can be included in the "hepatitis" section (see above).

RECOMMENDATION:

As per the previous action and the Advisory Committee recommendations, we anticipate approval of this NDA.

Labeling revisions should be incorporated as described above.

 *Lisa Rarick, MD*

Lisa Rarick, MD

Acting Deputy Director II

DMEDP, HFD-510

c:\wpfiles\20-169.smo

HFD-510/Sobel/Rarick/Fourcroy

NDA 20-169
Nilandron® (niulutamide) Tablets
Roussel-UCLAF (Besselaar Associates)

Group Leader's Memo

See Division Director's memo dated February 13, 1995

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-164 Trade (generic) names VILANDON (VILANDONAL) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

- ☐ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
- ☐ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(r) for A&MC studies in children.
- ☐ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- ☐ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
- ☐ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- ☐ a. The applicant has committed to doing such studies as will be required.
- ☐ (1) Studies are ongoing.
- ☐ (2) Protocols have been submitted and approved.
- ☐ (3) Protocols have been submitted and are under review.
- ☐ (4) If no protocol has been submitted, on the next page explain the status of discussions.
- ☐ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- ☒ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

~~Signature of Preparer~~

Date _____

cc: Orig NOA
HFD-___/Div File
NOA Action Package

NO ADVISORS

LLP

1/19/90

MAY - 2 1996

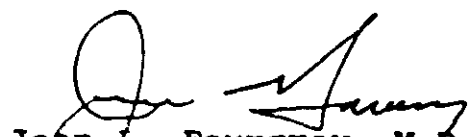
NDA 20-169
nilutamide/Nilandron
May 2, 1996

Re: requested label change regarding liver function

The sponsor has asked to substitute on page 5 of the proposed label the following:

The change is satisfactory except for two items which must be included:

This is in keeping with the current bicalutamide (Casodex) label and reflects our understanding of the potential liver toxicity of the antiandrogens.



Jean L. Fourcroy, M.D., PhD
Medical Officer
HFD-510
5/2/96

FEB - 1 1996

Re: NDA 20-169
Nilutamide - RU 23908/Nilandron
Sponsor: Hoechst Marion Roussel, Inc.
Contact: Carole Venetianer/Corning Besselaar
January 30, 1996

Summary

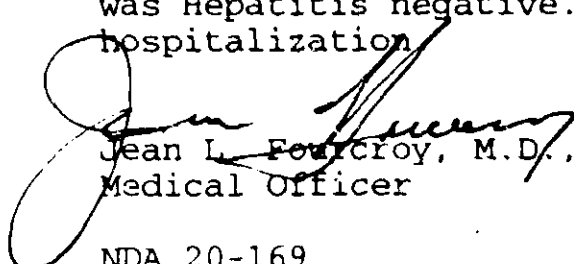
The Agency sent an approvable letter dated March 7, 1995 pending additional information necessary for approval of this NDA for nilutamide for the use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D2). The sponsor responded on December 13, 1996 with acceptable changes.

The following changes have been made as per FDA request:

- A new subsection of Animal Pharmacology and Toxicology to be added to the Precautions sections. This section clarifies the delayed dark adaptation. The addition is satisfactory.
- In the Dosage and Administration section the sponsor has deleted the sentence stating that

The final report regarding food bioavailability of Nilutamide after single oral administration has been provided to substantiate this change. The change is satisfactory.

A recently submitted serious adverse event dated 1/17/96 should be noted in the label, preferably in the Warnings Section under the discussion regarding hepatitis. A 65 year old man being treated for Benign Prostatic Hyperplasia presented on day 58 with jaundice and elevated liver enzymes. His ALT was 59 times normal, AST was 50 times normal and total bilirubin was 12.9. He was Hepatitis negative. He died two days later after hospitalization.


Jean L. Fourcroy, M.D., PhD
Medical Officer

NDA 20-169
HFD-510/J El-Hage/JFourcroy/1/30/96

1996

FEB 1 1996

1 Title and General Information

1.1 Title/Heading - Medical Officer's Review

1.1.1 NDA #20-169 (NDA #20-168 - original filing number)

1.1.2 M.O. Review

1.1.3 Submission March 7, 1994

1.1.4 Review completed January 28, 1995/Revised February 9, 1995/Revised January 30, 1996

1.2 Drug name

1.2.1 Generic name - nilutamide - RU 23908

1.2.2 Proposed trade name - Nilandron (Anandron)

1.2.3 Chemical name 5, 5,-dimethyl 3 - {4-nitro-3(trifluoromethyl)-phenyl} 2, 4-imidazolidine-dione

1.3 Sponsor: Roussel UCLAF, Romainville, France - Besselaar Associates, U.S.

1.4 Pharmacologic Category - non-steroidal antiandrogen low affinity binding of cytosol androgens (either testosterone or dihydrotestosterone) receptors in target organs. This peripheral androgen antagonist blocks by competition.

1.5 Proposed Indication: Indicated for use in combination with surgical castration or chemical castration with an gonadotropin agonist for the treatment of metastatic prostate cancer (stage D₂). This is palliative treatment of Advanced Prostate Cancer.

Prostate Specific Antigen (PSA) values should be monitored and patients whose values do not normalize by Month 3 should be reevaluated so that the benefit/risk ratio for continuation of treatment can be determined.

Maximum benefit from combination therapy is achieved in patients with good prognostic factors as reflected by baseline alkaline phosphatase equal or lower than twice the upper normal value for that laboratory.

1.6 Dosage Form and Route of Administration

1.7 NDA Drug Classification - P

1.8 Important Related Drugs: nonsteroidal antiandrogens,
e.g., flutamide.

1.9 Related Reviews :Statistics included in this review.

2 Table of Contents

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1	1	Title and General Information
	1.4	Pharmacologic Category:
	1.5	Proposed Indication:
	1.6	Dosage form
2	1.7	NDA Drug Classification
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3	4	Chemistry
3	5	Animal Pharmacology Toxicology
3	6	Clinical Background
15	7	Description of Clinical Data Sources
17	8	Clinical Studies
17	8.1	Trial # 908
22	8.2	Trial # 606
28	8.2	Supporting Studies
28	9	Overview of Efficacy
32	10	Overview of Safety
35	11	Labeling Review
36	12	Conclusions
36	13	Recommendations

3 Material Reviewed (volume numbers which serve basis for this review)

2.27 - Controlled Studies, Update and Predictive Analysis

2.38 - Integrated Summary of Efficacy

2.39 - Integrated summary of safety information

2.26 - 606 trial overview

2.24 - 908 trial overview

Desk copies of trials 908 and 606

Additional information - October 24, 1994 Safety Update

4 Chemistry - see Chemistry review.

5 Animal Pharmacology/Toxicology - see Pharmacology review.
A summary of the pharmacology review states that.

6 Clinical Background

6.1 Relevant Human Experience

- Incidence and prevalence of prostate cancer today

Today the incidence of cancer of the prostate has reached an estimated rate of 22% of all malignancies in men (1991). By the age of 50 up to 30% of men are found to have cancer of the prostate. The incidence for white men is estimated to be 122/100,000 and 132/100,000 for black men. The mortality rate in the black population is almost double that for white males. In the year 1992 there were 34,999 deaths from prostate cancer and 46,300 deaths for Breast cancer. (American Cancer Society) Although geographic differences in prostate cancer are known to exist no clear cause for this difference is known. Androgens and age are the only clear factors. Family of origin also plays a role. This is why guidelines for screening suggest a Digital Rectal Exam (DRE) and Prostate Specific Antigen (PSA) starting at the age of 50 for white males, 45 for black males and men with a close relative with a history of prostate cancer. Familial prostate cancer may account for 9% of prostate cancers with early age of onset of disease, and multiple affected family members (Carter, 1992)

- Staging of Prostate Cancer

In the U.S. the usual stage system for prostate cancer is the Whitmore-Jewett classification (see Appendix 3 for

complete description). World-wide the more common classification is the American Joint Committee for Cancer (AJCC) system. The following summary is true of all staging systems. Stage A is not found clinically; Stage B is palpable and confined to the prostate; Stage C is locally advanced to contiguous structures: bladder, seminal vesicles, and prostatic capsule; and Stage D is outside the prostatic adnexal area. Patients with D1 disease have presence of metastatic disease in the lymph nodes of the pelvis and Stage D2 patients have evidence of metastatic disease outside the pelvis. It is estimated that 25% of patients with newly diagnosed prostate cancer will present with distant metastatic cancer (Stage D2). This submission concerns studies for palliative treatment in men with Stage D2 prostatic cancer. This is defined as outside the pelvis in distant lymph nodes, bone or other organs.

Most patients presenting with symptomatic disease generally have cancer spread outside of the prostate gland and are incurable. The responses to androgen deprivation therapy are not durable and the cancers become hormone-refractory (Garnick, 1993). 75% of patients diagnosed with prostate cancer have clinical stage C or D disease at the time of initial diagnosis. The five year survival rate with treatment is approximately 72% for stage C disease. Stage D1 patients have a 5 year survival rate of 58% and patients with Stage D2 disease have a $\wedge$ survival rate of 2.5 years. (J Urol 1991. 146: 96-98.) median

(Impossible to compare 5-yr survival rates with median survival rates)

- Treatment of prostate cancer:

Metastatic PCA must be considered to be incurable (Griffiths). The purpose of treatment is to improve quality of life. 70% of men with metastatic diseases treated with androgen deprivation will experience a symptomatic and often a clinical regression

but most will relapse within 18 to 24 months.

There have been no advances in the treatment of Stage D since 1940 and the first hormone deprivation by orchiectomy and then DES. In 1984⁵ Leuprolide was first approved for medical castration but orchiectomy has remained the gold standard and the most economical approach. Labrie and the European community were the first proponents of blockade of the adrenal androgens and were the basis of the NCI 0036 studies comparing leuprolide with flutamide (the first antiandrogen) to leuprolide with placebo. This combination therapy for total androgen blockade was approved in 1988⁹. There is a continuing dialogue regarding the necessity of total androgen blockade and it's possible advantages. This

resulted in an international metanalysis pooling comparable studies.

Median life expectancy at time of progression is 6 months or less. It is not clear whether the quality of life is extended by any of these treatments.

Today there are two gonadotropins approved for medical castration: leuprolide (LUPRON - TAP) and goserelin (Zoladex - Zeneca). There is only one antiandrogen approved for use with a gonadotropin: flutamide (Eulexin - Schering). Two antiandrogens have been studied: nilutamide (Anandron - Roussel UCLAF) and bicalutamide (Casodex - Zeneca). The subject of this submission is nilutamide.

The **Efficacy Endpoints** used in most studies of Stage D prostate cancer are:

- Regression + stabilization
- Time to progression
- Survival time

Current terms and concepts:

CAT - combined androgen treatment

or

MAB maximal androgen blockade. OR **TAB** Total androgen blockade - primarily aimed to prevent the effect of metabolized adrenal androgens that may be present.

PSA - prostate specific antigen

ALP - alkaline phosphatase

PAP - Prostatic acid phosphatase

Review of concepts of meta-analysis of TAB

A total of 25 randomized trials have been identified to test the hypothesis that complete androgen blockade improves time to progression and ultimate survival time. A few of these studies are outlined in the following table. An attempt at meta-analysis has been undertaken to identify outcomes across comparable studies (see Cancer, December 15, 1992)

TABLE I ESTIMATES FROM COMPARABLE STUDIES

	RESPONSE RATE	PROGRESSION FREE SURVIVAL	DISEASE PROGRESSION	SURVIVAL
Leuprolide study group L (n=92) vs DES (n=94)				146 weeks L 136 weeks DES n.s.
NCI * 036 n=603			13.9 months 16.5 months	35.6 months vs 28.3 months
EORTC 30853 Zoladex/Flut vs orch ** n=327	n.s. between	increased with TAB	16.0 17.0 no diff	29.0 31.0 trends for surv
DAPROCA n=264			time to progression 16. months OR 16. months z/f	Median survival 27.6 months Or 22.7 months z/f
503 Anandron/ orchidectomy n=235 placebo/ orchidectomy n=201 33 inv.	13% nil 23% obs		time to obs 27.9 16 months vs 11.9 months obs	median 20.7 months 16.1 months 28.0 months not significant
505 Anandron/ LHRH n=209 placebo/LHRH n=202 33 inv. U.S.			median time to 27.9 26 months 11.5 months	not significant
Int PCA study grp Zolodex vs Zol+Flut n=571	obj response 67% ZOL 65% Zol/f		no difference in time to progression or time to failure	Time to treatment failure -n.s. 37.7 m Zol 42.4 m Zol/F

#* current submission

* patients with minimal disease and good performance status
received the greatest benefit.

Androgen Blockade:

It is estimated that there is a 90 to 95 % reduction in circulating androgens after removal of androgens either surgically, bilateral orchiectomy, or medically with estrogen (DES) or gonadotropin analogs. The first analog, leuprolide (Lupron), was approved in 1984 for the treatment of prostate cancer. Goserelin (Zoladex) was approved subsequently. Both of these analogs are approved only for the palliative treatment of Stage D2 prostate cancer.

Labrie and his group originally encouraged the concept of total androgen blockade on the basis of an increased 3 alpha diol, DHT thought to be metabolized via the adrenal DHEA to the prostate. This 7% adrenal origin androgens are the basis of all of the current studies. It is surmised that the adrenal androgens contribute 7 to 10% of the total androgens; total androgen ablation therapy is aimed to blocking the contribution of the adrenal androgens. Therefore in addition to either medical or surgical castration the addition of an antiandrogen was suggested. The first studies to test this theory were the NCI 0036 studies of leuprolide + flutamide versus leuprolide + placebo. This combination therapy was approved on the basis of these CI studies.

Prostate specific antigen:

Prostate specific antigen (PSA) has become an important marker in the management of prostate cancer patients.

- first identified in 1970 in prostate tissue
- identified independently in 1971 in seminal plasma
- identified as a serine protease which may play a role in semen liquefaction.
- identified as P-30 and routinely used as a rape marker
- approved by FDA as a diagnostic for identifying recurrence of prostate cancer.
- there is significant overlap in PSA levels between benign and malignant prostate tissue.

There are several issues concerning the use of prostate specific antigen (PSA) in the diagnosis, screening or follow-up of patients with prostate cancer. PSA was first approved by FDA for the diagnosis of recurrence of prostate cancer. Not until 1994 was PSA approved for the screening of prostate cancer in previously undiagnosed patients in conjunction with digital rectal examination. Prostate specific antigen is an androgen sensitive glycoprotein and may be increased independently by androgen stimulation. In addition it appears that the prolonged exposure to a nonsteroidal antiandrogen, e.g. flutamide, results in the selective proliferation of cancer cells containing a mutant androgen receptor that aberrantly recognizes flutamide metabolites

and nonandrogenic steroids as androgenic stimuli (Sartor et al, 1994).

The following PSA assays have been developed:

Hybritech*	Tandem E Tandem R Tandem ERA
Abbott*	IMX
Ciba Corning*	ACS
Toschmedix*	AIA pack

* FDA approved

It is important to remember that there are differing forms of the PSA molecule - both free and complexed. Further elucidation of these forms may increase the sensitivity and specificity of PSA in the future. The second generation of monoclonal assays have been termed ultrasensitive and are more specific and sensitive.

FORMS OF PSA

Free PSA	30kD
PSA-ACT	100kD bound to alpha ₁ antichymotrypsin
PSA-MG	~780kD complexed with alpha ₂ macroglobulin not immunoreactive. engulfed by inhibitor - not measured by any commercially available assay. (Christensson and Lilja, 1993)

The major forms of PSA circulating in serum are:

- Free PSA found in much lower concentrations in serum than complexed PSA is enzymatically nonactive.
- Complexed PSA - found in serum - irreversibly and covalently bound to alpha 1 antichymotrypsin and enzymatically nonactive.
- smaller quantities complexed to alpha₂ macroglobulin

These differences are important in comparing PSA assay results. One major assay may overestimate the free PSA and underestimate the complexed PSA.

Other methods to improve both the sensitivity and specificity of prostate cancer diagnosis and follow-up include differing ways to measure PSA:

- PSA density
Including a ratio of PSA with the volume of the prostate as measured by ultrasound.
- PSA velocity
Repeat measurements of PSA over time.
- PSA and AGE specific reference range.

Recent studies by Dr. Oesterling et al have further defined acceptable levels of PSA - Hybritech - by age based on a community based white male population (Minnesota).

TABLE AGE-RELATED PSA LEVELS (Hybritech)

PSA	AGE
0 - 2.5	40 - 49
0 - 3.5	50 - 59
0.0 - 4.5	60 - 69
0.0 - 6.5	70 - 79

PSA is not a perfect screening test for prostate cancer with up to 10% false positives. An ideal marker should have high sensitivity and specificity for distinguishing benign from malignant prostatic disease and provide prognostic information as well as improve treatment outcomes. The positive predictive value for PSA as a screen was only 47% (Powell). The margin of difference between benign and malignant is dependent on volume of tissue, grade of tissue and secretion into the plasma. Early detection has not yet been demonstrated to improve survival for men with prostate cancer.

FACTORS THAT DETERMINE SERUM PSA IN MEN WITH PROSTATE CANCER;

- Number of viable normal prostatic epithelial cells and the extent of differentiation of neoplastic prostatic epithelial cells
- hormonal milieu

- architectural integrity of the prostate gland and the location of malignant prostatic epithelium, either intraprostatic or metastatic.
- Rate of marker clearance.
(Petros and Andriole)

PSA REDUCTION (RESPONSE) AND PSA PROGRESSION (RELAPSE)

Castration, both medical and surgical, initiates extensive apoptosis of the secretory epithelial cells lining the ducts of the rat ventral prostate resulting in the striking reduction of male sexual accessory tissue.

Since PSA expression is influenced predominantly by androgens, the mutation of the receptor that can occur as prostate cancer cells become undifferentiated may affect the expression of the PSA gene.

A PSA increase is the first sign of progression after treatment in those patients with prostate cancer that secretes prostate specific antigen and a reduction in PSA is an indication of an apoptotic response by the prostate cancer cells. Elevation of PSA allows for identification of relapse at an earlier time than otherwise clinically evident. It is important to remember that poorly differentiated prostate cells may lose this ability to manufacture and secrete PSA. There appears to be an inverse relationship between histologic grade of the tumor and PSA production (Partin). It has been suggested that if the PSA decreases to less than 10 ng/ml at 6 months, the time to progression was 22.7 months and survival was 33.2 months; if the 6 month PSA exceeded 10 ng/ml time to progression was 12.5 and survival 18.8 months (Stamey).

The decline of PSA > 90% is thought to predict a prolonged progression free survival. A rise in PSA within the limits defined in the criteria for progression might be an indication for a change in therapy. It has recently been estimated by Soloway (1994) that responders with the lowest PSA (< 4) and a decrease in maximum PSA level by 95% or greater from baseline will have the best progression free intervals.

An example of this is seen in the percent reduction of PSA after 3 months of different doses of bicalutamide compared with surgical castration or flutamide (Dennis, Cancer supplement Dec 15, 1993 - 3890)

TABLE - PSA LEVELS WITH ANDROGEN DEPLETION

Bicalutamide monotherapy	10 mg	30 mg	50 mg	100 mg	150 mg
% PSA decline	57%	73%	90%	97%	97%
	medical castration	97%			
	flutamide	73%			

Androgen withdrawal and subsequent cellular apoptosis ultimately results in the relative enrichment of tumors with cells that are more undifferentiated and less responsive to hormonal therapy.

Additional chemical markers used for the monitoring of regression and progression of prostate cancer are:

Alkaline phosphatase - ALP
(reference: Chodak JAMA 1991 - 265: 618-621)

Prostatic acid phosphatase - PAP

Both of these markers have in large part been superseded by the use of PSA. PSA has also demonstrated its early sensitivity in progression of prostate cancer prior to clinical evidence. Changes in bone metastasis or pain will be preceded by elevations in PSA.

6.2 Important information from related drugs

The other antiandrogens that have been studied are:

- FLUTAMIDE - Eulexin

The active form is hydroxyflutamide which is thought to be twice as potent as Cyproterone acetate (CPA). It has a short half life of 5 - 6 hours and the dose is 250 mg tid for a total of 750 mg per day. The safety profile has been disappointing. There have been 20 reported deaths from hepatotoxicity and 26 patients who were hospitalized with serious hepatotoxicity. Other adverse events associated with flutamide are diarrhea and flutamide-withdrawal syndrome. The latter defined first by Sher reflects the agonist effect of flutamide on the androgen receptors.

- BICALUTAMIDE - Casodex

Refer to published material in Cancer

Agonist activity and withdrawal syndromes noted with flutamide and bicalutamide are probably common to all nonsteroidal antiandrogens and have been identified in the antiestrogen, tamoxifen. Reports were first noted with flutamide but have also been reported with bicalutamide. To date none have been reported with nilutamide.. It has been suggested that the prolonged exposure to flutamide results in the selective proliferation of cancer cells containing a mutant androgen receptor that aberrantly recognizes flutamide metabolites and nonandrogenic steroids as androgenic stimuli. (Sartor, 1994)

- Cyproterone Acetate (CPA) is a steroidal antiandrogen - closely related to structure to progestagens. CPA is a synthetic 21-carbon hydroxyprogesterone derivative which acts both centrally and peripherally and has both progestin and antigonadotropic properties. In the target prostatic cells it acts as a competitive inhibitor of the binding of dihydrotestosterone to cytosol receptor sites and inhibits the translocation of the androgen-receptor complex into the nucleus. In its central action it lowers LH and plasma testosterone because of its progestin-like activity. The side effects include thrombophlebitis in 5% of patients, fluid retention in 4% , gynecomastia in 13% and loss of libido in most men. The daily oral or injectable doses are 250 mg/day The mean duration of remission is 18 months (Goldenberg and Bruchovsky - Urol Clin 1991 : 18 : 111-122)

It is important to remember that little or no advances in the treatment of advanced prostate cancer have been made since the initiation of androgen ablation in 1939 by Huggins and Hodges. No other disease has such large economic and quality of life impact as advanced prostate cancer. It may be that the worst treatment we offer is continued androgen ablation allowing the growth of further undifferentiated cells. Only early detection and removal of the tumor has long term benefits and even then it is not known which prostate cancers needed treatment.

IND IND dated April 21, 1983 review April 21, 1983.

(Labrie - Canadian study) The dose was 100 mg T.I.D. and buserelin 500 mg per day sc. (discuss buserelin). 37 patients had no previous therapy and were treated from 1 - 12 months; 23 previously treated with DES and 7 castrated. The review states that results were not as good in patients previously treated by orchiectomy or DES but some drop in acid phosphatase.

Original doses planned were higher pushing to toxic levels and the sponsors thought that there was good tolerance

at daily doses of 300 to 600 mg. Several studies defined as the safe dose 300 mg per day or less.

Early studies with buserelin suggested improvement in pain within first weeks of treatment with the addition of nilutamide (Page 17 volume 2-2). Interestingly there is not an immediate decrease in testosterone although there is an early drop in alkaline phosphatase and prostate specific antigens. Studies F/85/908 and F/82/908/01 are thought by sponsor to demonstrate that nilutamide was effective in inhibiting the potential adverse effects associated with the initiation of LHRH agonist therapy.

6.3 Foreign experience

This drug has been approved in 28 states including Canada. It has not been approved in the U.K. It has been determined that the risk to benefit ratio is not satisfactory (from submission). The sponsor states that it is currently under review (telephone conversation with Dr. Ulman).

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics see Pharmacology review

The company has submitted 14 human pharmacokinetic studies which include bioavailability and pharmacokinetic studies. These have been included in the pharmacology review. The 300 mg dose for the first 30 days was chosen from initial studies. Study 8/78/2 was an uncontrolled pilot study to assess the safety and tolerance of nilutamide administered orally using 50 mg tablets for 7 days at doses of 50, 100, 300 and 600 mg/day to 18 hospitalized patients with metastatic prostate cancer who had failed other treatments. Demonstration of increasing plasma LH and testosterone concentration was noted. Increasing doses 300 mg and higher were associated with gastrointestinal symptoms. Treatment dose of 600 mg was associated with methemoglobinemia in one patient and anemia in one patient at 300 mg/day.

Study 9/79/1 was an uncontrolled pilot study at doses of 900 mg/day for 3 months in 4 hospitalized patients who had failed other treatments. One patient of 4 treated for 6.5 months had improvement in urinary symptoms and 'well-being' a decrease in prostate volume and PAP and an increase in hemoglobin concentration. The other patients had to discontinue this dose because of malaise, dizziness, and vomiting. It was concluded that doses of 300 mg tid (total 900 mg) could not be tolerated.

One of the four pharmacodynamic studies, NL/84/908/06, was done in 17 healthy men from 19 to 33 desiring gender reassignment. They received 150 mg bid (300 mg) for 8 weeks followed by addition of 100 µg of ethinylestradiol to the nilutamide for 16 additional weeks. In this study a full analysis of the androgen profile was monitored. This included androstanedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, estrone, estradiol, prolactin, sex hormone binding globulin (SHBG) luteinizing hormone (LH and follicle-stimulating hormone (FSH which were measured before and after four and eight weeks of treatment. 16 of the 17 completed the first eight weeks and seven subjects completed the full course of the study. One subject developed abnormal liver function and severe bone marrow depression. four subjects developed liver enzyme concentrations outside the normal range. and in two of these the enzyme concentrations returned toward normal in two of the patients. The third had return to normal after treatment discontinuation. The submission does not indicated at what point in the study.

Study F/85/908/10 was the first double-blind, placebo-controlled study to evaluate efficacy of treatment. 36 men with stage D2 prostate cancer and no previous therapy were evaluated for clinical symptoms such as the increase in metastatic pain. PSA in addition to PAP were used as markers. The men were treated with buserelin + nilutamide (300 mg) or buserelin + placebo. Hormonal assays included, LH, FSH, DHEA, DHEAs, estradiol and cortisol. A statistical difference in exacerbation of pain in patients with pain at baseline was noted (5/17, 29% placebo {n=19} vs 12/19 treated {n=17} , 63% with a p, 0.05). The chart (figure 1 of submission) demonstrates a rapid decrease in bone pain expressed as percentage change on a 100 mm visual analog scale. This chart also demonstrates the increase in pain in the first week of analog treatment consistent with 'flare'. There is a delayed associated change in the PAP levels and PSA. Testosterone levels reached castrate levels of 0.2 only after 18 days of treatment with combination treatment. Those men treated with buserelin alone never reached castrate level. Visual disorders consistent with nilutamide treatment was noted similar to that in larger trials. There were no reports of liver profile changes.

Adrenal function was evaluated in study FF/86/305/ANA/005. This study included 18 men with prostate cancer - both Stage C or D. The orchiectomy as done 45 days prior treatment. This study was done to determine if there were any adrenal hormonal changes. No significant differences were identified in

hydroxyprogesterone, androstenedione, androstenediol, DHEAs, or DHEA.

See Pharmacology review for full discussion of these studies. These studies were designed to demonstrate that the addition of nilutamide reduces bone pain and prevents the rise in the PAP and PSA.

6.5 Directions for use based on doses in pivotal trials:

The patients received 6 tablets of 50 mg (300 mg) nilutamide to be taken in the morning with water for the first month; subsequent doses after the first month were 3 tablets of 50 mg (150 mg). Doses were initiated with daily subcutaneous leuprolide in 606 and one day after the surgical castration in study 908.

7 Description of Clinical Data Sources

7.1 Study type and design/patient enumeration, demographics, extent of exposure

2,168 patients with prostate cancer have been treated with nilutamide in combination with surgical or medical castration between 1978 and 1989. 682 patients have been treated for 12 months or longer. There are 10 double-blind placebo-controlled studies, three uncontrolled studies, and seven studies for indications not included in the proposed labeling presented in this submission.

DOUBLE-BLIND PLACEBO-CONTROLLED STUDIES

Study NO.	Duration
*FF/86/908/01	18 months
*GHBA-606	18 months
CDN/83/908/05	24 months
F/82/908/03	24 months
F/82/908/01	24 months
F/84/908/01	24 month
CH/85/908/05	24 months
ZA/85/908/02	24 months
FF/86/ANA/01	6 months
F/85/908/10	28 days.

* PRIMARY CLINICAL TRIALS REVIEWED.

The primary parameters for the evaluation of efficacy used in the primary studies were best response to treatment (using modified NPCP criteria - refer to appendix) time to objective progression (i.e., progression-free survival), time to death due to prostate cancer (i.e., prostate cancer survival 908, and time to death due to any cause (i.e., overall survival). (See appendix)

Except for Study No. F/85/908/10, the primary parameter for the supportive studies was best objective response (NPCP criteria), with time to progression, time to death due to prostate cancer, and time to death due to any cause as secondary parameters. Other secondary parameters for efficacy were improvement in metastatic related pain, performance status, prostatic acid phosphatase (PAP), prostate specific antigen (PSA) (in the primary studies), bone scan isotope uptake, tumor volume, and alkaline phosphatase (ALP). Improvement in bone scan isotope uptake and tumor volume were not analyzed in some of the secondary studies. In Study No. F/85/908/10, a one-month study, the effect of nilutamide on pain, on laboratory markers of tumor activity (PAP, PSA, alkaline phosphatase), and on hormonal levels (e.g., testosterone, LH, and FSH) was evaluated as described in section 6.4.

Symptoms, metastatic related pain and urinary obstruction were rated on a three point scale (1=none, 2=moderate, 3=severe) and performance status on a five-point scale (from 1=normal to 5=bedridden).

Treatment differences were compared by means of the Wilcoxon rank sum test on the changes from baseline in the severity scores. The comparison was made only for visits performed at Months 1, 3, and 6.

After the sixth month, the number of patients withdrawn for progression became high and, for the patients withdrawn between two visits, no information on symptoms was available at the time of progression. Hence, the comparison between treatment groups after six months was biased, since it excluded all the patients withdrawn for progression between two visits. Prostatic acid phosphatase and alkaline phosphatase treatment differences were compared by means of the Wilcoxon rank sum test on the percent differences from baseline value. The raw data were first standardized so that the differences between assay methods would be erased. For symptoms, the comparison was made only for the first three visits on treatment. Best Response to treatment (NPCP criteria) among the objective responses were evaluated every 6 months, the best one for each patient was retained for the comparison of treatment groups. The percentages of regressions (partial or complete) and of regressions + stable diseases were compared by means of the likelihood ratio chi square test. Time to progression and time to death actuarial rates were computed by means of Kaplan Meier estimate and compared by means of the logrank test and the Gehan Wilcoxon test. Regarding time to progression, the date of progression was not recorded for some patients even though there had been a progression. In those cases, the date of progression was defined as follows: the patient never responded to treatment; the date of progression was taken as the date of

beginning of treatment plus 5 days but the treatment was stopped due to progression before the next planned visit. When the treatment was stopped for a reason other than lack of efficacy and a progression was not recorded in the CRF, the patient was censored at the time of treatment discontinuation. This description is from the sponsors submission.

A responder was identified as a patient with one with a PSA of less than 4.0 (Hybritech- 908 trial) or 2.5 (Pros-check 606 trial) at the 3 month visit.

7.2 Post-Marketing Experience

Nilutamide (Anandron) is approved in 28 countries. It has not been approved in the United Kingdom because of the risk versus benefit ration.

8 Clinical Studies

8.1 Trial # Study No. FF/86/908/01
(also known as GHBA 608/ U.S. GHBA 610)

*FF/86/908/01	nilutamide 300 mg + orchiectomy (150 mg > 30 days) versus placebo + orchiectomy	18 months 66 investigators International

Summary:

The median time to progression was longer for nilutamide patients - 19 months vs placebo patients - 14.9 months

The median survival time (any cause) was 28.3 months in the nilutamide group and 23.2 months in the placebo group. This was not statistically significant for the overall survival but close to statistical significance for the cancer-related survival (0.058; 0.006 from two sources)

8.1.1 Objective

This was a double-blind, randomized, placebo-controlled study to compare the efficacy and safety of nilutamide in combination with orchiectomy with that of orchiectomy alone - in the treatment of patients with previously untreated prostate cancer. The long-term safety and

tolerance of nilutamide in the treatment of prostate carcinoma (Stage D₂) was also to be determined.

8.1.2 Design

Starting on the day after orchiectomy, patients received either nilutamide (300 mg/day p.o. for one month followed by 150 mg/day p.o. thereafter) or placebo p.o.; the patients continued the double-blind medication until objective disease progression, the occurrence of an adverse experience, or any other event necessitating withdrawal from the study. Patients whose disease progressed while receiving nilutamide could continue nilutamide (150 mg/day, p.o.) on an open label basis following study discontinuation, while patients who had been receiving placebo were not permitted to receive nilutamide. Enrollment dates were June 1986 through February 1988; and cutoff date for data collection was 31 August 1989. The patients were randomly assigned to receive either nilutamide or placebo in a 1:1 ratio. The patients were assigned patient numbers in ascending order beginning with the lowest available number.

Two hundred seven of the 225 (92%) nilutamide patients and 216 of the 232 (93%) placebo patients were judged evaluable for efficacy analysis.

8.1.3 Protocol

8.1.3.1 Population

*FF/86/908/01	Race:	Countries:
	418 white	USA
	15 black	Europe
	18 Hispanic	Canada
	4 oriental	S American
	2 other	S. Africa

8.1.3.2 Endpoints

- Best Response To Treatment

Complete Or Partial Tumor Regression At Some Time
During The Study.

- Time To Objective Progression Or Progression-Free Survival
(NPCP criteria attached to appendix)
- Time To Death Due To Prostate Cancer

- Time To Death Due To Any Cause.

Secondary parameters:

- Improvement In Metastatic Related Pain
- Performance Status,
- Prostatic Acid Phosphatase -Pap
- Prostate Specific Antigen - PSA
- Alkaline Phosphatase - ALP
- Bone Scan Isotope Uptake
- Tumor Volume

8.1.3.3 Statistical review

(see complete statistical review)

Summary statement: from statistical review

"Study 908/01 provides statistical evidence of a lengthening of approximately 4 months of median time to objective progression. There is a suggestion of lower mortality due to prostate cancer, (p-value less <.10.)."

8.1.4 Results

8.1.4.1 Patient Disposition, comparability

Patient Disposition: A total of 457 patients with a primary diagnosis of previously untreated metastatic prostate carcinoma Stage D2 were enrolled in the study; 225 patients were randomized to receive nilutamide and 232 were randomized to receive placebo. 92% nilutamide and 93% placebo patients were evaluable. 415 patients entered and 164 completed. 34 patients were not evaluable: 18 were on nilutamide and 16 on placebo. The age for all patients ranged from 49 - 85 years with an average age of 71.2. 91% of enrolled patients were white.

Of the 350 patients who discontinued from the double-blind phase of the study, 199 (85 nilutamide, 114 placebo) discontinued because of objective progression, 28 (13 nilutamide, 15 placebo) because of subjective progression, 55 (35 nilutamide, 20 placebo) because of adverse experiences including intercurrent events, and 68 (35 nilutamide, 33 placebo) because of other reasons.

DISCONTINUED	NILUTAMIDE	PLACEBO
OBJ PROG	85	114
SUBJ PROG	13	15
ADVERSE EXP	35	20
OTHER	35	33

8.1.4.2 Efficacy endpoint outcomes

PERCENT (NUMBER) OF PATIENTS WITH COMPLETE OR PARTIAL REGRESSION#							
		nilutamide		placebo			
FF/86/908		41%		24%			p <0.001
	evaluable by NPCP	21/75		44/182			
			# best response at some time during the study				
PROGRESSION AS BEST OBJECTIVE RESPONSE							
FF/86/908		22%		36%			p 0.002
		39/175		66/182			
DIED OF PROSTATE CANCER		32%		40%			p=0.006
		53		86			
DIED OF ANY CAUSE		45%		52%			
		95		113			

MEDIAN TIME TO PROGRESSION						
FF/86/908		20.3 months		14.7 months		protocol 908/o1 attachment A.2.1
previous analysis		19 months		14.8 months		
FEWER OBJECTIVE PROGRESSIONS		50% 103/202		61% 126/208		no p value
Median Survival time		28.3 months		23.2 months		n.s p=0.145

The median survival time for any cause was 28.3 months in the nilutamide and 23.2 months in the placebo group. The difference in survival between the treatment groups was close to statistical significance for the cancer-related survival $p = 0.058$ and not statistically significant for the overall survival (0.145.)

Significantly more nilutamide patients (41% or 72/175) than placebo treated patients (24%, or 44/182 patients) had complete or partial tumor regression. The median time to progression was 19.0 months in the nilutamide group and 14.9 months in the placebo group.

Statistical differences in reduction in pain and ALP and normalization of PAP were seen at one month. PSA was significant at 3 months and 6 months. (Not available for all patients at one month.)

8.1.4.3 Safety comparisons

84% of nilutamide treated patients (188/225) and 78% of placebo patients (182/232) had one or more adverse experiences regardless of relationship to medication. 54% (nilutamide) versus 31% (placebo) adverse events were thought to be related to drug. There are several major areas of concern that effect the pulmonary, visual, gastroenteric and hepatic systems. In addition the drug appears to be associated with alcohol intolerance in 5% (11) of the patients. The major adverse events seen with nilutamide were:

pulmonary - Respiratory disorders appear to be the most troubling of the adverse events supposedly reversible upon discontinuation of treatment. In this study 17% (38) nilutamide patients and 15% (35) placebo patients had some respiratory disorder.

Seven (3.1%) nilutamide patients versus one placebo patient withdrew from the study because of respiratory disorders. Interstitial pneumonitis was diagnosis in one of the seven nilutamide patients, which resolved after discontinuation. A second patient demonstrated x-ray findings without respiratory symptoms while the other 5 patients had either dyspnea without other signs or symptoms of interstitial lung disease or unrelated respiratory events, supposedly. The time interval was within the first 3 months and usually in the first month. **It must be assumed that any dyspnea is a symptom of interstitial pneumonitis. This may have a relationship to the higher dose of nilutamide in the first 30 days.**

Visual - Visual disorders were frequently reported and related clearly to nilutamide. 20 (13% patients in the treated group and 3 (1%) patients in the placebo group reported impaired dark adaptation and. Abnormal vision was reported in 13 (6%) nilutamide patients and four (2%) of placebo patients. Chromatopsia, impaired light adaptation, and photophobia each

occurred in 3% of nilutamide patients and in no placebo patients.

hepatic - Since hepatic lesions are noted in the animal studies it is important to focus in on this adverse experience. One patient in the nilutamide group had hepatitis which resolved after treatment discontinuation and "one patient who had entered in the study in spite of marked liver dysfunction before inclusion, suddenly deteriorated and died after 47 days of treatment".

GI - Gastrointestinal symptoms occurred more frequently in the nilutamide group ($p=0.044$). this included constipation, nausea (9%) vs 6% vomiting 4% and 3% .

anemia occurred in 4% of nilutamide patients and 7% of placebo patients.

8.1.5 Reviewer's Comments

The sponsor has not demonstrated any survival advantage in this submission; however there is an advantage in the 908 trials in percent of patients with complete or partial regression, progression as the best objective response and death from prostate cancer. The secondary endpoints of pain from cancer and chemical markers of PAP and ALP improved statistically by one month with statistical improvement over placebo group in PAP, ALP and PSA (not drawn at one month) by 3 months. These biochemical assays probably reflect regression of tumor. Although there is no advantage with nilutamide treatment with survival the addition of nilutamide does offer some additional progression free time as evidenced by complete and partial regression (41% nilutamide versus 24% placebo; progression as best objective response 22% nilutamide vs 36% placebo). This edge may be of clinical importance to the patient for the short period in the control of symptoms.

Although it is clear that there is a drug related increase in respiratory, visual and gastrointestinal symptoms no hepatic toxicity is truly noted in this study. It can be assumed that every case of dyspnea associated with drug use.

8.2 Trial # Study No. GHBA-606 leuprolide study

*GHBA-606	Nilutamide 300 mg (150 >30 days) + leuprolide versus placebo + leuprolide	18 MONTHS 38 investigators Domestic

Summary:

No difference in progression as best objective response, early progression. Only the percent patients with complete or partial regression demonstrates a difference between treatment groups.

Median time to progression was 25.0 months in the nilutamide group and 24.5 months in the placebo group

Median survival time cannot be calculated because only 42% of the evaluable patients had died as of the data cutoff point.

"The significant improvement for the nilutamide group compared with the placebo group in the number of complete or partial tumor regressions and in the secondary efficacy parameters such as pain, performance status, and laboratory evidence of disease clearly show the efficacy of nilutamide." from sponsor submission.

8.2.1 Objective

A double-blind, randomized, placebo-controlled study to compare the efficacy and safety of nilutamide in combination with leuprolide with that of leuprolide alone in the treatment of patients with previously untreated prostate cancer (Stage D2) followed by an extended treatment period to evaluate the long-term safety of nilutamide in 38 centers in the United States.

8.2.2 Design

Patients were randomized to be started on leuprolide 1 mg/day subcutaneously in addition to nilutamide at 300 mg/day for the first month which was decreased to 150 mg/day thereafter or placebo with leuprolide.

If objective progression occurred patients were withdrawn from the study but nilutamide patients could continue to receive the drug on an open label.

8.2.3 Protocol

A total of 411 patients: 209 nilutamide and leuprolide and 202 received placebo plus leuprolide. 292 patients discontinued from the double blind phase ; 153 with objective progression (73 nilutamide and 80 placebo). An additional 37 patients withdrew because of subjective progression (20 and 17 respectively) and 65 because of adverse experiences (41 nilutamide and 24 placebo). 37 withdrew for other reasons. 21 patients (12 and 9) were not evaluable for efficacy analysis. The average age was 67 years of age.

8.2.3.1 Population, procedures

GHBA-606	Race:	Country:
	319 white	
	80 black	USA
	11 Hispanic	38 investigators
	1 oriental	

8.2.3.2 Endpoints (both trials used the same endpoints)

- Best Response To Treatment

Complete Or Partial Tumor Regression At Some Time During The Study.

- Time To Objective Progression Or Progression-Free Survival

- Time To Death Due To Prostate Cancer

- Time To Death Due To Any Cause.

Secondary parameters:

- Improvement In Metastatic Related Pain
- Performance Status,
- Prostatic Acid Phosphatase -Pap
- Prostate Specific Antigen - PSA
- Alkaline Phosphatase - ALP
- Bone Scan Isotope Uptake
- Tumor Volume

Assessments were made as for the previous study at months 0, 1, 3, 6, 12, and 18 months continuing every 6 months during the continued treatment.

8.2.3.3 Statistical discussion

see statistical review

Notes from statistical review:

- The resulting progression-free survival and survival profiles are essentially superimposable without evidence of any trend in either treatment group's favor.
- The results for Best Response to Treatment according to NPCP criteria were mixed. After excluding 33 patients with no NPCP data, the p-value was .037 for regression (57% on drug, 46% on placebo). However with regression grouped with stable disease, the p-value was .254.
- Change in metastatic pain demonstrated no statistical differences; approximately 65- 70% of the patients improved from baseline up to 3 months after randomization.
- Karnofsky improvement was demonstrated only at 6 months
- Survival analysis that was restricted to the groups of patients with a PSA of less than 4 ng (hybritech) at 3 months failed to show any survival advantage in the nilutamide-treated group.
see statistics for further conclusions

8.2.4 Results

8.2.4.1 Patient Disposition, comparability

The patients in both arms of the study were deemed comparable on basis of age, race, metastatic related pain urinary obstruction, Karnofsky performance status, testosterone, hemoglobin, PAP, PSA and ALP and tumor burden. Only the length of time between diagnosis and treatment differed between groups; the nilutamide patients having had a significantly longer mean duration of time from diagnosis by 2.2 months than placebo (1.2 months).

Patients who discontinued the study were similar between the arms except for adverse experiences.

TABLE - DISCONTINUED PATIENTS

Study 606 DISCONTINUED	NILUTAMIDE	PLACEBO
OBJ PROG	73	80
SUBJ PROG	20	17
ADVERSE EXP	41 (20%)	24 (12%)

OTHER

18

19

8.2.4.2 Efficacy endpoint outcomes

PERCENT (NUMBER) OF PATIENTS WITH COMPLETE OR PARTIAL REGRESSION# AT SOME TIME DURING TREATMENT							
		nilutamide		placebo			
PERCENT PATIENTS WITH COMPLETE OR PARTIAL REGRESSION#							
GHBA-606		54%		43%			P =0.020
		92/169		71/165			
		# best response at some time during the study					
PROGRESSION AS BEST OBJECTIVE RESPONSE							
GHBA-606		15%		19%			
		26/169		31/165			p=0.446
FEWER EARLY PROGRESSION ON OR BEFORE MONTH 12							
GHBA-606		19%					
		19% 54%		25%			
		37/194		47/191			
MEDIAN TIME TO PROGRESSION							
FROM INTEGRATED SUMMARY		2.5 MONTHS		24.5 MONTHS			

Median survival time has not been reached

The sponsor believes that the best objective response, including complete and partial response, was significantly greater between treated and placebo patients. However, there is no difference between the other endpoints. Median survival time has not been reached.

At month 1 there was no statistically significant difference between treatment with respect to change from pretreatment in metastatic related pain. but a larger proportion of patients than placebo patients improved (60% vs 49%). There is no difference statistically either at month 3 or 6.

There is a statistical difference in median changes and normalization from baseline at 1 and 3 months for PAP, PSA and ALP as well as statistical changes in normalization of PSA favoring nilutamide. Cancer pain improves (p=.065) between treatment arms at the first time measured 6 months. **Normalization** of PSA occurred at month 1, month 3 and month 6 statistically favoring the nilutamide treated arm. Normalization is defined as at or below 2.5 using the Proscheck assay.

8.2.4.3 Safety comparisons

The major adverse events seen with nilutamide versus placebo appeared similar to the 908 trial except for the increase in Impaired dark adaptation in the 606 trial.

pulmonary - Interstitial Lung disease is listed in 7 (3.3%) of patients versus 1 (0.5%) placebo group. The update for 606 identifies this number as 8 patients or 4% of the patients and in one - 1% placebo patient with Interstitial lung disease. There are 22 patients in treatment arm (10.5%) versus 13 (6.4%) with dyspnea which may be a more sensitive sign of drug-related pulmonary problems. In addition 10 versus 6 patients had pneumonia (4.8% vs 3.0%) although the reverse is true for upper respiratory infection. The increase incidence of dyspnea should be considered a possibly related to interstitial pneumonitis.

The sponsor believes that the **interstitial lung disease was severe in five of the eight cases, mild in one and moderate in one.** All cases presented with progressive exertional dyspnea and seven had confirmed x-ray findings with alveolar-interstitial changes. All seven patients recovered. The eighth case had rib metastases thought to be the cause of the dyspnea. (case reports from NDA attached in appendix).

visual - Dark adaptation was the most frequent adverse event with a delay of a few seconds to 30 minutes in adaptation to darkness. Five minutes was the most common time. A total of 118 patients (56.5%) versus 11 (5.4%) reported impairment of dark adaptation. Two patients withdrew from the study because of this problem. 48 cases are thought to have resolved during treatment. An additional 18 reports (8.6%) complained of chromatopsia and 15 (7.2% versus 2 (1%) complained of light adaptation impairment. These disorders are drug related and may be dose related.

hepatic - In all patients increases in SGOT and SGPT occurred in 26 (12%) and 19 (9%) patients. One case of jaundice was noted in a placebo treated patient. One nilutamide patient (117) was discontinued due to elevated GOT/SGPT values on day 86 of the study with an elevation of 499 U/L and 776 U/L respective enzymes.

GI - Nausea occurred in 52 (25%) of nilutamide treated patients. The majority of the nausea complaints were related to the 300 mg dose. There were no changes in RBC, SGOT, SGPT or glucose noted.

8.2.5 Reviewer's Comments

A significantly higher proportion of nilutamide patients than placebo patients demonstrated a better response to complete or partial tumor regression at some time during the study. There is not a statistically significant survival advantage demonstrated with the addition of nilutamide to leuprolide treatment. Neither survival time or time to objective progression are mature enough according to the sponsor to detect significant differences since only 42% of the evaluable patients had died at the time of the data cutoff.

The study does not provide adequate data demonstrating efficacy with the addition of nilutamide. This was partially due to the patient population in this study who did extremely well regardless of treatment.

8.3 - Supporting studies

The sponsor has provided an additional eight randomized, double-blind, placebo-controlled trials of nilutamide in combination with orchiectomy in patients with metastatic prostate cancer who were previously untreated in this submission. This included: Study Nos. **CDN/83/908/05** {with buserelin}, **F/82/908/03** {orchiectomy and two doses of nilutamide 300 and 150}, **F/82/908/01** {3 studies comparing orchiectomy, buserelin and DES arms}, **F/84/908/01** {orchiectomy - Stage C and D}, **CH/85/908/05** {orchiectomy - only 300 mg dose}, **F/85/908/10** {Buserelin}, **ZA/85/908/02** {orchiectomy - only 300 mg dose}, **FR/86/ANA/001** {orchiectomy - 300 mg dose}. Each of these were small studies and a review is not included at this time. (see list on page)

9 Overview of Efficacy :

In neither of the studies is there any demonstration of a survival benefit. If any improvement is to be seen it is in the early treatment stages to stop progression. The 908 trial provides data demonstrating a clear advantage; significantly more nilutamide patients than placebo treated patients had a complete or partial tumor

regression. The median time to progression was 19.0 months in the nilutamide group and 14.9 months in the placebo group. Statistical differences were seen in the reduction of pain, and normalization of PAP and ALP by 3 months. These are important benefits and suggest that quality of life will be clinically improved. These biochemical assays may reflect regression of tumor. Progression-free survival time is a small but important addition for many men with prostate cancer.

The second trial, 606, demonstrates neither survival nor the short term benefits one should gain with the addition of an antiandrogen. Although there is an increased percent patients with complete or partial regression there is no other evidence of a benefit over placebo patients. The proportion of responders in the placebo group is larger than placebo patients in 908. The difference in median times to objective progression is not significantly different between the two arms of the study (25.0 and 24.5 months for the nilutamide and placebo patients respectively).

The difference between the two survival curves in 908 was not statistically significant. The median survival was 28.3 months in the nilutamide group and 23.2 months in the placebo group ($p=0.058$). The median time to death due to prostate cancer had not been reached in study 606.

Other endpoints that should benefit the patient's quality of life include pain and markers of regression of cancer cells and bone involvement. In 606 with respect to change in metastatic pain, there were no statistical differences with approximately 65 - 70% of the patients improving from baseline up to 3 months after randomization. Among those with pain at baseline in study 908 at 3 months, 85% of the nilutamide patients had improved over placebo ($p=0.001$); at 6 months 80% had improved over placebo ($p=0.06$). (see statistical review for further discussion)

Pain: The improvement at 1 month in metastatic related pain is 52 vs 41% in Study 908 and 39 vs 28% in Study GHBA 606.

METASTATIC RELATED PAIN - EVALUABLE PATIENTS

	FF/86/908/01		GHBA-606	
	Nilutamide	Placebo	Nilutamide	Placebo
Month 1	198	204	197	193
Improved	52%	41%	39%	28%
Month 3	185	192	186	186
improved	59%	42%	44%	38%

NORMALIZATION OF PAP

(to normal range for individual labs):

PAP	FF/86/908/01		GHBA-606	
	Nilutamide	Placebo	Nilutamide	Placebo
Month 1/n	43/85	23/71	61/116*	36/124
normalize	51%	32%	53%	29%
month 3/n	59/90	34/68	75/106	50/103
normalize	62%	50%	71%	49%

page 000028 Integrated efficacy
volume 2.38

When these studies were initiated PSA was just beginning to be used widely. In study 908 54% of nilutamide and 63% placebo patients had PSA data. In study 606 58% of nilutamide and 68% of placebo patients had PSA data.

NORMALIZATION OF PSA To Normal Levels in Patients with PSA Evaluations

PSA base elevated	FF/86/908/01 hybritech 4 ng		GHBA-606 Pros-check 2.5 ng	
	Nilutamide	Placebo	Nilutamide	Placebo
Month 1	18/107	14/99	41/112	15/116
normalize	17%	14%	37%	13% #
Month 3	62/108	25/90 #	77/101	51/99
normalize	57%	28%	76%	52% #
Month 6	50/88	22/79	75/96	51/87
	57%	28% #	78%	59% ##
Endpoint	53/128	23/116	69/127	53/127
	41%	20% #	54%	42%

Note that not all patients had PSA evaluations

#P = 0.001

p = 0.003

It is noteworthy that only 7 patients in FF/86/908/01 and 2 patients in GHBA-606 had normal

PSA (below the upper limit of normal) levels at the time of inclusion.

ALKALINE PHOSPHATASE

	FF/86/908/01		GHBA-606	
	Nilutamide	Placebo	Nilutamide	Placebo
Month 3	29/110	25/122	30./83	11/85
	26%	12% #	36%	13%
Month 6	41/100	39/106	44/78	23/77
	41%	28% ##	56%	30% #

0.005 ##0.039

(page 8 of volume 2-38 states that changes from baseline in PAP and ALP were categorized as increase by 25% or more, no change or decrease by 25% or more.)

From the statistical review:

- 1) The proportion of responders in the 'placebo' group in study 606 was substantially larger than that in Study 908/01.
- 2) The survival profile of placebo patients in study 606 was better than that of the nilutamide patients in study 908/01.
- 3) The general condition of evaluable patients in study 606 was better than those in study 908/01. Patients in the latter were older, had more urinary obstruction and lower average Karnofsky status.

Regarding Surrogate Markers or positive predictors:

The sponsors have reanalyzed the data to identify a predictive marker in terms of progression-free interval at 3 months and overall survival in both the studies.

The sponsors believe that normalization of PSA (to the upper limits of normal of that assay) 3 months after initiation of therapy are a good predictive marker in terms of progression-free interval and overall survival in those patients whose **initial ALP was less than twice upper limit of normal.** They believe this to be true in both trials. PAP, a non-specific marker, is unrelated to the outcome; this is not surprising.

The sponsors further suggest that if the ALP is above twice the upper limit of normal at inclusion than the normalization of PSA is marginal at best. This is somewhat similar to the sub-group analysis of the NCI 0036 trials where the true benefit of treatment appears to be in the group with the minimal disease severity.

A full discussion of the predictive marker analysis is included in the statistical review of David Hoberman.

10 Overview of Safety

At time of the submission of this NDA over 3,195 patients had been treated with nilutamide. This included 3,102 men with prostate cancer, 19 with other cancers, 9 women with polycystic ovarian disease and 65 healthy subjects. Over 10,000 patients with prostate cancer have been treated for over two months in several countries. It would appear that only 88 patients have been on nilutamide as monotherapy and this included the women subjects

There are slight discrepancies in total numbers which probably reflect differences between first submission and resubmission. The statistical differences noted reflect differences in calculation, e.g. actuarial rate calculations. The major safety concerns include pulmonary, visual, hepatic and gastrointestinal system effects.

- Pulmonary disorders and in particular signs and symptoms of Interstitial Pneumonitis with progressive exertional dyspnea and radiological changes of interstitial and/or alveolo-interstitial changes are the most important concern. The cases in clinical trials have occurred within the first 3 months of treatment and have resolved with removal of drug and steroid therapy. 8% of patients treated with orchiectomy and 3.5% of patient treated with LHRH agonist developed a lung syndrome known as interstitial pneumonitis.

Of particular concern was the incidence of interstitial pneumonitis in a small Japanese study where 8 patients out of 47 patients treated developed the disease. There has been no identification of markers or patient population at risk. There was no indication of increased infection with drug treatment.

If the drug is to be approved, the sponsor needs to identify in a controlled study setting possible patient population or environmental risks.

In February 1988 the sponsor was required to include a warning statement in the investigator information brochure. This was as a result of 5 cases of interstitial pneumonitis in study 606. It was requested that all patients have pretreatment chest x-rays and pulmonary function tests done at months 1,2,3, and 6. This occurred after the completion of study 908. Only 23 patients were enrolled after this request; therefore,

little information was gathered after this time. However, only a total of 16 patients - 11 on nilutamide and 5 placebo were evaluated with repeat tests; 7 of the 23 patients did not have repeat tests. One of the treated patients developed subclinical interstitial disease and withdrew consent.

- **visual disturbances** - These appear to be reversible upon treatment discontinuation or scheduled dose decrease from 300 mg to 150 mg; Some disturbances appeared to have resolved during treatment.

There were visual disturbances in 23% (908) of orchiectomized patients and 57% (606) of patients receiving leuprolide plus nilutamide. The placebo arm had 1% and 5% (606). There was a much higher incidence in the gonadotropin treated study.

The delay in dark adaptation took from several seconds to 30 minutes. It is suggested that the label strongly warn the patient regarding night or tunnel driving as well as
living machinery in the dark.

The impaired adaptation to darkness, photophobia, impaired light adaptation, or chromatopsia are all reversible upon treatment discontinuation or dose decrease at the end of the first month of treatment on 300 mg. These disturbances lead to discontinuation in 1% to 2% of cases.

- **Hepatitis** or marked increases in liver enzymes leading to discontinuation occurred in 1% of nilutamide patients in controlled clinical trials.

There was one death related to liver disease. One 78 year old man developed jaundice and a febrile condition (possible UTI) one month after entering the study and died one week later. The death may have been secondary to prostate carcinoma; however, it was in the first month of 300 mg treatment (study 908). Three patients or 1.3 % in 908 were withdrawn because of an increase in liver transaminases. Treatment withdrawal for hepatitis was seen in 1% of patients. The sponsor notes that in study 908 Between 7 and 11% versus 4% placebo patients had SGOT and SGPT values more than twice the upper limit of normal and in study 606 there were SGOT and SGPT values elevated 20% versus 15%. The time frame has not been identified.

In study 606 there were increases in SGOT and SGPT which occurred in 26 (12%) nilutamide and 19(9%) placebo patients. There was one case of jaundice in placebo treated patient. One nilutamide patient was

discontinued due to elevated SGOT/SGPT values on day 86 of the study with an elevation of 499 U/L and 776 U/L respective in the enzymes. (see chart Table Y in appendix from sponsor.)

The preclinical studies demonstrated fatal liver toxicity in dogs at drug exposure levels similar to human doses. The hepatic problems are **nonreversible when recognized** and there is no data that identifies risks or identifiable markers at the reversible point. This propensity for liver damage appears to be a problem for all antiandrogens at least at the doses used.

- GI - Although no diarrhea is reported with this compound there is also a high degree of drug-related nausea reported in the trials.

- alcohol intolerance appeared to be dose related. The incidence is <1% in placebo-treated patients and in 4 % to 5% if nilutamide patients. 6 patients resolved with doses at 150 mg.

There were no apparent age related changes in the above safety concerns and no data to identify how many patients had more than one problem at the same time.

One hundred fourteen (34%) patients receiving nilutamide and 59 (18%) patients receiving placebo discontinued the double-blind part of the study because of adverse experiences, including intercurrent events. The most frequent reason for discontinuation of treatment in the pooled orchiectomy studies was death. Seventeen percent of patients in the nilutamide group and 14% of patients in the placebo group are listed as having been discontinued for this reason. In the nilutamide group, seven (2%) patients were discontinued because of dizziness, five (2%) because of interstitial lung disease, three (1%) because of hepatitis, and six (2%) because of visual disturbances. No patient in the placebo group was discontinued for these reasons.

The largest incidence of adverse experiences considered treatment related by the sponsor occurred in the special senses category. Impaired adaptation to darkness was considered related in 9% of patients who received nilutamide compared with 1% of placebo patients. Chromatopsia was considered related in 3% of nilutamide patients and none of the placebo patients.

The endocrine system had the second highest incidence of treatment-related adverse experiences. All the adverse experiences reported here are the expected effects of

orchiectomy with or without antiandrogen treatment and thus considered related to treatment in these studies.

In the body as a whole, alcohol intolerance occurred at a higher rate in the nilutamide group (4%) than in the placebo group (0%).

10.2.4 Drug-Demographic Interactions

The Japanese study may reflect either environmental changes or ethnic differences in the metabolism of the drug. If this drug was approvable it would necessitate studies to identify more clearly the toxic changes to the lungs and liver seen in this population.

10.2.5 Drug-Disease Interactions

Only studied extensively in advanced prostate cancer

10.2.6 Drug-Drug Interactions

The sponsor states that drug-drug interactions must be considered when nilutamide is used with drugs with a low therapeutic margin. The sponsor believes this includes drugs such as vitamin K antagonists, phenytoin and theophylline which could result in delayed elimination and increases in their serum half-life.

10.2.7 Withdrawal Phenomena/Abuse Potential

There is no abuse potential or withdrawal phenomena noted.

11 Labeling Review

The sponsor would label the drug as contraindicated in the following patients:

- severe hepatic impairment
- with severe respiratory insufficiency
- with hypersensitivity to nilutamide or any component of this preparation.
- not indicated in women.

The sponsor would presumably add a statement regarding PSA normalization at 12 weeks for continued therapy and state ineligibility for treatment if ALP more than twice the normal at baseline.

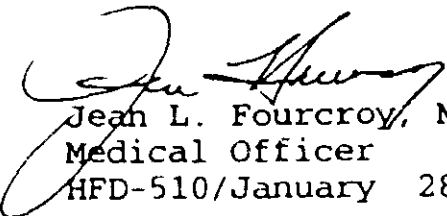
12 Conclusions

There is insufficient evidence in this submission that the risk versus the benefit truly offers a clinical benefit for the palliative treatment of prostate cancer. Although study 908 offers good evidence that there is short term benefit in progression, and the PSA data in particular suggest good normalization of the disease process over placebo and perhaps importantly a diminution of the pain associated with prostate cancer. The 606 study demonstrates no advantage to the addition of an antiandrogen to medical castration. It would appear that the patients entered into this trial did exceedingly well in all parameters regardless of treatment and compared to expectations from other trials. Unfortunately there is no data within the study that identifies why this patient population appears different and it would suggest that again total androgen blockade is of little benefit.

The risks of this compound appear to outweigh the clinical benefits. The preclinical submission defines areas of concern including both liver and lung toxicity at drug levels similar to human drug levels. The clinical data also suggests pulmonary and liver problems similar to the preclinical data. The margins of benefit are very narrow therefore the adverse risks are less acceptable even when considering cancer treatment.

13 Recommendations

The final decision for approval of this drug was deferred until after the Advisory Committee meeting of February 24, 1995. However, the risks of this compound appear to outweigh the clinical benefits.


Jean L. Fourcroy, M.D., PhD
Medical Officer

HFD-510/January 28, 1995/revised January 30, 1996

See also gray headed mem

Plurichon

2-1-96

1 Title and General Information

1.1 Title/Heading - Medical Officer's Review

1.1.1 NDA #20-169 (NDA #20-168 - original filing number)

1.1.2 M.O. Review

1.1.3 Submission March 7, 1994

1.1.4 Review completed January 28, 1995/Revised February 9, 1995

1.2 Drug name

1.2.1 Generic name - nilutamide - RU 23908

1.2.2 Proposed trade name - Nilandron (Anandron)

1.2.3 Chemical name 5, 5,-dimethyl 3 - {4-nitro-3(trifluoromethyl)-phenyl} 2, 4-imidazolidine-dione

1.3 Sponsor: Roussel UCLAF, Romainville, France - Besselaar Associates, U.S.

1.4 Pharmacologic Category - non-steroidal antiandrogen
low affinity binding of cytosol androgens either testosterone or dihydrotestosterone receptors in target organs. Peripheral androgen antagonist. blocks by competition, the binding of androgens with their receptors.

1.5 Proposed Indication: Indicated for use in combination with surgical castration or chemical castration with an gonadotropin agonist for the treatment of metastatic prostate cancer (stage D₂)

Prostate Specific Antigen (PSA) values should be monitored and patients whose values do not normalize by Month 3 should be reevaluated so that the benefit/risk ratio for continuation of treatment can be determined.

Maximum benefit from combination therapy is achieved in patients with good prognostic factors as reflected by baseline alkaline phosphatase equal or lower than twice the upper normal value for that laboratory..

The palliative treatment of Advanced Prostate Cancer

1.6 Dosage Form and Route of Administration

Nilutamide 300 mg/day for 1 month, then 150 mg/day thereafter. The drug is to be taken orally. 6 tablets of 50 mg each once a day. It is to be taken before breakfast with a glassful of water.

1.7 NDA Drug Classification - P

1.8 Important Related Drugs: nonsteroidal antiandrogens, e.g., flutamide.

1.9 Related Reviews: Statistics and Pharmacology

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3 Material Reviewed (volume numbers which serve basis for this review)

2.27 - Controlled Studies, Update and Predictive Analysis

2 - 38 Integrated Summary of Efficacy

2.39 - Integrated summary of safety information

2.26 - 606 trial overview

2.24 - 908 trial overview

Desk copies of trials 908 and 606

Additional information - October 24, 1994 Safety Update

- 4 Chemistry - see Chemistry review.
- 5 Animal Pharmacology/Toxicology - see Pharmacology review.
A summary of the pharmacology review states that.

6 Clinical Background

- Incidence and prevalence of prostate cancer today

Today the incidence of cancer of the prostate has reached an estimated rate of 22% of all malignancies in men (1991). By the age of 50 up to 30% of men are found to have cancer of the prostate. The incidence for white males is estimated to be 88/100,000 white men and 132/100,000 for black men. The mortality rate in the black population is almost double that for white males. In the year 1992 there were 34,999 deaths from prostate cancer and 46,300 deaths for Breast cancer (American Cancer Society). Although geographic differences in prostate cancer are known to exist no clear cause for this difference is known. Androgens and age are the only clear factors. Family of origin also plays a role. This is why guidelines for screening suggest a Digital Rectal Exam (DRE) and Prostate Specific Antigen (PSA) starting at the age of 50 for white males, 45 for black males and men with a close relatives with a history of prostate cancer. Familial prostate cancer may account for 9% of prostate cancers with early age of onset of disease, and multiple affected family members (Carter, 1992)

- Staging of Prostate Cancer

In the U.S. the usual stage system for prostate cancer is the Whitmore-Jewett classification. World-wide the more common classification is the American Joint Committee for Cancer (AJCC) system. Stage A is not found clinically; Stage B is palpable and confined to the prostate; Stage C

is locally advanced to contiguous structures: bladder, seminal vesicles, and prostatic capsule; and Stage D is outside the adnexal area. It is estimated that 25% of patients with newly diagnosed prostate cancer will present with Stage D2 disease. This submission concerns clinical studies for palliative treatment in men with Stage D2 prostatic cancer. This is disease defined as outside the pelvis in distant lymph nodes, bone or other organs.

Most patients presenting with symptomatic disease generally have cancer spread outside of the prostate gland and are incurable. The responses to androgen deprivation therapy are not durable and the cancers become hormone-refractory (Garnick, 1993). 75% of patients diagnosed with prostate cancer have clinical stage C or D disease at the time of initial diagnosis. The five year survival rate with treatment is approximately 72% for stage C disease. Stage D1 have a 5 year survival rate of 58% and Stage D2 disease have a median survival rate of 2.5 years. (J Urol 1991. 146: 96-98.)

- Treatment of prostate cancer:

Metastatic PCA must be considered to be incurable (Griffiths). The purpose of treatment is to improve quality of life. 70% of men with metastatic diseases treated with androgen deprivation will experience a symptomatic and often a clinical regression with androgen deprivation - but most will relapse within 18 to 24 months. Median life expectancy at time of progression is 6 months or less. It is not clear whether the quality of life is extended by any of these treatments. There have been no advances in the treatment of Stage D since 1940 and the first hormone deprivation by bilateral orchiectomy. ⁸⁵ Subsequently diethylstilbesterol (DES) was used. In 1984 Leuprolide was first approved for medical castration but orchiectomy has remained the gold standard and the most economical approach. Labrie and the European community were the first proponents of blockade of the adrenal androgens; this concept was the basis of the NCI 0036 studies comparing leuprolide with flutamide (the first nonsteroidal antiandrogen) to leuprolide with placebo. This combination therapy for total androgen blockade was approved in 1988. ⁸⁷ There is a continuing dialogue regarding the necessity of total androgen blockade and it's possible advantages and resulted in an international metanalysis pooling comparable studies.

Today there are two gonadotropins approved for medical castration: leuprolide (LURPON - TAP) and goserelin

(Zoladex - Zeneca). There is only one antiandrogen approved for use with a gonadotropin: flutamide (Eulexin - Schering). Two antiandrogens have been studied: nilutamide (Anandron - Roussel UCLAF) and bicalutamide (Casodex - Zeneca) The subject of this submission is nilutamide.

The **Efficacy Endpoints** used in most studies of Stage D prostate cancer are:

- Regression + stabilization
- Time to progression
- Survival time

Current terms and abbreviations:

PCA - prostate cancer

CAT - combined androgen treatment

or

MAB maximal androgen blockade. OR **TAB** Total androgen blockade - primarily aimed to prevent the effect of metabolized adrenal androgens that may be present.

PSA - prostate specific antigen

ALP - alkaline phosphatase

PAP - Prostatic acid phosphatase

Review of concepts of meta-analysis of TAB

A total of 25 randomized trials have been identified to test the hypothesis that complete androgen blockade improves time to progression and ultimate survival time. A few of these studies are outlined in the following table. An attempt at meta-analysis has been undertaken to identify outcomes across comparable studies (see Cancer, December 15, 1992)

TABLE I ESTIMATES FROM COMPARABLE STUDIES

	Response Rate	Progression Free Survival	Disease Progression	Survival
Leuprolide Study Group LEU vs DES	Obj Res 86% Leu 85% DES	Surv 1 yr 87% Leu 78% DES		146 Weeks Leu 136 Weeks DES no difference
NCI/SWOG 0036 N=603 L+F vs L+Pbo		Months 16.5 Flut 13.9 Pbo (p 0.039)		Months 35.6 Flut 28.3 Pbo (p = 0.035)
Eortc 30853 Zoladex/Flut (Z/F) Vs Orch N=327			Difference in median progression 35 weeks for Zol/flu	7 month ext of survival - p=0.05 *
Daproca-86 Orch vs Zol/F N=264	No difference in time to progression or median survival.		Time To Progression Months 16.Orchiectomy 16.Zol/F	Median Survival Months 27.6 Orch 22.7 Zol/F
Inter PCA Study Grp Zolodex vs Zol + Flut N=571	Obj Response 67% Zol 65% Zol/F		No Difference In Time To Progression Or Time To Failure	Time To Treatment Failure not significant 37.7 M Zol 42.4 M Zol/F

current submission

* patients with minimal disease and good performance status received the greatest benefit in 0036 and EORTC 30853.
based on data from Cancer Supplement, December 1993.

Prostate specific antigen

Prostate specific antigen (PSA) has become an important marker in the management of prostate cancer patients.

- first identified 1970 - prostate tissue
- seminal plasma 1971 - rape marker - P-30 serine protease - may play a role in semen liquefaction.
- approved first for predicting relapse.
- significant overlap between BPH AND PCA

There are several issues concerning the use of prostate specific antigen (PSA) in the diagnosis, screening or follow-up of patients with prostate cancer. PSA was first approved by FDA for the diagnosis of recurrence of prostate cancer. Not until 1994 was PSA approved for the screening of prostate cancer in previously undiagnosed patients in conjunction with digital rectal examination. Prostate specific antigen is an androgen sensitive glycoprotein and may be increased independently by androgen stimulation. In addition it appears that the prolonged exposure to a nonsteroidal antiandrogen, e.g. flutamide, results in the selective proliferation of cancer cells containing a mutant androgen receptor that aberrantly recognizes flutamide metabolites and nonandrogenic steroids as androgenic stimuli (Sartor et al, 1994).

PSA has been developed by several methods:

Hybritech*	Tandem E Tandem R Tandem ERA
Abbott*	IMX
Ciba Corning*	ACS
Toschmedix*	AIA pack

* FDA approved

It is important to remember that there are differing forms of the PSA molecule - both free and complexed. Further elucidation of these forms may increase the sensitivity and specificity of PSA in the future. It is expected that newer monoclonal antibodies will be more specific and sensitive. This second generation of assays have been termed ultrasensitive.

FORMS OF PSA

Free PSA 30kD
 PSA-ACT 100kD bound to alpha₁
 antichymotrypsin
 PSA-MG ~780kD complexed with alpha₂
 macroglobulin not immunoreactive.
 engulfed by inhibitor - not measured
 by any commercially available assay.
(Christensson and Lilja, 1993)

The major forms of PSA circulating in serum are:

- Free PSA found in much lower concentrations in serum than complexed PSA is enzymatically nonactive..
- Complexed PSA - found in serum - irreversibly and covalently bound to alpha 1 antichymotrypsin and enzymatically nonactive
- smaller quantities complexed to alpha₂ macroglobulin

These differences are important in comparing PSA assay results. One major assay may overestimate the free PSA and underestimate the complexed PSA.

Other methods to improve both the sensitivity and specificity of prostate cancer diagnosis include differing ways to measure PSA:

- PSA density
Including a ratio of PSA with the volume of the prostate as measured by ultrasound.
- PSA velocity
Repeat measurements of PSA over time.
- PSA and AGE specific reference range

Recent studies by Dr. Oesterling et al have further defined acceptable levels of PSA - Hybritech - by age based on a community based white male population (Minnesota).

TABLE AGE-RELATED PSA LEVELS (Hybritech)

PSA	AGE
0 - 2.5	40 - 49
0 - 3.5	50 - 59
0.0 - 4.5	60 - 69
0.0 - 6.5	70 - 79

PSA is not a perfect screening test for prostate cancer with up to 10% false positives. An ideal marker should have high sensitivity and specificity for distinguishing benign from malignant prostatic disease and provide prognostic information as well as improve treatment outcomes. The positive predictive value for PSA as a screening assay was only 47% (Powell). The margin of difference between benign and malignant is dependent on volume of tissue, grade of tissue and secretion into the plasma. Early detection has not yet been demonstrated to improve survival for men with prostate cancer.

PSA REDUCTION (RESPONSE) AND PSA PROGRESSION (RELAPSE)

Castration initiates extensive apoptosis of the secretory epithelial cells lining the ducts of the rat ventral prostate resulting in the striking reduction of male sexual accessory tissue.

Since PSA expression is influenced predominantly by androgens, the mutation of the receptor that can occur as prostate cancer cells become undifferentiated may affect the expression of the PSA gene.

FACTORS THAT DETERMINE SERUM PSA IN MEN WITH PROSTATE CANCER;

- Number of viable normal prostatic epithelial cells and the extent of differentiation of neoplastic Prostatic epithelial cells
- hormonal milieu
- architectural integrity of the prostate gland location of malignant prostatic epithelium -intraprostatic or metastatic.
- Rate of marker clearance.

(Petros and Andriole)

A PSA increase is the first sign of progression after treatment in those patients with prostate cancer that secrete prostate specific antigen and a reduction in PSA is an indication of an apoptotic response by the prostate cancer cells. Elevation of PSA allows for identification of relapse at an earlier time than otherwise clinically evident. It is important to remember that poorly differentiated prostate cells may lose this ability to manufacture and secrete PSA. There appears to be an inverse relationship between histologic grade of the tumor

and PSA production (Partin). It has been suggested that if the PSA decreases to less than 10 ng/ml at 6 months, the time to progression was 22.7 months and survival was 33.2 months; if the 6 month PSA exceeded 10 ng/ml time to progression was 12.5 and survival 18.8 months (Stamey).

The decline of PSA > 90% is thought to predict a prolonged progression free survival. A rise in PSA within the limits defined in the criteria for progression might be an indication for a change in therapy. It has recently been estimated by Soloway (1994) that responders after treatment with the lowest PSA (< 4) and a decrease in maximum PSA level by 95% or greater from baseline will have the best progression free intervals. This is a preliminary report.

An example of this is seen in the percent reduction of PSA after 3 months of different doses of bicalutamide compared with surgical castration or flutamide as monotherapy (Dennis, Cancer supplement Dec 15, 1993 - 3890).

TABLE - PSA LEVELS WITH ANDROGEN DEPLETION

Bicalutamide monotherapy	10 mg	30 mg	50 mg	100 mg	150 mg
% PSA decline	57%	73%	90%	97%	97%
	Surgical castration	97%			
	Flutamide monotherapy	73%			

Androgen withdrawal and subsequent cellular apoptosis ultimately results in the relative enrichment of tumors with cells that are more undifferentiated and less responsive to hormonal therapy.

The three antiandrogens that have been studied are:

- FLUTAMIDE - Eulexin

The active form is hydroxyflutamide which is thought to be twice as potent as Cyproterone acetate (CPA). It has a short half life of 5 - 6 hours. The dose is 250 mg tid for a total of 750 mg per day. The safety profile has been disappointing. There have been 20 reported deaths from hepatotoxicity and 26 patients who were hospitalized with serious hepatotoxicity. Other adverse events associated

with flutamide are diarrhea and "flutamide-withdrawal syndrome". The latter defined first by Sher reflects the agonist effect of flutamide on the androgen receptors that are perhaps mutated.

- BICALUTAMIDE - Casodex

Refer to published material in Cancer

- NILUTAMIDE -Nilandron

Nilutamide has a half life of 45 hours.

- CYPROTERONE ACETATE (CPA) is steroidal antiandrogen - closely related to structure to progestogens. CPA is a synthetic 21-carbon hydroxyprogesterone derivative - acts both centrally and peripherally and has both progestin and antigonadotropic properties. In the target Prostatic cells it acts as a competitive inhibitor of the binding of dihydrotestosterone to cytosol receptor sites and inhibits the translocation of the androgen-receptor complex into the nucleus. In its central action it lowers LH and plasma testosterone because of its progestin-like activity. The side effects include thrombophlebitis in 5% of patients, fluid retention in 4% , gynecomastia in 13% and loss of libido in most men. The daily oral or injectable doses are 250 mg/day The mean duration of remission is 18 months (Goldenberg and Bruchovsky - Urol Clin 1991 : 18 : 111-122)

Agonist activity and withdrawal syndromes noted with flutamide are probably common to all nonsteroidal antiandrogens and have been identified in the antiestrogen, tamoxifen. Reports were first noted with flutamide but have also been reported with bicalutamide. To date none have been reported with nilutamide. It has been suggested that the prolonged exposure to flutamide results in the selective proliferation of cancer cells containing a mutant androgen receptor that aberrantly recognizes flutamide metabolites and nonandrogenic steroids as androgenic stimuli. (Sartor, 1994)

Androgen Blockade:

It is estimated that there is a 90 to 95 % reduction in circulating androgens after removal of androgens either surgically, bilateral orchiectomy, or medically with estrogen (DES) or gonadotropin analogs. The first analog, Leuprolide (Lupron), was approved in 1984. Goserelin (Zoladex) was approved subsequently. Both of these analogs

are approved only for the palliative treatment of Stage D2 prostate cancer.

Labrie and his group originally encouraged the concept of total androgen blockade on the basis of increased adrenal androgens thought to be metabolized to DHT in the prostate cancer cells. It is surmised that the adrenal androgens contribute 7 to 10% of the total androgens; total androgen ablation therapy is aimed at blocking the contribution of the adrenal androgens to the metabolic pathway in the prostate cancer cells by blocking the androgen receptor. The first studies to test this theory were the NCI 0036 studies of leuprolide + flutamide versus leuprolide + placebo. This combination therapy was approved on the basis of this NCI study.

Additional chemical markers used for the monitoring of regression and progression of prostate cancer used in these studies are:

Alkaline phosphatase - ALP
(Chodak JAMA 1991 - 265: 618-621).

Prostatic acid phosphatase - PAP

Both of these markers have in large part been superseded by the use of PSA. PSA has also demonstrated its early sensitivity in progression of prostate cancer prior to clinical evidence. Changes in bone metastasis or pain will be preceded by elevations in PSA.

Little advance has been made in the treatment of advanced prostate cancer, Stage D, since the initiation of androgen ablation in 1939 by Huggins and Hodges. No other disease has such a large economic impact or effects the quality of life as much as advanced prostate cancer. Only early detection and removal of the tumor has long term benefits; only palliative therapy is available for Stage D disease.

6.3 Foreign experience

Nilutamide has been improved in 28 countries including Canada. It has not been approved in the U.K. where it had been determined that the risk to benefit ratio is not satisfactory (from submission). The sponsor states that it is currently under review, possibly a resubmission, and approval is expected in May 1995. (telephone conversation with Dr. Ulman)..

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics see Pharmacology review

The company has submitted 14 human pharmacokinetic studies which include bioavailability and pharmacokinetic studies. These have been included in the pharmacology review. The 300 mg dose for the first 30 days was chosen from initial studies. Higher doses are associated with vomiting, gastrointestinal symptoms, sinus tachycardia and methemoglobinemia. Study 8/78/2 was an uncontrolled pilot study to assess the safety and tolerance of nilutamide administered orally using 50 mg tablets for 7 days at doses of 50, 100, 300 and 600 mg/day to 18 hospitalized patients with metastatic prostate cancer who had failed other treatments. Demonstration of increasing plasma LH and testosterone concentration was noted. Increasing doses 300 mg and higher were associated with gastrointestinal symptoms. Treatment dose of 600 mg was associated with methemoglobinemia in one patient and anemia in one patient at 300 mg/day

Study 9/79/1 was an uncontrolled pilot study at doses of 900 mg/day for 3 months in 4 hospitalized patients who had failed other treatments. One patient of 4 treated for 6.5 months had improvement in urinary symptoms and 'well-being' a decrease in prostate volume and PAP and an increase in hemoglobin concentration. The other patients had to discontinue this dose because of malaise, dizziness, and vomiting. It was concluded that doses of 300 mg tid (total 900 mg) could not be tolerated.

One of the four pharmacodynamic studies, NL/84/908/06, was done in 17 healthy men, ages 19 to 33, desiring gender reassignment. They received 150 mg bid (300 mg) for 8 weeks followed by addition of 100 µg of ethinylestradiol to the nilutamide for 16 additional weeks. In this study a full analysis of the androgen profile was monitored. This included androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, estrone, estradiol, prolactin, sex hormone binding globulin (SHBG) luteinizing hormone (LH and follicle-stimulating hormone (FSH) which were measured before and after four and eight weeks of treatment. 16 of the 17 completed the first eight weeks and seven subjects completed the full course of the study. One subject developed abnormal liver function and severe bone marrow depression, four subjects developed liver enzyme concentrations outside the normal range and in two of these patients the enzyme concentrations returned toward normal. The third patient had a return to normal after treatment discontinuation. The submission does not indicate at what point in the study. (The table from this study is included in the appendix.) ✓

Study F/85/908/10 was the first double-blind, placebo-controlled study to evaluate efficacy of treatment in 36 men with stage D2 prostate cancer with no previous therapy evaluating clinical symptoms such as the increase in metastatic pain and using PSA in addition to PAP as markers. The men were treated with buserelin + nilutamide (300 mg) or placebo. Hormonal assays also included, LH, FS, DHEA, DHEAS, estradiol and cortisol. The sponsor claims a statistical difference in pain compared to baseline between nilutamide treated and placebo treated patients. Pain was thought to be significantly less frequent in the nilutamide group (5/17, 29%) than in the control group (12/19 patients or 63%) with a $p < 0.05$. All patients were treated for 4 weeks with Buserelin. The chart (figure 1 of submission) demonstrates a rapid decrease in bone pain expressed as percentage change on a 100 mm visual analog scale. This chart also demonstrates the increase in pain in the first week of analog treatment consistent with 'flare'. The graph is seen in appendix. There is a delayed associated change in the PAP levels and PSA. Testosterone levels reach castrate levels of 0.2 ng/mL only after 18 days of treatment with combination treatment. Treatment with buserelin alone never reaches castrate level. see appendix for graphs of PAP, PSA and testosterone levels. Visual disorders consistent with nilutamide treatment were noted similar to that in larger trials. There were no reports of liver profile changes.

Adrenal function was evaluated in study FF/86/305/ANA/005. This study included 18 men with prostate cancer - both Stage C or D. The orchiectomy was done 45 days prior treatment. This study was done to determine if there were any adrenal hormonal changes. No significant differences were identified in hydroxyprogesterone, androstenedione, androstenediol, DHEAs, or DHEA. Study FF/85/305/ANA/005 also evaluated the effect of nilutamide in 18 castrated patients with Stage C or D prostate Cancer and did not demonstrate any changes in the synthesis of adrenal androgens.

See Pharmacology review for full discussion of these studies. These studies demonstrated that addition of nilutamide appeared to reduce bone pain and prevented the rise in the PAP and PSA.

6.6 Directions for Use based on doses in pivotal trials:

The patients received 6 tablets of 50 mg (300 mg) to be taken in the morning with water for the first month; subsequent doses after the first month were 3 tablets

of 50 mg (150 mg). Doses were initiated with daily subcutaneous leuprolide in 606 and one day after the surgical castration in study 908.

7 Description of Clinical Data Sources (both IND and non-IND)

IND IND dated April 21, 1983 review April 21, 1983.

(Labrie - Canadian study) The dose of nilutamide used was 100 mg T.I.D. and buserelin 500 mg per day sc. 37 patients had no previous therapy and were treated from 1 - 12 months; 23 had been previously treated with DES and 7 had been castrated and presumably received only nilutamide. The review states that results were not as good in patients previously treated by orchiectomy or DES but some drop in acid phosphatase.

Original doses planned were higher and pushed to toxic levels. Initially the sponsors thought that there was good tolerance at daily doses of 300 to 600 mg. After several studies the "safe" dose was defined as 300 mg per day or less.

Early studies with buserelin suggested improvement in pain within first weeks of treatment with the addition of nilutamide (Page 17 volume 2-2) Interestingly there is not an immediate decrease in testosterone although there is an early drop in alkaline phosphatase and prostate specific antigens. Studies F/85/908 and F/82/908/01 are thought by the sponsor to demonstrate that nilutamide was effective in inhibiting the potential adverse effects associated with the initiation of LHRH agonist therapy or the flare..

7.2 Post-Marketing Experience

Nilutamide (Anandron) is approved in 28 countries. It has not been approved in the United Kingdom because of the risk versus benefit ratio; however, the sponsor states that they are expecting approval in the United Kingdom.

8 Clinical Studies

2,168 patients with prostate cancer have been treated with nilutamide in combination with surgical or medical castration between 1978 and 1989. 682 patients have been treated for 12 months or longer. There are 10 double-blind placebo-controlled studies, three uncontrolled studies, and seven studies for indications not included in the proposed labeling .

DOUBLE-BLIND PLACEBO-CONTROLLED STUDIES

Study NO.	Duration
*FF/86/908/01	18 months
*GBA-606	18 months
CDN/83/908/05	24 months
F/82/908/03	24 months
F/82/908/01	24 months
F/84/908/01	24 months
CH/85/908/05	24 months
ZA/85/908/02	24 months
FF/86/ANA/01	6 months
F/85/908/10	28 days.

* PRIMARY CLINICAL TRIALS REVIEWED.

The primary parameters for the evaluation of efficacy used in the primary studies were best response to treatment (using modified NPCP criteria), time to objective progression (i.e., progression-free survival), time to death due to prostate cancer (i.e., prostate cancer survival), and time to death due to any cause (i.e., overall survival). (See appendix)

Except for Study No. F/85/908/10, the primary parameter for the supportive studies was best objective response (NPCP criteria), with time to progression, time to death due to prostate cancer, and time to death due to any cause as secondary parameters. Other secondary parameters for efficacy were improvement in metastatic related pain, performance status, prostatic acid phosphatase (PAP), prostate specific antigen (PSA) (in the primary studies), bone scan isotope uptake, tumor volume, and alkaline phosphatase (ALP). Improvement in bone scan isotope uptake and tumor volume were not analyzed in some of the secondary studies. In Study No. F/85/908/10, a one-month study, the effect of nilutamide on pain, on laboratory markers of tumor activity (PAP, PSA, alkaline phosphatase), and on hormonal levels (e.g., testosterone, LH, and FSH) was evaluated.

Symptoms, metastatic related pain and urinary obstruction were rated on a three point scale (1=none, 2=moderate, 3=severe) and performance status on a five-point scale (from 1=normal to 5=bedridden).

After the sixth month, the number of patients withdrawn for progression became high and, for the patients withdrawn between two visits, no information on symptoms was available at the time of progression. Hence, the comparison between treatment groups after six months was biased, since it excluded all the patients withdrawn for progression between two visits. Prostatic acid phosphatase and alkaline phosphatase treatment differences were

compared by means of the Wilcoxon rank sum test on the percent differences from baseline value. The raw data were first standardized so that the differences between assay methods would be erased. For symptoms, the comparison was made only for the first three visits on treatment. Best Response to treatment (NPCP criteria) among the objective responses evaluated every 6 months, the best one for each patient was retained for the comparison of treatment groups. The percentages of regressions (partial or complete) and of regressions + stable diseases were compared by means of the likelihood ratio chi square test. Time to progression and time to death actuarial rates were computed by means of Kaplan Meier estimate and compared by means of the logrank test and the Gehan Wilcoxon test. Regarding time to progression, the date of progression was not recorded for some patients even though there had been a progression. In those cases, the date of progression was defined as follows: the patient never responded to treatment; the date of progression was taken as the date of beginning of treatment plus 5 days but the treatment was stopped due to progression before the next planned visit. When the treatment was stopped for a reason other than lack of efficacy and a progression was not recorded in the CRF, the patient was censored at the time of treatment discontinuation. This is description is from the sponsors submission. (see Statistical Review)

A responder was identified as a patient with one with a PSA of less than 4.0 (Hybritech- 908 trial) or 2.5 (Pros-check 606 trial) at the 3 month visit.

8.1 Trial # Study No. FF/86/908/01
(also known as GHBA 608/ U.S. GHBA 610)

*FF/86/908/01	nilutamide 300 mg + orchiectomy (150 mg > 30 days) versus placebo + orchiectomy	18 months 66 investigators International

Summary:

The median time to progression was longer for nilutamide patients - 19 months vs placebo patients - 14.9 months

The median survival time (any cause) was 28.3 months in the nilutamide group and 23.2 months in the placebo group. This was not statistically

significant for the overall survival but close to statistical significance for the cancer-related survival (0.058.)

8.1.1 Objective

This was a double-blind, randomized, placebo-controlled study to compare the efficacy and safety of nilutamide in combination with orchiectomy with that of orchiectomy alone - in the treatment of patients with previously untreated prostate cancer. The long-term safety and tolerance of nilutamide in the treatment of prostate carcinoma (Stage D2) was also to be determined.

8.1.2 Design

Starting on the day after orchiectomy, patients received either nilutamide (300 mg/day p.o. for one month followed by 150 mg/day p.o. thereafter) or placebo p.o.; the patients continued the double-blind medication until objective disease progression, the occurrence of an adverse experience, or any other event necessitating withdrawal from the study. Patients whose disease progressed while receiving nilutamide could continue nilutamide (150 mg/day, p.o.) on an open label basis following study discontinuation, while patients who had been receiving placebo were not permitted to receive nilutamide. Enrollment dates were June 1986 through February 1988; and cutoff date for data collection was 31 August 1989. On day one post-orchiectomy patients received either nilutamide (300 mg/day) for the first month followed by 150 mg/day thereafter or placebo. The patients were randomly assigned to receive either nilutamide or placebo in a 1:1 ratio. The patients were assigned patient numbers in ascending order beginning with the lowest available number.

If objective progression occurred, patients who had been receiving nilutamide were permitted to continue nilutamide on an open-label basis, while patients who had been receiving placebo were withdrawn from the study and could receive any treatment other than nilutamide.

Two hundred seven of the 225 (92%) nilutamide patients and 216 of the 232 (93%) placebo patients were judged evaluable for efficacy analysis. This was defined as "adherence to protocol entry criteria".

8.1.3 Protocol

8.1.3.1 Population

*FF/86/908/01	Race: 418 white 15 black 18 Hispanic 4 oriental 2 other	ages - 46 to 92 evaluable pts Countries: USA Europe Canada S American S. Africa

8.1.3.2 Endpoints

- Best Response To Treatment

Complete Or Partial Tumor Regression At Some Time
During The Study.

- Time To Objective Progression Or Progression-Free Survival.
(NPCP criteria attached to appendix)
- Time To Death Due To Prostate Cancer
- Time To Death Due To Any Cause.

Secondary parameters:

- Improvement In Metastatic Related Pain
- Performance Status,
- Prostatic Acid Phosphatase -Pap
- Prostate Specific Antigen - PSA
- Alkaline Phosphatase - ALP
- Bone Scan Isotope Uptake
- Tumor Volume

8.1.3.3 Statistical review

(see complete statistical review)

Summary statement: "Study 908/01 provides statistical evidence of a lengthening of approximately 4 months of median time to objective progression. There is a suggestion of lower mortality due to prostate cancer, only (p-value less <.10 .) Although this study does suggest an overall relationship between PSA level at 3 months and mortality, mortality was less in the placebo group among those who had PSA measurements. "

8.1.4 Results

8.1.4.1 Patient Disposition, comparability

Patient Disposition: A total of 457 patients with a primary diagnosis of previously untreated metastatic prostate carcinoma Stage D were enrolled in the

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study; 225 patients were randomized to receive nilutamide and 232 were randomized to receive placebo. 92% nilutamide and 93% placebo patients were evaluable. The age for all patients ranged from 50 - 85 years with an average age of 71.2. 91% of enrolled patients were white.

Of the 350 patients who discontinued from the double-blind phase of the study, 199 (85 nilutamide, 114 placebo) discontinued because of objective progression, 28 (13 nilutamide, 15 placebo) because of subjective progression, 55 (35 nilutamide, 20 placebo) because of adverse experiences including intercurrent events, and 68 (35 nilutamide, 33 placebo) because of other reasons.

The patients were comparable in respect to pain, Karnofsky scores, performance status, testosterone, hemoglobin, PSA, PAP and tumor burden estimate.

TABLE - DISCONTINUED PATIENTS		
DISCONTINUED	NILUTAMIDE	PLACEBO
OBJ PROG	85	114
SUBJ PROG	13	15
ADVERSE EXP	35	20
OTHER	35	33

8.1.4.2 Efficacy endpoint outcomes

PERCENT (NUMBER) OF PATIENTS WITH COMPLETE OR PARTIAL REGRESSION#							
				placebo			
FF/86/908				24%			p <0.001
	evaluable by NPCP			44/182			
				# best response at some time during the study			
PROGRESSION AS BEST OBJECTIVE RESPONSE							
FF/86/908				36%			p 0.002
				66/182			
DIED OF PROSTATE CANCER				40%			p=0.006
				86			
DIED OF ANY CAUSE				52%			
				113			

MEDIAN TIME TO PROGRESSION						
FF/86/908		19.0 months		14.7 months		protocol 908/o1 attachment A.2.1
previous analysis		19.0 months		14.8 months		
FEWER OBJECTIVE PROGRESSIONS		50% 103/202		61% 126/208		no p value
Median Survival time		28.3 months		23.2 months		n.s. (0.058)

The median survival time for any cause was 28.3 months in the nilutamide and 23.2 months in the placebo group. The difference in survival between the treatment groups was close to statistical significance for the cancer-related survival $p = 0.058$ and not statistically significant for the overall survival (0.145.)

Significantly more nilutamide patients (41% or 72/175) than placebo treated patients (24%, or 44/182 patients) had complete or partial tumor regression. The median time to progression was 19.0 months in the nilutamide group and 14.9 months in the placebo group.

Statistical differences in reduction in pain and ALP and normalization of PAP were seen at one month. PSA was significant at 3 months (not evaluable at one month) (see table in appendix.)

8.1.4.3 Safety comparisons

see charts from submission in appendix.

84% of nilutamide treated patients (188/225) and 78% of placebo patients (182/232) had one or more adverse experiences regardless of relationship to medication. 54% (nilutamide) versus 31% (placebo) adverse events were thought to be related to drug. There are several major areas of concern that effect the pulmonary, visual, gastroenteric and hepatic systems. In addition that drug appears to be associated with alcohol intolerance in 5% (11) of the patients. The major adverse events seen with nilutamide were:

pulmonary - Respiratory disorders appear to be the most troubling of the adverse events supposedly reversible upon discontinuation of treatment. In this study 17% (38) nilutamide patients and 15% (35) placebo patients had some respiratory disorder.

Seven patients (3.1%) nilutamide patients versus one placebo patient withdrew from the study because of respiratory disorders. Interstitial pneumonitis was diagnosis in one of the seven nilutamide patients, which resolved after discontinuation. A second patient demonstrated x-ray findings without respiratory symptoms while the other 5 patients had either dyspnea without other signs or symptoms of interstitial lung disease or unrelated respiratory events, supposedly. The time interval was within the first 3 months and usually in the first month. It must be assumed that any dyspnea is a symptom of interstitial pneumonitis. This may have a relationship to the higher dose of nilutamide in the first 30 days.

(see appendix table 44.1

Visual - Visual disorders were frequently reported and related clearly to nilutamide. 20 (13%) patients in the treated group and 3 (1%) patients in the placebo group reported impaired dark adaptation and. Abnormal vision was reported in 13 (6%) nilutamide patients and four (2%) of placebo patients. Chromatopsia, impaired light adaptation, and photophobia each occurred in 3% of nilutamide patients and in none of the placebo patients. see appendix table 43.1.

hepatic - Since hepatic lesions are noted in the animal studies it is important to focus in on this adverse experience. One patient in the nilutamide group had hepatitis which resolved after treatment discontinuation and "one patient who had entered in the study in spite of marked liver dysfunction before inclusion, suddenly deteriorated and died after 47 days of treatment".

GI - Gastrointestinal symptoms occurred more frequently in the nilutamide group ($p=0.044$. this included constipation, nausea (9% vs 6%) vomiting (4% vs 3%).

anemia occurred in 4% of nilutamide patients and 7% of placebo patients.

8.1.5 Reviewer's Comments

The sponsor has not demonstrated any survival advantage in this submission; however there is an advantage in the 908 trials in Percent of patients with complete or partial regression, progression as the best objective response, death from prostate cancer. The secondary endpoints of pain from cancer and chemical markers of PAP and ALP improved statistically by one month with statistical improvement over placebo group in PAP, ALP

and PSA (not drawn at one month) by 3 months. These biochemical assays probably reflect regression of tumor. Although there is no advantage with nilutamide treatment with survival the addition of nilutamide does offer some additional progression free time as evidence by complete and partial regression (41% nilutamide versus 24% placebo; progression as best objective response 22% nilutamide vs 36% placebo. This edge may be of clinical importance to the patient for the short period in the control of symptoms.

Although it is clear that there is a drug related increase in respiratory, visual and gastrointestinal symptoms no hepatic toxicity is truly noted in this study. It can be assumed that every case of dyspnea is associated with drug use.

8.2 Trial # Study No. GHBA-606 leuprolide study

*GHBA-606	Nilutamide 300 mg (150 >30 days) + leuprolide versus placebo + leuprolide	18 MONTHS 38 investigators Domestic

Summary:

No difference in progression as best objective response, early progression. Only the percent patients with complete or partial regression demonstrates a difference between treatment groups.

Median time to progression was 25.0 months in the nilutamide group and 24.5 months in the placebo group

Median survival time cannot be calculated because only 42% of the evaluable patients had died as of the data cutoff point.

"The significant improvement for the nilutamide group compared with the placebo group in the number of complete or partial tumor regressions and in the secondary efficacy parameters such as pain, performance status, and laboratory evidence of disease clearly show the efficacy of nilutamide." from sponsor submission.

8.2.1 Objective

A double-blind, randomized, placebo-controlled study to compare the efficacy and safety of nilutamide in combination with leuprolide with that of leuprolide alone in the treatment of patients with previously untreated prostate cancer (Stage D₂) followed by an extended treatment period to evaluate the long-term safety of nilutamide in 38 centers in the United States.

8.2.2 Design

Patients were randomized to be started on leuprolide 1 mg/day subcutaneously in addition to nilutamide at 300 mg/day for the first month which was decreased to 150 mg/day thereafter or placebo with leuprolide.

If objective progression occurred patients were withdrawn from the study but nilutamide patients could continue to receive the drug on an open label

8.2.3 Protocol

A total of 411 patients: 209 nilutamide and leuprolide and 202 received placebo plus leuprolide. 292 patients discontinued from the double blind phase ; 153 with objective progression (73 nilutamide and 80 placebo). An additional 37 patients withdrew because of subjective progression (20 and 17 respectively) and 65 because of adverse experiences (41 nilutamide and 24 placebo). 37 withdrew for other reasons. 21 patients (12 and 9 were not evaluable for efficacy analysis. The average age was 67 years of age.

8.2.3.1 Population, procedures

GHBA-606	Race:	ages - 40 to 86
	319 White	Country:
	80 Black	USA
	11 Hispanic	38 investigators
	1 Oriental	

8.2.3.2 Endpoints (both trials used the same endpoints)

- Best Response To Treatment

Complete Or Partial Tumor Regression At Scme Time During The Study.

- Time To Objective Progression Or Progression-Free Survival

- Time To Death Due To Prostate Cancer
- Time To Death Due To Any Cause.

Secondary parameters:

- Improvement In Metastatic Related Pain
- Performance Status,
- Prostatic Acid Phosphatase -Pap
- Prostate Specific Antigen - PSA
- Alkaline Phosphatase - ALP
- Bone Scan Isotope Uptake
- Tumor Volume

Assessments were made as for the previous study at months 0, 1,3,6, 12, and 18 months continuing every 6 months during the continued treatment.

8.2.3.3 Statistical discussion
see statistical review

Notes from statistical review:

- The resulting progression-free survival and survival profiles are essentially superimposable without evidence of any trend in either treatment group's favor.
- The results for Best Response to Treatment according to NPCP criteria were mixed. After excluding 33 patients with no NPCP data, the p-value was .037 for regression (57% on drug, 46% on placebo). However with regression grouped with stable disease, the p-value was .254.
- Change in metastatic pain demonstrated no statistical differences; approximately 65- 70% of the patients improved from baseline up to 3 months after randomization.
- Karnofsky improvement was demonstrated only at 6 months
- Survival analysis that was restricted to the groups of patients with a PSA of less than 4 ng (hybritech) at 3 months failed to show any survival advantage in the nilutamide-treated group.

8.2.4 Results

8.2.4.1 Patient Disposition, comparability

The patients in both arms of the study were deemed comparable on basis of age, race, metastatic related pain urinary obstruction, Karnofsky performance status, testosterone, hemoglobin, PAP, PSA and ALP and tumor burden. Only duration of diagnosis was differed between groups; the nilutamide patients having had a significantly longer mean duration of diagnosis by 2.2 months than placebo (1.2 months)

Patients who discontinued the study were similar between the arms except for adverse experiences.

TABLE - DISCONTINUED PATIENTS		
Study 606	NILUTAMIDE	PLACEBO
DISCONTINUED		
OBJ PROG	73	30
SUBJ PROG	20	17
ADVERSE EXP	41 (20%)	24 (12%)
OTHER	18	19

8.2.4.2 Efficacy endpoint outcomes

PERCENT (NUMBER) OF PATIENTS WITH COMPLETE OR PARTIAL REGRESSION# AT SOME TIME DURING TREATMENT							
				placebo			
PERCENT PATIENTS WITH COMPLETE OR PARTIAL REGRESSION#							
GHBA-606				43%			P =0.020
				71/165			
				# best response at some time during the study			
PROGRESSION AS BEST OBJECTIVE RESPONSE							
GHBA-606				19%			not mature?
				31/165			0.446
FEWER EARLY PROGRESSION ON OR BEFORE MONTH 12							
GHBA-606							
				25%			
				47/191			
MEDIAN TIME TO PROGRESSION							
FROM INTEGRATED SUMMARY				24.5 MONTHS			
FROM MOST RECENT UPDATE??				29%			
				56			

Median survival time has not been reached

The sponsor believes that the best objective response was significantly greater between treated and placebo patients. However, there is no difference between the other endpoints. Median survival time has not been reached.

At month 1 there was no statistically significant difference between treatment with respect to change from pretreatment in metastatic related pain. but a larger proportion of patients than placebo patients improved (60% vs 49%). There is no difference statistically either at month 3 or 6.

There is a statistical difference from baseline in changes from baseline at one month and 3 months for PAP, PSA and ALP as well as statistical changes in normalization of PSA. see appendix chart. Cancer pain improves ($p=.065$) between treatment arms at the first time measured 6 months. **Normalization** of PSA occurred at month 1, month 3 and month 6 statistically favoring the nilutamide treated arm. Normalization is defined as at or below 2.5 (Proscheck) .

8.2.4.3 Safety comparisons

(representative charts from submission in appendix).

The major adverse events seen with nilutamide versus placebo appeared similar to the 908 trial except for the increase in Impaired dark adaptation in the 606 trial.

pulmonary - 16 patients (7.66%) versus 8 patients (3.96 %) had adverse experiences related to the respiratory system. see chart from sponsor on overall incidence of adverse experiences by body system.

Table 44.1 (sponsor) lists the number and percent of patients regardless of relationship to study drug. Interstitial Lung disease is listed in 7 (3.3%) of patients versus 1 (0.5%) placebo group. The update for 606 identifies this number as 8 patients or 4% of the patients and in one - 1% placebo patient with Interstitial lung disease. The chart also notes 22 patients in treatment arm (10.5%) versus 13 (6.4%) with dyspnea which may be a more sensitive sign of pulmonary problems drug related. In addition 10 versus 6 patients had pneumonia (4.8% vs 3.0%) although the

reverse is true for upper respiratory infection. The increase incidence of dyspnea should be considered a possibly related to interstitial pneumonitis.

The sponsor believes that the **interstitial lung disease was severe in five of the eight cases, mild in one and moderate in one.** All cases presented with progressive exertional dyspnea and seven had confirmed x-ray findings with alveolar-interstitial changes. All seven patients recovered. The eighth case had rib metastases thought to be the cause of the dyspnea. (case reports attached).

visual - Dark adaptation was the most frequent adverse event with a delay of a few seconds to 30 minutes in adaptation to darkness. Five minutes was the most common time. A total of 118 patients (56.5%) versus 11 (5.4%) reported impairment of dark adaptation. Two patients withdrew from the study because of this problem. 48 cases are thought to have resolved during treatment. An additional 18 reports (8.6%) complained of chromatopsia and 15 (7.2%) versus 2 (1%) complained of light adaptation impairment. These disorders are drug related and may be dose related. see appendix table 44.1 for total list.

hepatic - (described under the metabolic and nutritional system)

Increases in SGOT and SGPT occurred in 26 (12%) and 19(9%) patients. One case of jaundice in placebo treated patient. One nilutamide patient (117) was discontinued due to elevated SGOT/SGPT values on day 86 of the study with an elevation of 499 U/L and 776 U/L respective enzymes. (see chart Table Y in appendix from sponsor).

GI - Almost every one (except 1% of placebo patients) had one or more adverse experiences. Nausea occurred in 52 (25%) of nilutamide treated patients. The majority of the nausea complaints were related to the 300 mg dose. There were no changes in RBC, SGOT, SGPT or glucose noted.

8.2.5 Reviewer's Comments

A significantly higher proportion of nilutamide patients than placebo patients demonstrated a better response to complete or partial tumor regresssion at some time during the study. There is not a statistically significant

advantage demonstrated with the addition of nilutamide to leuprolide treatment. Neither survival time or time to objective progression are mature enough according to the sponsor to detect significant differences since only 42% of the evaluable patients had died at the time of the data cutoff.

The study does not provide adequate data demonstrating efficacy with the addition of nilutamide. This was partially due to the patient population in this study who did extremely well regardless of treatment.

8.3 - Supporting studies

The sponsor has provided an additional eight randomized, double-blind, placebo-controlled trials of nilutamide in combination with orchiectomy in patients with metastatic prostate cancer who were previously untreated were included in the submission. This included: Study Nos. **CDN/83/908/05** (with Buserelin), **F/82/908/03** (orchiectomy and two doses of nilutamide 300 and 150), **F/82/908/01** {3 studies comparing orchiectomy, buserelin and DES arms}, **F/84/908/01** (orchiectomy - Stage C and D), **CH/85/908/05** (orchiectomy - only 300 mg dose), **F/85/908/10** (Buserelin), **ZA/85/908/02** (orchiectomy - only 300 mg dose), **FF/86/ANA/001** (orchiectomy - 300 mg dose). Each of these were small studies and a review is not included at this time.

9 Overview of Efficacy :

In neither of the studies is there any demonstration of a survival benefit. If any improvement is to be seen it is in the early treatment stages to halt progression. The 908 trial provides data demonstrating a clear advantage; significantly more nilutamide patients than placebo treated patients had a complete or partial tumor regression. The median time to progression was 19.0 months in the nilutamide group and 14.9 months in the placebo group. Statistical differences were seen in the reduction of pain, and normalization of PAP and ALP by 3 months. These are important benefits and suggest that quality of life will be clinically improved. These biochemical assays may reflect regression of tumor. Progression-free survival time is a small but important addition for many men with prostate cancer.

The second trial, 606, demonstrates neither survival nor the short term benefits one should gain with the addition of an antiandrogen. Although there is an increased percent of patients with complete or partial regression of cancer there is no other evidence of a drug benefit over placebo. The proportion of responders in the placebo group is larger than placebo patients in 908. The difference in median times to objective progression is not significantly different between the two arms of the study (25.0 and 24.5 months for the nilutamide and placebo patients).

The difference between the two survival curves in 908 was not statistically significant. The median survival was 28.3 months in the nilutamide group and 23.2 months in the placebo group (0.058). (page 20) The median time to death due to prostate cancer had not been reached in study 606. (page 26)

Other endpoints that should benefit the patients quality of life include Pain and markers of regression of cancer cells and bone involvement. In 606 with respect to change in metastatic pain, there were no statistical differences with approximately 65 - 70% of the patients improving from baseline up to 3 months after randomization. Among those with pain at baseline in study 908 at 3 months, 85% of the nilutamide patients had improved over placebo (p=0.001); at 6 months 80% had improved over placebo (p=0.06). (see statistical review for further discussion)

Pain: The improvement at 1 month in metastatic related pain is 52 vs 41% in Study 908 and 39 vs 28% in Study GHBA 606.

METASTATIC RELATED PAIN - EVALUABLE PATIENTS

	FF/86/908/01		GHBA-606	
	Nilutamide	Placebo	Nilutamide	Placebo
Month 1	198	204	197	193
Improved	52%	41%	39%	28%
Month 3	185	192	186	186
improved	59%	42%	44%	38%

NORMALIZATION OF PAP

(to normal range for individual labs):

PAP	FF/86/908/01		GHBA-606	
	Nilutamide	Placebo	Nilutamide	Placebo
Month 1/n	43/85	23/71	61/116	36/124
normalize	51%	32%	53%	29%
month 3/n	59/90	34/68	75/106	50/103
normalize	62%	50%	71%	49%

page 000028 Integrated efficacy
volume 2.38

When these studies were initiated PSA was just beginning to be used widely. In study 908 54% of nilutamide and 63% placebo patients had PSA data. In study 606 58% of nilutamide and 68% of placebo patients had PSA data.

NORMALIZATION OF PSA To Normal Levels

PSA base elevated	FF/86/908/01 hybritech 4 ng		GHBA-606 Pros-check 2.5 ng	
	Nilutamide	Placebo	Nilutamide	Placebo
Month 1	18/107	14/99	41/112	15/116
normalize	17%	14%	37%	13% #
Month 3	62/108	25/90	77/101	51/99
normalize	57%	28% #	76%	52% #
Month 6	50/88	22/79	75/96	51/87
	57%	28% #	78%	59% ##
Endpoint	53/128	23/116	69/127	53/127
	41%	20%	54%	42%

P = 0.001

p = 0.003

It is noteworthy that only 7 patients in FF/86/908/01 and 2 patients in GHBA-606 had normal PSA (below the upper limit of normal) at the time of inclusion.

ALKALINE PHOSPHATASE

	FF/86/908/01		GHBA-606	
	Nilutamide	Placebo	Nilutamide	Placebo
Month 3	29/110	25/122	30./83	11/85
	26%	12% ##	36%	13%
Month 6	41/100	39/106	44/78	23/77
	41%	28% ##	56%	30% #

0.005 ##0.039

(on page 8 of volume 2-38 states that changes from baseline in PAP and ALP were categorized as increase by 25% or more - no change or decrease by 25% or more.)

From the statistical review:

1) The proportion of responders by prostate cancer criteria in the 'placebo' group in study 606 was substantially larger than that in Study 908/01.

2) The survival profile of placebo patients in study 606 was better than that of the nilutamide patients in study 908/01.

3) The general condition of evaluable patients in study 606 was better than those in study 908/01. Patients in the latter were older, had more urinary obstruction and lower average Karnofsky status.

Regarding Surrogate Markers or positive predictors:

The sponsors have reanalyzed the data to identify a predictive marker in terms of progression-free interval at 3 months and overall survival in both the studies.

The sponsors believe normalization PSA (to the upper limits of normal of that assay) 3 months after initiation of therapy is a good predictive marker in terms of progression-free interval and overall survival in those patients whose **initial ALP was less than twice upper limit of normal**. They believe this to be true in both trials. PAP, a non-specific marker, is unrelated to the outcome; this is not surprising.

The sponsors further suggest that if the ALP is above twice the upper limit of normal at inclusion than the normalization of PSA is marginal at best. This is somewhat similar to the sub-group analysis of the NCI 0036 trials where the true benefit of treatment appears to be in the group with the minimal disease severity.

A full discussion of the predictive marker analysis is included in the statistical review of David Hoberman.

10 Overview of Safety

At time of the submission of this NDA over 3,195 patients had been treated with nilutamide. This included 3,102 men with prostate cancer, 19 with other cancers, 9 women with polycystic ovarian disease and 65 healthy subjects. Over 10,000 patients with prostate cancer have been treated for over two months in several countries. It would appear that only 88 patients have been on nilutamide as monotherapy and this included the women subjects

There are slight discrepancies in total numbers which probably reflect differences between first submission and resubmission. The major safety concerns include pulmonary, visual, hepatic and gastrointestinal system.

- Pulmonary disorders and in particular signs and symptoms of Interstitial Pneumonitis with progressive exertional dyspnea and radiological changes of interstitial and/or alveolo-interstitial changes are the most important concern. The cases in clinical trials have occurred within the first 3 months of treatment. and have resolved with removal of drug and steroid therapy. 8% of patients treated with orchiectomy and 3.5% of patient treated with LHRH agonist developed a lung syndrome known as interstitial pneumonitis.

Of particular concern was the incidence of interstitial pneumonitis in a small Japanese study where 8 patients out of 47 patients treated developed the disease. There has been no identification of markers or patient population at risk. There was no indication of increased infection with drug treatment.

If the drug was to be approved, the sponsor needs to identify in a control study setting possible patient population or environmental risks.

In February 1988 the sponsor was required to include a warning statement in the investigator information brochure. This was as a result of 5 cases of interstitial pneumonitis in study 606. It was requested that all patients have pretreatment chest x-rays and pulmonary function tests du at months 1,2,3, and 6. This occurred after the completion of study 908. Only 23 patients were enrolled after this request; therefore little information was gathered after this time. However, total of 16 patients - 11 on nilutamide and 5 placebo were evaluated; 7 of the 23 patients had no repeat tests

done. One of the treated patients developed subclinical interstitial disease and withdrew consent.

- **visual disturbances** - These appear to be reversible upon treatment discontinuation or scheduled dose decrease from 300 mg to 150 mg; Some disturbances appeared to have resolved during treatment.

There were visual disturbances in 23% (908) of orchiectomized patients and 57% (606) of patients receiving leuprolide plus nilutamide. The placebo arm had 1% and 5% (606). There was a much higher incidence in the gonadotropin treated study.

The delay in dark adaptation took from several seconds to 30 minutes. It would be necessary to strongly label night or tunnel driving or machinery in the dark.

The impaired adaptation to darkness, photophobia, impaired light adaptation, or chromatopsia are all reversible upon treatment discontinuation or dose decrease at the end of the first month of treatment on 300 mg. These disturbances lead to discontinuation in 1% to 2% of cases.

- Hepatitis or marked increases in liver enzymes leading to discontinuation occurred in 1% of nilutamide patients in controlled clinical trials.

There was one death related to liver disease. One 78 year old man developed jaundice and a febrile condition (possible UTI) one month after entering the study and died one week later. The death may have been secondary to prostate carcinoma; however, it was in the first month of 300 mg treatment. (study 908) Three patients or 1.3 % in 908 were withdrawn because of an increase in liver transaminases. Treatment withdrawal for hepatitis was seen in 1% of patients. The sponsor notes that in study 908 Between 7 and 11% versus 4% placebo patients had SGOT and SGPT values more than twice the upper limit of normal and in study 606 there were SGOT and SGPT values elevated 20% versus 15%. The time frame has not been identified.

In study 606 there were increases in SGOT and SGPT which occurred in 26 (12%) nilutamide and 19(9%) placebo patients. There was one case of jaundice in placebo treated patient. One nilutamide patient was discontinued due to elevated SGOT/SGPT values on day 86 of the study with an elevation of 499 U/L and 776 U/L

respective in the enzymes. (see chart Table Y in appendix from sponsor.)

The preclinical studies demonstrates fatal liver toxicity in dogs at drug exposure levels similar to human doses. The hepatic problems are **nonreversible when recognized** and there is no data that identifies risks or identifiable markers at the reversible point. This propensity for liver damage appears to be a problem for all antiandrogens at least at the doses used.

- GI - Although no diarrhea is reported with this compound there is a high degree of drug-related nausea reported in 9 - 10% of nilutamide and 4- 6% orchiectomy and 25% in 606 . check

- alcohol intolerance appeared to be dose related. The incidence is <1% in placebo-treated patients and in 4 % to 5% if nilutamide patients. 6 patients resolved with doses at 150 mg ,

There were no apparent age related changes in the above safety concerns and no data to identify how many patients had more than one problem at the same time.

One hundred fourteen (34%) patients receiving nilutamide and 59 (18%) patients receiving placebo discontinued the double-blind part of the study because of adverse experiences, including intercurrent events. The most frequent reason for discontinuation of treatment in the pooled orchiectomy studies was death. Seventeen percent of patients in the nilutamide group and 14% of patients in the placebo group are listed as having been discontinued for this reason. In the nilutamide group, seven (2%) patients were discontinued because of dizziness, five (2%) because of interstitial lung disease, three (1%) because of hepatitis, and six (2%) because of visual disturbances. No patient in the placebo group was discontinued for these reasons.

The largest incidence of adverse experiences considered treatment related by the sponsor occurred in the special senses category. Impaired adaptation to darkness was considered related in 9% of patients who received nilutamide compared with 1% of placebo patients. Chromatopsia was considered related in 3% of nilutamide patients and none of the placebo patients.

The endocrine system had the second highest incidence of treatment-related adverse experiences. All the adverse experiences reported here are the expected effects of

orchiectomy with or without antiandrogen treatment and thus considered related to treatment in these studies.

In the body as a whole, alcohol intolerance occurred at a higher rate in the nilutamide group (4%) than in the placebo group (0%).

10.2.4 Drug-Demographic Interactions

Japanese study may reflect either environmental changes or ethnic differences in the metabolism of the drug. If this drug was approvable it would necessitate studies to identify more clearly the toxic changes to the lungs and liver seen in this population.

10.2.5 Drug-Disease Interactions

Only studied extensively in advanced prostate cancer

10.2.6 Drug-Drug Interactions

The sponsor states that drug-drug interactions must be considered when nilutamide is used with drugs with a low therapeutic margin. The sponsor believes this includes drugs such as vitamin K antagonists, phenytoin and theophylline which could result in delayed elimination and increases in their serum half-life.

10.2.7 Withdrawal Phenomena/Abuse Potential

There is no abuse potential or withdrawal phenomena noted.

11 Labeling Review

The sponsor would label the drug as contraindicated in the following patients:

- severe hepatic impairment
- with severe respiratory insufficiency
- with hypersensitivity to nilutamide or any component of this preparation.
- not indicated in women.

The sponsor would presumably at a statement regarding PSA normalization at 12 weeks for continued therapy and state ineligibility for treatment if ALP more than twice the normal at baseline.

The labeling review will be completed after the Advisory meeting of February 24, 1995.

12 Conclusions

There is insufficient evidence in this submission that the risk versus the benefit truly offers a clinical benefit for the palliative treatment of prostate cancer. Although study 908 offers good evidence that there is short term benefit in progression, and the PSA data in particular suggest good normalization of the disease process over placebo and perhaps importantly a diminution of the pain associated with prostate cancer. The 606 study demonstrates no advantage to the addition of an antiandrogen to medical castration. It would appear that the patients entered into this trial did exceedingly well in all parameters regardless of treatment and compared to expectations from other trials. Unfortunately there is no data within the study that identifies why this patient population appears different and it would suggest that again total androgen blockade is of little benefit.

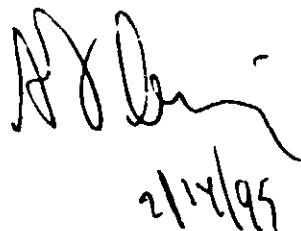
The risks of this compound appear to outweigh the clinical benefits. The preclinical submission defines areas of concern including both liver and lung toxicity at drug levels similar to human drug levels. The clinical data also suggests pulmonary and liver problems similar to the preclinical data. The margins of benefit are very narrow therefore the adverse risks are less acceptable even when considering cancer treatment.

13 Recommendations

A final decision will be made on the approvability of this submission after the Advisory Committee meeting, February 24, 1995.



Jean L. Fourcroy, M.D., PhD
Medical Officer
HFD-510/February 9, 1995



APPENDIX

- 1. PROTOCOL OUTLINE 908 (SIMILAR TO 606)**
- 2. KARNOFSKY PERFORMANCE STATUS**
- 3. TUMOR STAGING**
- 4. NPCP CRITERIA**
- 5. OUTLINE STUDIES NILUTAMIDE**
- 6. INVESTIGATORS - 606 Trial - U.S.**
- 7. SECONDARY CRITERIA OF PAIN, PERFORMANCE, PAP, PSA, ALP - 606 AND 908**
- 8. SUMMARY OF HEPATIC EVENTS IN BOTH TRIALS**
- 9. SUMMARY OF VISUAL EVENTS IN BOTH TRIALS**
- 10. SUMMARY OF PULMONARY EVENTS IN BOTH TRIALS**
- 11. RESPIRATORY CASES FROM 908**
- 12. REPRESENTATIVE GRAPHS FROM SPONSOR**
 - a. PROGRESSION - FREE SURVIVAL - 908**
 - b. PROSTATE CANCER SURVIVAL EVALUABLE PATIENTS 908**
 - c. PROSTATE CANCER SURVIVAL ALL PATIENTS 908**
 - d. OVERALL SURVIVAL - 908**
 - e. PROGRESSION - FREE SURVIVAL - EVALUABLE PATIENTS - 606**
 - f. PROGRESSION FREE SURVIVAL ALL PATIENTS - 606**

STUDY NO. 77/86/968/81

Protocol CRBA-610

Prostatic Carcinoma

	STUDY MONTH	PART A						PART B ^a
		0	1	3	6	12	18 ^f	
		1	2	3	4	5	6	
INFORMED CONSENT	X ^c							
HISTORY	X ^c							
CLINICAL EXAMINATION - FULL	X ^c				X	X	X	
- ABBREVIATED			X	X				X
BIOPSY	X ^c							
PAIN ASSESSMENT	X	X	X	X	X	X	X	X
PERFORMANCE STATUS	X	X	X	X	X	X	X	X
IVP/NEPHROGRAM ^b	X ^c			X ^b	X ^{d,e}	X ^{d,e}	X ^{d,e}	X ^{d,e}
CHEST X-RAY	X ^c			X ^b	X	X	X	X
BONE SCAN	X ^c			X ^b	X	X	X	X
ULTRASOUND ^g	X ^c			X ^b	X	X	X	X
X-RAY ^f	X ^c			X ^b	X	X	X	X
CAT SCAN ^h	X ^c			X ^b	X	X	X	X
LIDOWOGRAPHY ^h	X ^c			X ^b	X	X	X	X
HEMATOLOGY ⁱ	X ^c	X	X	X	X	X	X	X
PROTHROMBIN TIME	X ^c	X	X	X	X	X	X	X
BLOOD CHEMISTRIES	X ^c	X	X	X	X	X	X	X
URINALYSIS	X ^c	X	X	X	X	X	X	X
ACID PHOSPHATASE/BONEWAX ASSAYS	X ^c	X	X	X	X	X	X	X
OVERALL EVALUATION (HPCF)				X ^b	X	X	X	X
GLOBAL EVALUATION	X	X	X	X	X	X	X	X
DIETARY MEDICATION	X	X	X	X	X	X	X	X

- a Extended treatment patients evaluated at 6 month intervals
- b Another appropriate technique (e.g., ultrasound) may be substituted if patient is allergic to injection dye or if another technique is preferred
- c May be performed within 4 weeks prior to visit 1
- d To be performed if previously abnormal or to evaluate suspected new structural abnormalities
- e If required to evaluate metastatic involvement
- f Two or three representative sites at which bone scan is positive are to be followed throughout the study. X-ray may also be used to characterize possible new areas of metastatic involvement.
- g If a patient is discontinued prematurely all three assessments must be completed
- h Evaluation performed only if objective progression (HPCF criteria) has occurred and it is necessary to determine whether objective progression (HPCF criteria) has occurred
- i A blood sample for hematology will be obtained at months 9 and 15
- j To be dispensed only if the patient is continuing in the study

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Attachment 1
Page 1 of 1

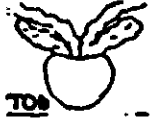
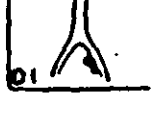
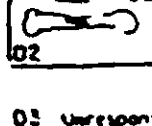
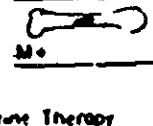
KARNOFSKY PERFORMANCE STATUS SCALE

Percent

Able to carry on normal activity; no special care is needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home; cares for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or do active work
	60	Requires occasional assistance but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled, requires special care and assistance
	30	Severely disabled; hospitalization is indicated though death not imminent
	20	Very sick; hospitalization is necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

000091

CARCINOMA OF THE PROSTATE
TUMOR STAGING, UICC SYSTEM
TUMOR, NODE AND METASTASIS (TNM)

MODIFIED WHITMORE-JEWETT	UICC	% + RIA for PAP	% + Lymph Nodes
		12	2
			23
*Poorly differentiated A2			
		30	18
			
			35
			
		45	50
			80
			100
		90	—
D3 Unresponsive to Endocrine Therapy		—	—

Attachment 3
Page 1 of 1

CARCINOMA OF THE PROSTATE

TUMOR STAGING

(Whitmore - Jewitt Systems)

Stage A Not palpable clinically but is found histopathologically following prostatectomy and can be divided into:

Stage A1 - focal or well differentiated carcinoma

Stage A2 - diffuse or poorly differentiated carcinoma

Stage B Tumors limited to the prostate and on rectal examination can be divided into:

Stage B1 - a solitary nodule involving less than one lobe of the prostate

Stage B2 - cancer in which one lobe or more is involved

Stage C Tumors extend beyond the prostatic capsule but have not metastasized

Stage D Metastatic carcinoma of the prostate

Stage D1 - presence of metastatic disease in lymph nodes of pelvis

Stage D2 - patients with clinical metastatic carcinoma (defined as distant metastases, e.g., metastases of lymph nodes above the diaphragm)

000093

- 1858 -

Attachment 4
Page 1 of 3

NPCP CRITERIA (MODIFIED)

1. Complete Objective Regression (All of the following):

- A. Return of an elevated prostatic acid phosphatase, if previously present, to normal.
- B. Absence of any clinically detectable soft tissue tumor mass.
- C. All osteolytic lesions in sites being followed have recalcified.
- D. There is no evidence of progression of any osteoblastic lesion and all cancer related areas of increased uptake on bone scan have disappeared.
- E. If hepatomegaly is a significant indicator there must be a complete reduction in liver size, and normalization of all pre-treatment abnormalities of liver function.
- F. As compared to baseline there is no significant cancer-related weight loss (>10%) and the general category of Karnofsky Performance Status has improved or remained the same (if previously normal).
- G. If symptomatic from prostate cancer the patient has become completely asymptomatic.

2. Partial Regression

Any of the following criteria:

- A. Recalcification of one or more osteolytic lesion.
- B. At least one previously measurable soft tissue metastasis is reduced by 50% in cross-sectional area as compared to baseline.
- C. If hepatomegaly is a significant indicator, there must be a reduction in liver size and at least a 30% improvement in all pre-treatment abnormalities of liver function.

And all of the following:

- D. There must not be any increase in cross-sectional area of any soft tissue metastasis, and no worsening of any bone lesion being followed.
- E. There is no new soft-tissue metastasis or bone lesion.
- F. Return of an elevated prostatic acid phosphatase, if previously

000094

- 1859 -

Attachment 4
Page 2 of 3

present, to normal.

- G. As compared to baseline there is no significant cancer-related weight loss (>10%), symptoms, and the general category of Karnofsky Performance Status has improved or remained the same.

3. Objectively Stable Disease (All of the following):

- A. Elevated prostatic acid phosphatase, if previously present, has decreased though not necessarily to normal.

NOTE: An increase in prostatic acid phosphatase unaccompanied by subjective or objective evidence of progressive disease will be considered stable disease.

- B. Insufficient regression of soft tissue metastasis to meet the criteria above.
- C. Less than 25% increase in any previously measurable soft-tissue metastasis.
- D. All bone lesions have remained stable (do not appear to worsen).
- E. There is no new soft-tissue metastasis or bone lesion.
- F. If hepatomegaly is a significant indicator it must not have worsened by a clinically significant degree and all pre-treatment abnormalities of liver function have not worsened.
- G. As compared to baseline there is no significant cancer-related weight loss (>10%), symptoms, and the general category of Karnofsky Performance Status has improved or remained the same.

4. Subjective Progression (Any of the following):

- A. Deterioration in Karnofsky Performance Status (at least one general category level).
- B. As compared to baseline there has been a cancer-related weight loss of 10% or greater.
- C. There is increased cancer-related pain as evidenced by the need for increased analgesia.

5. Objective Progression (of relapse after adequate therapy)

Any of the following:

- A. The presence of a new measurable soft-tissue metastasis.
- B. An increase in any soft-tissue metastasis present at baseline by greater than 25% in cross-sectional area as compared to

000095

Attachment 4
Page 3 of 3

baseline.

- C. A greater than 25% increase in the area of bone lesion involvement (entire body) or in the number of bone lesions as compared to baseline.

NOTE: An increase in acid and/or alkaline phosphatase alone is not to be considered an indication of progression. These should be used in conjunction with other criteria.

000096

OUTLINE OF STUDIES IN THE
NILUTAMIDE CLINICAL PROGRAM

	<u>Number of Subjects/Patients</u>	
	<u>Nilutamide</u>	<u>Total</u>
1. <u>14 HP&B STUDIES</u>		
a) Pilot Studies: 2 studies	7	7
b) Bioavailability Studies: 3 studies	36	36
c) Pharmacokinetic Studies: 7 studies	36	36
d) In Vitro Studies: 2 studies	<u>N.A.</u>	<u>N.A.</u>
Subtotal:	79	79
2. <u>6 CLINICAL PHARMACOLOGY STUDIES</u>		
a) Dose-Range Studies: 2 studies	22	22
b) Pharmacodynamic Studies: 4 studies	<u>39</u>	<u>39</u>
Subtotal:	61	61
3. <u>10 CONTROLLED CLINICAL STUDIES</u>		
a) Primary Studies: 2 studies	434	868
b) Supportive Studies: 8 studies	<u>596</u>	<u>1,068</u>
-Previously untreated patients - 7 studies		
-Previously treated patients- 1 study		
Subtotal:	1,030	1,936
4. <u>7 UNCONTROLLED CLINICAL STUDIES</u>		
a) Long-Term Safety Studies: 3 studies	913	913
b) Short-Term Safety Study: 1 study	39	39
c) Safety and Short-Term Efficacy Studies: 3 studies	<u>114</u>	<u>114</u>
Subtotal:	1,066	1,066
5. <u>2 OTHER STUDIES</u>		
a) Study in Other Cancer Indications	19	19
b) Study in Women	<u>18</u>	<u>18</u>
Subtotal:	37	37
OVERALL TOTAL:	2,273	3,179

Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
 GHBA Protocol 606
 Investigator: Combined

8SEP93

TABLE 1
 (Page 1 of 2)

DISTRIBUTION OF PATIENTS RANDOMIZED

Investigator	Leuprolide + Nilutamide	Leuprolide + Placebo
Al-Juburi	8	8
Balducci/Khansur	3	4
Belville	4	4
Elock	7	7
Boileau/Ireton/Lange	3	4
Bracken	6	8
Callahan	4	3
Crawford	10	10
DeVere White	3	3
Fisher/Wilbur	2	4
Gandara	6	6
Gibbons	3	3
Graham	4	4
Greenberg	4	3
Haller	4	4
Hodge	7	7
Huben	2	3
Kasimis	6	5
Khanna	2	0
Lama	6	6
Lange/Lightner/Zhang	14	14
Lynch D.	11	8
Lynch J.	1	1
Miles	5	6
Montie/Pontes	4	3
Moon	6	5
Nyberg/Albertson	2	1
Pessis	2	1
Rajfer	10	12
Scardino	4	2
Schmidt	5	4

000017

done. One of the treated patients developed subclinical interstitial disease and withdrew consent.

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STATISTICALLY SIGNIFICANT DIFFERENCES AND
TRENDS^a FAVORING NILUTAMIDE OVER PLACEBO

908

Criterion	Month:	P-value					Endpoint ^b
		1	3	6	12	18	
Cancer Pain		.046 #	.007 #	.030	---	---	---
Decrease from Baseline							
PAP ^c		.021 #	.044	---	.013	---	.021
PSA ^c		---	.038	---	---	---	.048
Alk. Phos. ^c		<.001 #	.062	.038	.021	---	.040
Normalization of Values							
PAP		.027	---	---	---	---	.044
PSA		---	<.001	<.001	---	---	<.001
Alk. Phos.		---	.005	.039	.002	.065	.057
Median % Change From Baseline							
PAP		---	.006	---	.097	---	.014
PSA		---	<.001	<.001	---	---	<.001
ALP		<.001 #	.007	.012	.003	---	.003
Bone Scan Isotope Uptake		---	.005	.010	<.001	---	.011
Tumor Volume		---	---	---	---	.072	---

^a P-values >0.05 and <0.10).

^b Endpoint is the final study evaluation.

^c PAP=prostatic acid phosphatase; PSA=prostate specific antigen; ALP=alkaline phosphatase.

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Criterion	Month:	P-value					Endpoint ^b
		1	3	6	12	18	
Cancer Pain		---	---	.065	---	---	---
Performance Status		---	---	.025	---	---	---
Decrease from Baseline							
PAP ^c		<.001	.076	.026	---	---	---
PSA ^c		---	---	---	---	---	---
Alk. Phos. ^c		<.001	<.001	<.001	---	.091	.019
Normalization of Values							
PAP		<.001	<.001	<.001	---	---	.037
PSA		<.001	<.001	.003	.034	---	.025
Alk. Phos.		---	.002	.005	.031	---	---
Median % Change from Baseline							
PAP		<.001	.007	---	---	.051	.002
PSA		<.001	<.001	.002	.033	---	---
ALP		<.001	<.001	<.001	---	.047	.017
Investigators Global Assessment		---	---	.013	.077	---	---
Bone Scan Isotope Uptake		---	---	.002	---	.091	.066
Primary Tumor Volume		---	---	---	---	.095	.033

^a P-values >0.05 and <0.10).

^b Endpoint is the final study evaluation.

^c PAP=prostatic acid phosphatase; PSA=prostate specific antigen; ALP=alkaline phosphatase.

Roussel-UCLAF
 Nilutamide versus Placebo
 in orchiectomized Patients
 Protocol FF/86/908/01
 Investigator: Combined

15SEP93

TABLE 45.1
 SUMMARY OF SERIOUS ADVERSE EXPERIENCES
 (INCLUDING INTERCURRENT EVENTS) REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION
 (ALL PATIENTS, DOUBLE-BLIND PHASE OF STUDY)

Adverse Experience	Orchiectomy + Nilutamide		Orchiectomy + Placebo	
	N	(%)	N	(%)
DIGESTIVE SYSTEM				
Anorexia	1	(0.4)	0	(0.0)
Cholelithiasis	1	(0.4)	0	(0.0)
Cirrhosis of liver	0	(0.0)	1	(0.4)
Colitis	1	(0.4)	0	(0.0)
Constipation	1	(0.4)	0	(0.0)
Diarrhea	1	(0.4)	1	(0.4)
Gastrointestinal carcinoma	4	(1.8)	4	(1.7)
Gastrointestinal hemorrhage	4	(1.8)	2	(0.9)
Hepatitis	1	(0.4)	0	(0.0)
Ileus	0	(0.0)	1	(0.4)
Intestinal obstruction	1	(0.4)	0	(0.0)
Jaundice	1	(0.4)	1	(0.4)
Liver necrosis	0	(0.0)	1	(0.4)
Melena	2	(0.9)	0	(0.0)
Nausea	4	(1.8)	1	(0.4)
Rectal disorder	1	(0.4)	1	(0.4)
Vomiting	3	(1.3)	2	(0.9)
SUBTOTAL	18	(8.0)	13	(5.6)

SUBTOTALS and TOTALS - Numbers of patients having one or more clinical and/or laboratory adverse experiences

Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
 GHBA Protocol 606
 Investigator: Combined

8SEP93

TABLE 46.1
 (Page 4 of 8)

SUMMARY OF SERIOUS ADVERSE EXPERIENCES
 (INCLUDING INTERCURRENT EVENTS), REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION
 (ALL PATIENTS, DOUBLE-BLIND PHASE OF STUDY)

Adverse Experience	Leuprolide + Nilutamide (N= 209)	Leuprolide + Placebo (N= 202)
	No. of Pts. (%)	No. of Pts. (%)
HEMIC & LYMPHATIC SYSTEM		
FIBRIN INCREASED	0	1 (0.5)
FIBRINOGEN INCREASED	0	1 (0.5)
LYMPHOMA LIKE REACTION	1 (0.5)	0
THROMBOCYTOPENIA	2 (1.0)	0
SUBTOTAL	5 (2.4)	5 (2.5)
METABOLIC & NUTRITIONAL SYSTEM		
ALKALINE PHOSPHATASE INCREASED	1 (0.5)	0
BILIRUBINEMIA	0	1 (0.5)
DIABETES MELLITUS	0	1 (0.5)
EDEMA	1 (0.5)	0
GOUT	0	1 (0.5)
HYPERCALCEMIA	1 (0.5)	0
HYPERGLYCEMIA	1 (0.5)	2 (1.0)
HYPOGLYCEMIA	1 (0.5)	0
KETOSIS	0	1 (0.5)
LACTIC DEHYDROGENASE INCREASED	0	1 (0.5)
PERIPHERAL EDEMA	2 (1.0)	2 (1.0)
SGOT INCREASED	0	1 (0.5)
SGPT INCREASED	0	1 (0.5)
SUBTOTAL	6 (2.9)	6 (3.0)
MUSCULO SKELETAL SYSTEM		
ARTHRITIS	1 (0.5)	0

SUBTOTALS and TOTALS = Numbers of patients having one or more clinical and/or laboratory adverse experience during the double-blind phase of the study.

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Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
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 Investigator: Combined

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TABLE 44.1
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NUMBER AND PERCENT OF PATIENTS WITH SPECIFIC ADVERSE EXPERIENCES
 (INCLUDING INTERCURRENT EVENTS) REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION
 (ALL PATIENTS, DOUBLE-BLIND PHASE OF STUDY)

Adverse Experience	Leuprolide + Nilutamide (N= 209)	Leuprolide + Placebo (N= 202)
	No. of Pts. (%)	No. of Pts. (%)
SPECIAL SENSES:		
BLINDNESS	1 (0.5)	2 (1.0)
CATARACT NOS	9 (4.3)	5 (2.5)
CHROMATOPSIA	(18) (8.6) •	0
COLOR BLINDNESS	1 (0.5)	0
CONJUNCTIVITIS	1 (0.5)	2 (1.0)
CORNEAL LESION	0	1 (0.5)
DARK ADAPTATION IMPAIRMENT	118 (56.5) •	11 (5.4)
DEAFNESS	1 (0.5)	1 (0.5)
DIPLOPIA	1 (0.5)	2 (1.0)
EAR DISORDER	0	1 (0.5)
EYE DISORDER	0	3 (1.5)
EYE PAIN	0	3 (1.5)
GLAUCOMA	1 (0.5)	2 (1.0)
KERATOCONJUNCTIVITIS	0	1 (0.5)
LACRIMATION DISORDER	0	1 (0.5)
LIGHT ADAPTATION IMPAIRMENT	15 (7.2) •	2 (1.0) •
NIGHT BLINDNESS	0	1 (0.5)
PAROSMIA	1 (0.5)	0
PHOTORHOBIA	2 (1.0)	2 (1.0)
RETINAL DEGENERATION	1 (0.5)	0
RETINAL DISORDER	1 (0.5)	1 (0.5)
TASTE LOSS	1 (0.5)	0
TASTE PERVERSION	3 (1.4)	4 (2.0)
TINNITUS	2 (1.0)	4 (2.0)

Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
 GHBA Protocol 606
 Investigator: Combined

8SEP93

TABLE 44.1
 (Page 11 of 15)

NUMBER AND PERCENT OF PATIENTS WITH SPECIFIC ADVERSE EXPERIENCES
 (INCLUDING INTERCURRENT EVENTS) REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION
 (ALL PATIENTS, DOUBLE-BLIND PHASE OF STUDY)

<u>Adverse Experience</u>	<u>Leuprolide</u> <u>+</u> <u>Nilutamide</u> <u>(N= 209)</u>	<u>Leuprolide</u> <u>+</u> <u>Placebo</u> <u>(N= 202)</u>
	<u>No. of</u> <u>Pts. (%)</u>	<u>No. of</u> <u>Pts. (%)</u>
RESPIRATORY SYSTEM		
ASPIRATION PNEUMONIA	0	1 (0.5)
ASTHMA	3 (1.4)	3 (1.5)
ATELECTASIS	2 (1.0)	0
BRONCHITIS	3 (1.4)	8 (4.0)
CARCINOMA OF LUNG	1 (0.5)	1 (0.5)
COUGH INCREASED	6 (2.9)	8 (4.0)
DYSPNEA	22 (10.5) *	13 (6.4) *
EPISTAXIS	1 (0.5)	2 (1.0)
HEMOPTYSIS	1 (0.5)	2 (1.0)
HYPOXIA	1 (0.5)	0
INTERSTITIAL LUNG DISEASE	7 (3.3) *	1 (0.5) *
LUNG DISORDER	8 (3.8)	7 (3.5)
LUNG EDEMA	1 (0.5)	2 (1.0)
LUNG FIBROSIS	1 (0.5) *	0
PHARYNGITIS	2 (1.0)	7 (3.5)
PNEUMONIA	10 (4.8)	6 (3.0)
PULMONARY EMBOLUS	0	1 (0.5)
PULMONARY THROMBOSIS	1 (0.5)	0
RESPIRATORY DISORDER	1 (0.5) *	2 (1.0)
RHINITIS	6 (2.9)	7 (3.5)
SINUSITIS	2 (1.0)	2 (1.0)
UPPER RESPIRATORY INFECTION	17 (8.1)	21 (10.4)
<u>SUBTOTAL</u>	<u>69 (33.0)</u>	<u>67 (33.2)</u>

SUBTOTALS and TOTALS = Numbers of patients having one or more
 clinical and/or laboratory adverse experience during the
 double-blind phase of the study.

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9. *Respiratory system*

Thirty-eight (17%) patients in the nilutamide group and 35 (15%) in the placebo group had an adverse experience of the respiratory system. Thirteen (6%) patients receiving nilutamide and 14 (6%) receiving placebo had dyspnea. See Table 49.9 for the severity, relationship to study medication, outcome, and treatment required for the cases of dyspnea reported in both treatment groups during the double-blind phase of the study. In the nilutamide group, 11 of the cases of dyspnea were mild or moderate and two were severe (patients Nos. [redacted] see below). In the placebo group, all cases of dyspnea were mild or moderate.

Dyspnea was considered possibly or probably related to the study medication in six (46%) nilutamide patients and no placebo patient. Five of the patients with dyspnea in the nilutamide group reported resolution of that adverse experience during the course of the study, and five still had dyspnea at the end of the patients' participation in the study. In the placebo group, six of the 14 patients reported resolution of dyspnea during the course of the study, and eight patients still had dyspnea at the end of the patients' participation in the study. In the nilutamide and the placebo groups, no treatment for dyspnea was required in seven and 11 of the patients, respectively, and hospitalization was required or prolonged in five and one of the patients, respectively. The five nilutamide patients with dyspnea who were hospitalized were:

Patient No. [redacted] was hospitalized after 8 months of treatment for dyspnea due to a lung infection which the investigator considered unrelated to study medication. He was treated successfully with antibiotics. Patient No. [redacted] was hospitalized two weeks after the onset of treatment because of dyspnea and dizziness, which the investigator considered to be possibly related to the study drug. The patient improved after withdrawal from the study but had two other episodes of dyspnea while off study drug. Patient No. [redacted] was hospitalized after two days of treatment because of dyspnea and concomitant malaise, nausea and dizziness. The symptoms, considered as possibly related to the study drug, resolved upon discontinuation of treatment. Patient No. [redacted] who had concomitant chronic obstructive pulmonary disease, angina and cardiac insufficiency was hospitalized twice for dyspnea, and recovered with treatment of heart failure. The investigator did not consider these episodes as related to study medication. Patient No. [redacted] was hospitalized because of dyspnea due to pleural effusion after 13 months in the study. The investigator considered this event possibly related to treatment which was nevertheless continued. The pleural effusion and dyspnea persisted when treatment was discontinued due to objective cancer progression.

Lung disorders (costart term) occurred in nine (4%) nilutamide patients and four (2%) placebo patients: in the nilutamide group, three patients (Nos. [redacted], [redacted], [redacted]) had exacerbation of chronic obstructive pulmonary disease, which required hospitalization for two patients, and were considered possibly related to the study drug for patient No. [redacted] and not or remotely related for the other two. One patient (No. [redacted]) had an aspiration pneumonia during hospitalization, considered as an intercurrent event, which resolved during hospitalization. Three patients (Nos. [redacted], [redacted], [redacted]) had respectively scattered wheezes, crepitations, and bilateral rhonchi which improved or resolved without treatment and were considered unrelated or remotely related to the study drug. Patient No. [redacted] had chronic airway disease related to pleural effusion, and thought to be possibly related to the study drug (see discussion of dyspnea, above). Patient No. [redacted] who had lung fibrosis before entry, was found to have increased lung markings on the chest X-ray after five months in the study. Three months later, the picture had deteriorated. The drug was discontinued due to both progression of cancer and this pulmonary event which the investigator considered possibly related to nilutamide. In the placebo group, the four lung disorders were crepitations, chronic obstructive airway disease, pulmonary congestion, and lung wheezes and did not require hospitalization.

Respiratory disorders (costart term) occurred in four (2%) nilutamide patients, and one (0.4%) placebo patient. In the nilutamide group, the respiratory disorder was hyperinflation in patients No. [redacted] and moderate bronchospasm in patient No. [redacted]. None of the three patients required discontinuation of treatment or hospitalization. Patient No. [redacted] was hospitalized after four days in the study for severe bronchospasm, pulmonary edema and left ventricular failure which the investigator considered as intercurrent events (see also cardiovascular system). In the placebo group, the respiratory disorder was not otherwise specified, but was of moderate intensity and did not require hospitalization or study drug discontinuation.

Patient No. [redacted] was hospitalized for interstitial pneumonitis after 2.5 months in the study. Nilutamide was discontinued and the patient recovered. The investigator considered this event to be probably related to study medication.

PROBABILITY OF PROGRESSION - FREE SURVIVAL
OBJECTIVE AND SUBJECTIVE PROGRESSION
Evaluable patients

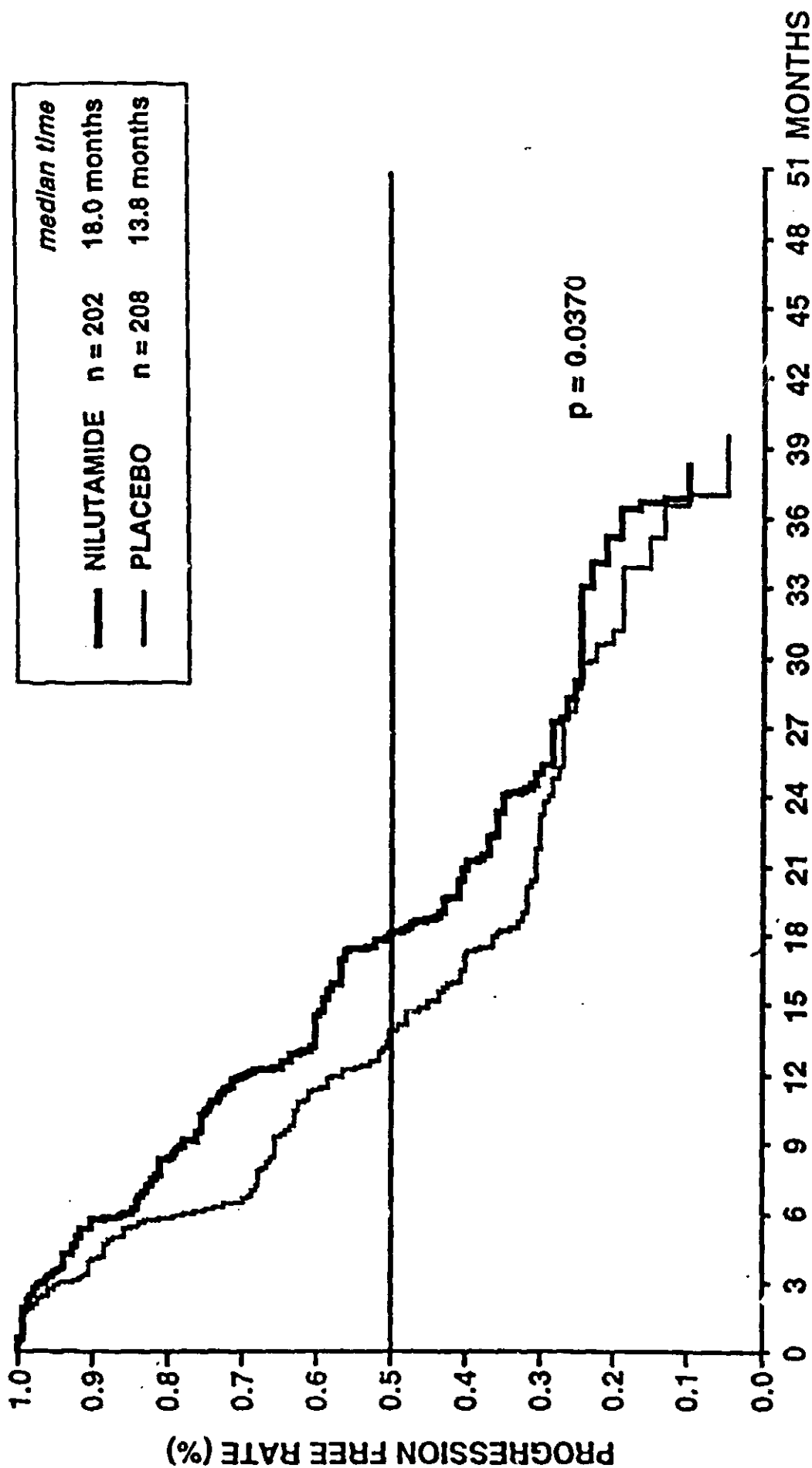


FIGURE 2:

PROBABILITY OF PROSTATE CANCER SURVIVAL Evaluable patients

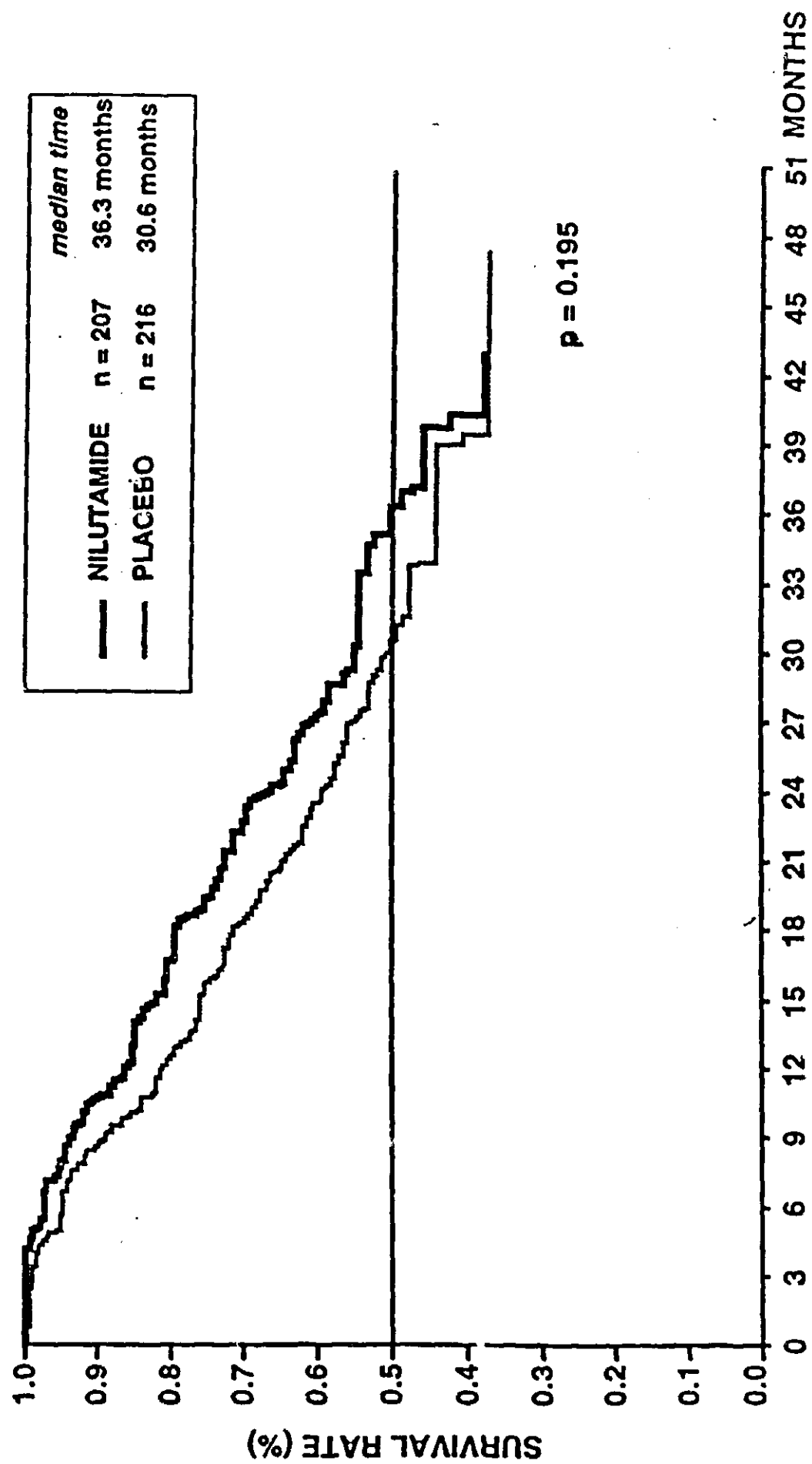


FIGURE 5:

PROBABILITY OF PROSTATE CANCER SURVIVAL
All patients

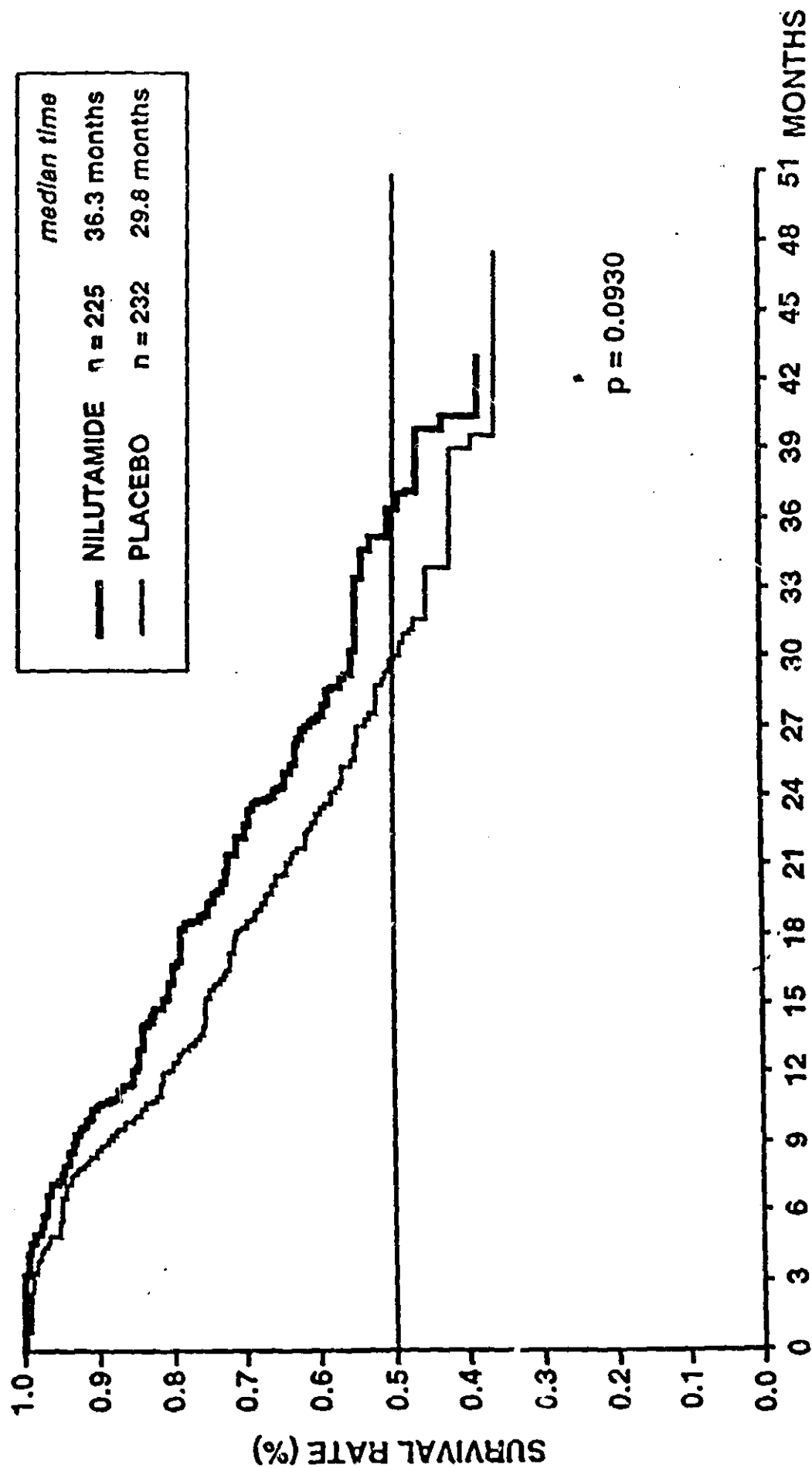


FIGURE 6:

PROBABILITY OF OVERALL SURVIVAL
Evaluable patients

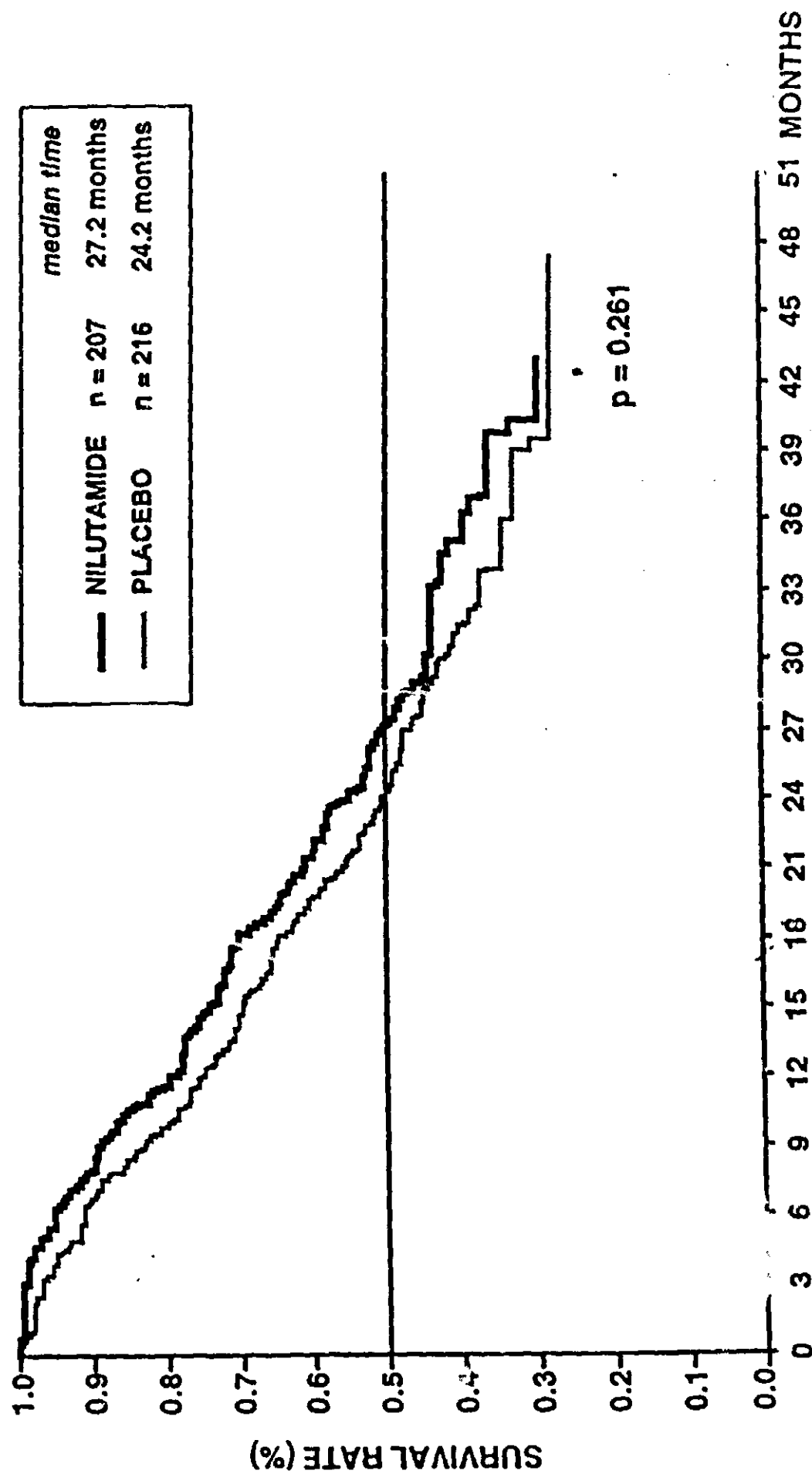


FIGURE 7:

FIGURE 1
 PROBABILITY OF PROGRESSION-FREE SURVIVAL
 (EVALUABLE PATIENTS)

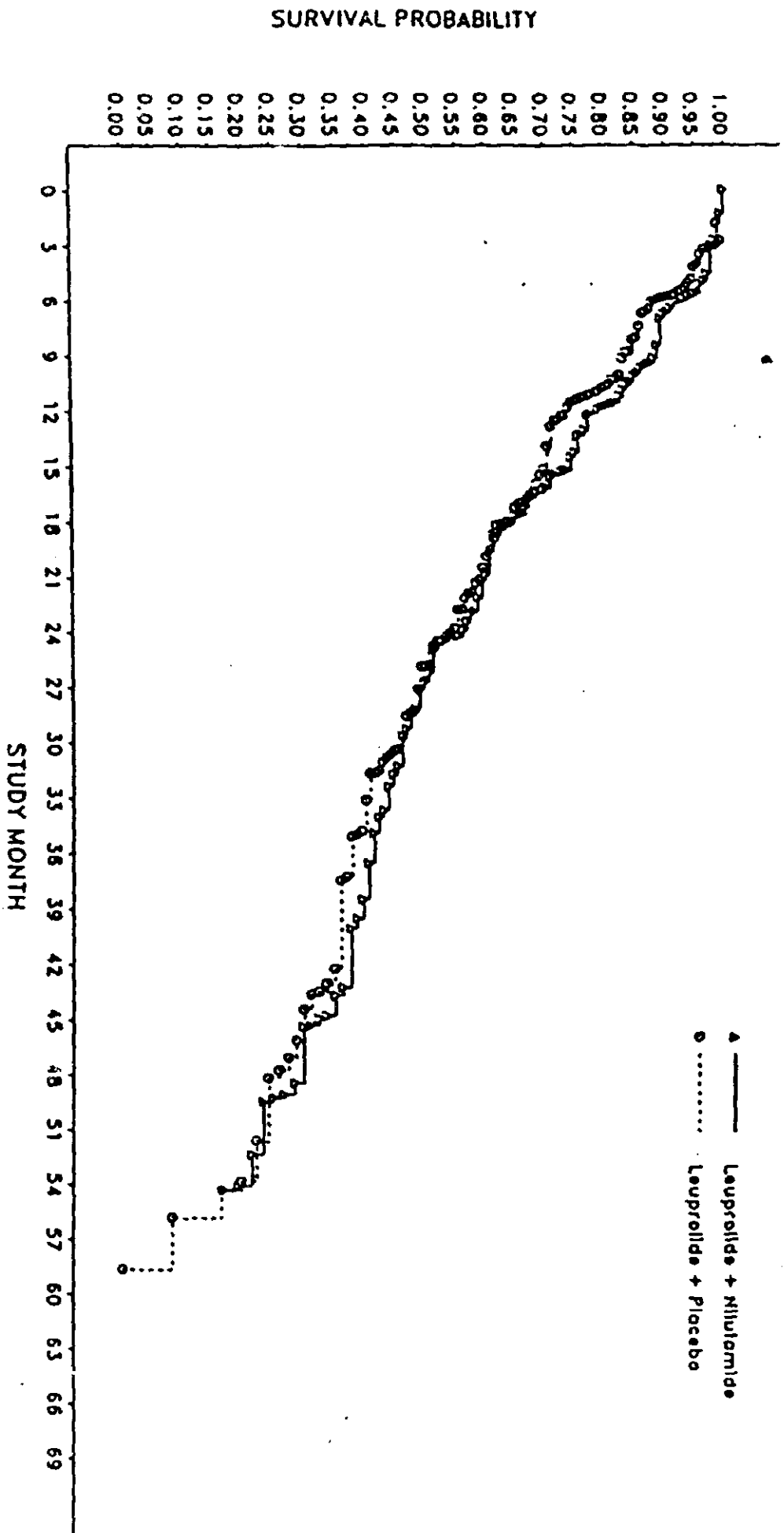
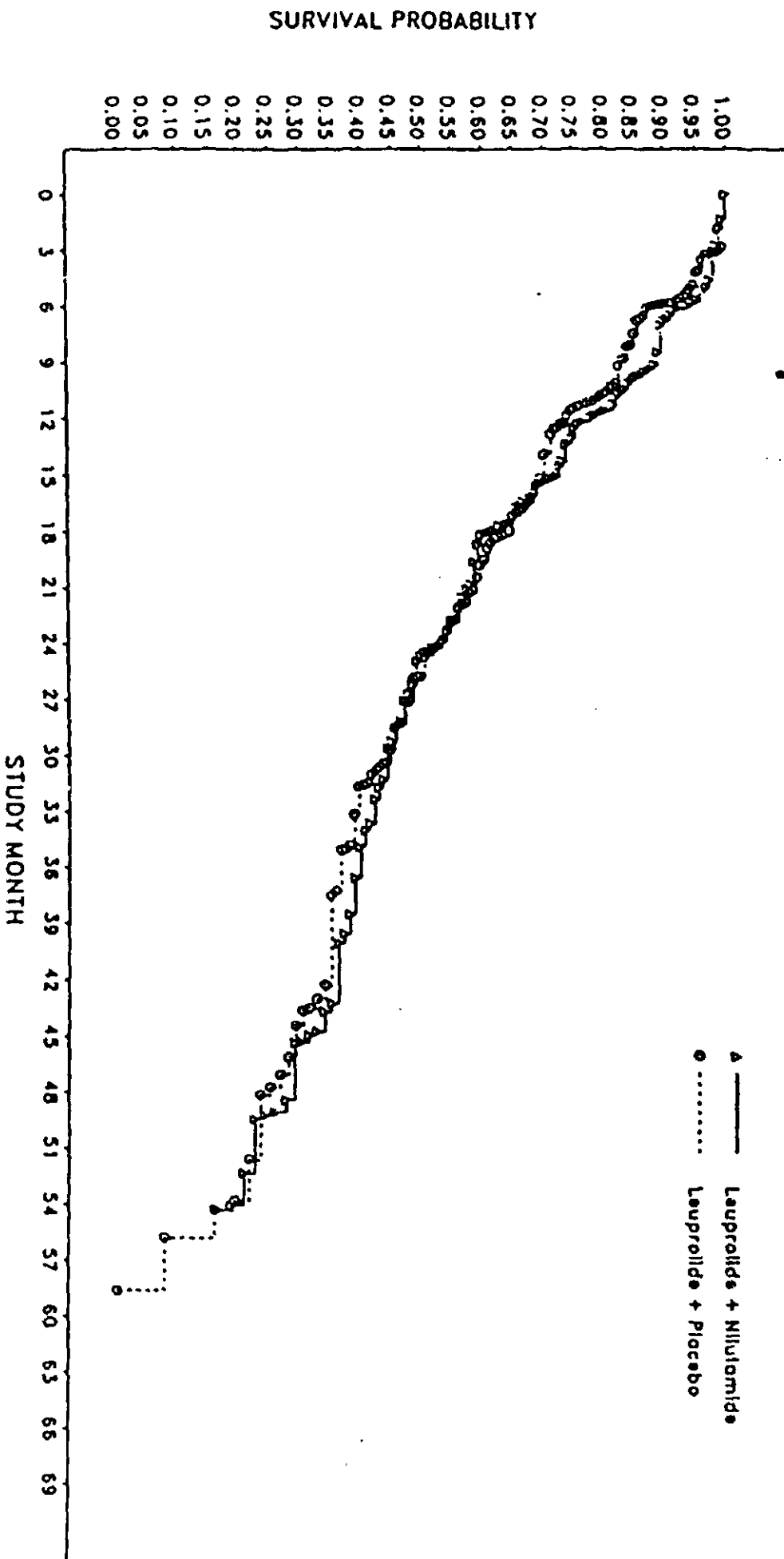


FIGURE 2
 PROBABILITY OF PROGRESSION-FREE SURVIVAL
 (ALL PATIENTS)



080000

Re: NDA 20-169
Nilutamide - RU 23908/Nilandron
Sponsor: Hoechst Marion Roussel, Inc.
Contact: Carole Venetianer/Corning Besselaar
February 8, 1996

Regarding the safety update of February 5, 1996

There were 9 cases of death, serious adverse experiences and adverse experiences resulting in discontinuation subsequent to August 15, 1995 in the updated safety report. In addition to progression of disease, depression, cerebral contusion and death there are three serious cases of respiratory insufficiency and one death of the three cases. The following cases are noted:

Patient - acute pulmonary edema

The patient was a 72 year old man who presented with exertional dyspnea. He had been started on nilutamide at 150 mg per day 2 years prior. Nilutamide was stopped but restrictive pulmonary distress continued until patient was treated with prednisone. The patient was reported to be in good condition at present.

Patient - respiratory insufficiency

The patient was a 90 year old started on 300 mg nilutamide daily as well as triptoreline. Three weeks after start of treatment the patient was hospitalized for acute respiratory failure. The drug was stopped and the patient was started on corticoid steroids. One and a half years after nilutamide was stopped bilateral interstitial syndrome of the lower lobes persisted with chronic hypoxemia despite chronic treatment with oxygen.

Patient - respiratory insufficiency

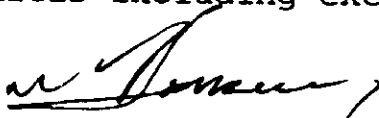
The patient was a 75 year old male started on nilutamide on April 24, 1995. On July 11 1995 he presented with respiratory insufficiency. Death was due to vascular and respiratory disorders. It should be noted that the patient was continued on nilutamide after presenting with dyspnea several weeks prior to his demise.

Signs and symptoms of respiratory insufficiency associated with nilutamide continue to be a major adverse problem that needs close monitoring.

908
This update did not include the 65 year old man (noted in review of 1/29/96) who was being treated for ~~Benign Prostatic Hyperplasia~~ and died after hospitalization with elevated liver enzymes.

In the pivotal clinical trials 8% of patients treated with orchiectomy and nilutamide and 3.5% of patient treated with LHRH agonists and nilutamide developed interstitial pneumonitis. The cases noted above demonstrate the importance of continued monitoring of both liver enzymes and signs and symptoms of intersitial pneumonitis including exertional dyspnea.

Jean
Medi


Fourcroy, M.D., PhD
Officer

NDA 20-
HFD-510

roy/2/8/96

Re: NDA 20-169
Nilutamide - RU 23908/Nilandron
Sponsor: Hoechst Marion Roussel, Inc.
Contact: Carole Venetianer/Corning Besselaar
February 8, 1996

FEB - 8 1996

Regarding the safety update of February 5, 1996

There were 5 cases of serious adverse experiences resulting in discontinuation and death subsequent to August 15, 1995 in the updated safety report. There were 4 further cases of serious adverse event which led to discontinuation.

Three deaths resulted from progression of disease, one from cerebral contusion and one from respiratory insufficiency. Other serious adverse events which did not lead to death include depression, kidney stones and the two cases of respiratory insufficiency. As respiratory insufficiency is of particular concern, the following cases are noted:

Patient - acute pulmonary edema

The patient was a 72 year old man who presented with exertional dyspnea. He had been started on nilutamide at 150 mg per day 2 years prior. Nilutamide was stopped but restrictive pulmonary distress continued until patient was treated with prednisone. The patient was reported to be in good condition at present.

Patient - respiratory insufficiency

The patient was a 90 year old started on 300 mg nilutamide daily as well as triptoreline. Three weeks after start of treatment the patient was hospitalized for acute respiratory failure. The drug was stopped and the patient was started on cortico-steroids. One and a half years after nilutamide was stopped bilateral interstitial syndrome of the lower lobes persisted with chronic hypoxemia despite chronic treatment with oxygen.

Patient - respiratory insufficiency

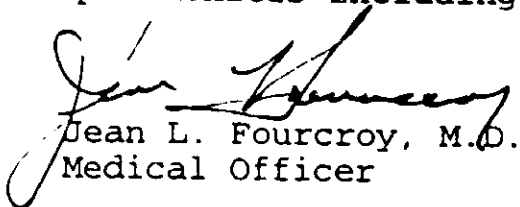
The patient was a 75 year old male started on nilutamide on April 24, 1995. On July 11 1995 he presented with respiratory insufficiency. Death was due to vascular and respiratory disorders. It should be noted that the patient was continued on

nilutamide after presenting with dyspnea several weeks prior to his demise.

Signs and symptoms of respiratory insufficiency associated with nilutamide continue to be a major adverse problem that needs close monitoring.

This update included further data regarding the 65 year old man (noted in review of 1/29/96) who was supposedly being treated for Benign Prostatic Hyperplasia and died after hospitalization with elevated liver enzymes. The full report in this safety update states that he was started on leuprolide and nilutamide, 150 mg per day, following a transurethral resection of the prostate and the diagnosis of prostate cancer. The reference to benign prostatic hyperplasia should be noted and changed under item 3 in the approval letter and read "There has been a recent report of a death after use of Nilandron in a 65 year old man being treated for prostate cancer (not benign prostatic hyperplasia). The label should therefore be changed and read "prostate cancer" instead of "benign prostatic hyperplasia".

In the pivotal clinical trials 8% of patients treated with orchiectomy and nilutamide and 3.5% of patient treated with LHRH agonists and nilutamide developed interstitial pneumonitis. The cases noted above demonstrate the importance of continued monitoring of both liver enzymes and signs and symptoms of intersitial pneumonitis including exertional dyspnea.


Jean L. Fourcroy, M.D., PhD
Medical Officer

NDA 20-169
HFD-510/JFourcroy/2/8/96

NDA 20-169

Nilandron® (nilutamide) Tablets

Roussel-UCLAF (Besselaar Associates)

Safety Update Review

Included in the medical review dated February 7, 1995.

NILUTAMIDE FOR PROSTATE CANCER SUMMARY OF NDA

VI. SUMMARY OF SAFETY

A. OVERVIEW

The safety of nilutamide was summarized in NDA 20-169 dated 7 March 1994 and in an update to the original NDA dated 14 October 1994. In general, from the time of submission of NDA 20-169 to the safety update, there has been no unexpected increase in the incidence of any specific adverse experience in this population, and no new or unusual adverse experience has occurred.

The original NDA 20-169 for nilutamide summarized clinical trials in which over 2,261 subjects or patients have been treated with nilutamide to date. Among these subjects or patients were 2,168 patients with prostate cancer, including 682 patients who were treated with nilutamide for 12 months or more.

The following table identifies the data cutoff dates for NDA 20-169 and the Safety Update.

Data Cutoff Dates

Study No.	NDA 20-169	Safety Update
Primary Studies		
FF/86/908/01	31 August 1989	31 December 1992
GHBA-606	28 February 1990	17 March 1993
Supportive Studies		
F/82/908/03	31 August 1989	30 June 1994
CDN/83/908/05	31 August 1989	30 June 1994

At the time of the data cutoff for NDA 20-169, 350 patients (168 nilutamide, 182 placebo) had discontinued treatment in Study No. FF/86/908/01, and 292 patients (152 nilutamide, 140 placebo) had discontinued treatment in Study No. GHBA-606. The safety update is based on data for the remaining 107 patients (57 nilutamide, 50 placebo) in Study No. FF/86/908/01 and the remaining 119 patients (57 nilutamide, 62 placebo) in Study No. GHBA-606, but the presentation of adverse experience data and laboratory data is cumulative, with rates based on the total population. It should be noted that the Safety Update represents more than 3 additional years of follow-up for each of the primary studies.

B. ADVERSE EXPERIENCE RATES

Adverse experiences for the 10 controlled studies are briefly summarized, with the major focus on the primary studies, Nos. FF/86/908/01 and GHBA-606.

Study No. FF/86/908/01

The following table summarizes the incidence (in both NDA 20-169 and the Safety Update) of the most frequent adverse experiences during the double-blind part of Study No. FF/86/908/01. The adverse experiences are presented in decreasing order of occurrence for nilutamide patients in the original NDA. In the nilutamide group, the incidence did not increase for five of the 13 most frequent adverse experiences, increased by one or two patients for seven of the adverse experiences, and increased by five patients for the remaining adverse experience, death, which was an expected outcome in this population. Increases in incidences were comparable in placebo-treated patients.

Number (%) of Patients With the Most Frequently Reported Adverse Experiences in Study No. FF/86/908/01 (Double-Blind Phase)

Adverse Experience	Nilutamide + Orchiectomy (N = 225)		Placebo + Orchiectomy (N = 232)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
Hot Flashes	63 (28)	64 (28)	51 (22)	52 (22)
Death	34 (15)	39 (17)	28 (12)	32 (14)
Impaired Adaptation to Darkness	29 (13)	29 (13)	3 (1)	3 (1)
Nausea	20 (9)	22 (10)	13 (6)	13 (6)
SGOT Increased	18 (8)	18 (8)	9 (4)	9 (4)
SGPT Increased	17 (8)	17 (8)	10 (4)	10 (4)
Dizziness	16 (7)	16 (7)	9 (4)	8 (3)
Urinary Tract Infection	16 (7)	18 (8)	18 (8)	21 (10)
Constipation	14 (6)	16 (7)	8 (3)	9 (4)
Abnormal Vision	13 (6)	15 (7)	4 (2)	4 (2)
Dyspnea	13 (6)	14 (6)	14 (6)	17 (7)
Hypertension	11 (5)	12 (5)	5 (2)	6 (3)
Alcohol Intolerance	11 (5)	11 (5)	1 (<1)	1 (<1)

^a Data cutoff: 31 August 1989.

^b Data cutoff: 31 December 1992.

Adverse experience rates regardless of frequency of occurrence for the double-blind study periods of the Study No. FF/86/908/01 were compared with updated (cumulative) adverse experience rates at the new data cutoff (31 December 1992). The following table shows the incidence of specific adverse experiences by body system during the double-blind part of the study that increased from the original NDA to the data cutoff for this update for Study No. FF/86/908/01. As can be seen from this table, for about 73% of adverse experiences in each treatment group, the increased incidence of a specific adverse experience reflects an increase of only one patient.

Number (%) of Patients With Adverse Experiences Regardless of Relationship to Treatment
(Double-Blind Phase of Study No. FF/86/908/01): NDA 20-169 and Update

BODY SYSTEM/Adverse Experience	Nilutamide+Orchiectomy (N=225)		Placebo+Orchiectomy (N=232)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
BODY AS A WHOLE	75 (33)	86 (38)	63 (27)	70 (30)
Accidental Injury	0 (0)	0 (0)	0 (0)	1 (<1)
Asthenia	3 (1)	5 (2)	8 (3)	9 (4)
Back Pain	4 (2)	5 (2)	4 (2)	5 (2)
Death	34 (15)	39 (17)	28 (12)	32 (14)
Drug Interaction	0 (0)	1 (<1)	1 (<1)	1 (<1)
Hernia	1 (<1)	2 (1)	0 (0)	0 (0)
Pain	3 (1)	7 (3)	5 (2)	6 (3)
Shock	0 (0)	1 (<1)	0 (0)	0 (0)
Surgery	5 (2)	7 (3)	3 (1)	5 (2)
CARDIOVASCULAR SYSTEM	42 (19)	44 (20)	31 (13)	40 (17)
Aortic Aneurism	2 (1)	2 (1)	2 (1)	3 (1)
Cerebral Infarct	0 (0)	0 (0)	1 (<1)	2 (1)
Cerebrovascular Accident	4 (2)	4 (2)	1 (<1)	2 (1)
Heart Failure	6 (3)	6 (3)	4 (2)	5 (2)
Hypertension	11 (5)	12 (5)	5 (2)	6 (3)
Phlebitis	0 (0)	0 (0)	0 (0)	2 (1)
Postural Hypotension	3 (1)	3 (1)	1 (<1)	2 (1)
Pulmonary Embolus	1 (<1)	1 (<1)	0 (0)	1 (<1)
Syncope	0 (0)	1 (<1)	0 (0)	2 (<1)
Thrombophlebitis	0 (0)	1 (<1)	2 (<1)	2 (<1)
Vascular Disorder	0 (0)	1 (<1)	1 (<1)	1 (<1)

**Number (%) of Patients With Adverse Experiences Regardless of Relationship to Treatment
(Double-Blind Phase of Study No. FF/86/903/01): NDA 20-169 and Update**

BODY SYSTEM/Adverse Experience	Nilutamide+ Orchiectomy (N=225)		Placebo+ Orchiectomy (N=232)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
DIGESTIVE SYSTEM	70 (31)	78 (35)	52 (22)	54 (23)
Anorexia	7 (3)	8 (4)	5 (2)	5 (2)
Cholelithiasis	1 (<1)	2 (1)	0 (0)	0 (0)
Constipation	14 (6)	16 (7)	8 (3)	9 (4)
Esophagitis	0 (0)	1 (<1)	0 (0)	0 (0)
Gastrointestinal Carcinoma	3 (1)	4 (2)	4 (2)	4 (2)
Gastrointestinal Disorder	7 (3)	7 (3)	1 (<1)	2 (1)
Gastrointestinal Hemorrhage	3 (1)	4 (2)	2 (1)	2 (1)
Hemorrhoids	1 (<1)	1 (<1)	0 (0)	1 (<1)
Hepatomegaly	3 (1)	4 (2)	3 (1)	3 (1)
Melena	3 (1)	4 (2)	1 (<1)	1 (<1)
Nausea	20 (9)	22 (10)	13 (6)	13 (6)
Nausea and Vomiting	0 (0)	1 (<1)	0 (0)	0 (0)
Rectal Disorder	1 (<1)	2 (1)	3 (1)	3 (1)
Sialoadenitis	0 (0)	1 (<1)	0 (0)	0 (0)
Tooth Disorder	0 (0)	0 (0)	1 (<1)	2 (1)
ENDOCRINE SYSTEM	63 (28)	65 (29)	52 (22)	53 (23)
Hot Flushes	63 (28)	64 (28)	51 (22)	52 (22)
HEMIC & LYMPHATIC SYSTEM	18 (8)	20 (9)	32 (14)	33 (14)
Anemia	9 (4)	11 (5)	16 (7)	17 (7)
METABOLIC & NUTRITIONAL SYSTEM	49 (22)	51 (23)	47 (20)	50 (22)
Acid Phosphatase Increased	1 (<1)	1 (<1)	0 (0)	1 (<1)
Alkaline Phosphatase Increased	8 (4)	9 (4)	4 (2)	5 (2)
Edema	2 (<1)	3 (1)	1 (<1)	1 (<1)
Hyperphosphoremia	2 (1)	2 (1)	0 (0)	1 (<1)
Peripheral Edema	8 (4)	9 (4)	15 (7)	16 (7)
Uremia	0 (0)	0 (0)	2 (1)	3 (1)
MUSCULOSKELETAL SYSTEM	18 (8)	21 (9)	15 (6)	19 (8)
Accidental Fall	7 (3)	8 (4)	4 (2)	5 (2)
Arthralgia	3 (1)	4 (2)	1 (<1)	1 (<1)
Arthrosis	0 (0)	0 (0)	2 (1)	3 (1)
Myalgia	1 (<1)	1 (<1)	1 (<1)	3 (1)
Spontaneous Bone Fracture	1 (<1)	2 (1)	2 (1)	2 (1)
Twitching	0 (0)	1 (<1)	0 (0)	0 (0)

**Number (%) of Patients With Adverse Experiences Regardless of Relationship to Treatment
(Double-Blind Phase of Study No. FF/86/908/01): NDA 20-169 and Update**

BODY SYSTEM/Adverse Experience	Nilutamide+Orchiectomy (N=225)		Placebo+Orchiectomy (N=232)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
NERVOUS SYSTEM	52 (23)	56 (25)	39 (17)	43 (19)
Concentration Ability Impaired	0 (0)	0 (0)	0 (0)	1 (<1)
Dementia	0 (0)	1 (<1)	0 (0)	1 (<1)
Depression	6 (3)	7 (3)	4 (2)	6 (3)
Emotional Lability	0 (0)	0 (0)	0 (0)	1 (<1)
Hypesthesia	2 (1)	3 (1)	1 (<1)	1 (<1)
Parkinsonism	1 (<1)	3 (1)	0 (0)	0 (0)
Sweating Increased	2 (1)	3 (1)	6 (3)	9 (4)
RESPIRATORY SYSTEM	38 (17)	41 (18)	35 (15)	43 (19)
Asthma	0 (0)	0 (0)	0 (0)	1 (<1)
Bronchitis	0 (0)	0 (0)	2 (<1)	4 (2)
Carcinoma of Lung	0 (0)	0 (0)	0 (0)	1 (<1)
Dyspnea	13 (6)	14 (6)	14 (6)	17 (7)
Epistaxis	0 (0)	1 (<1)	0 (0)	0 (0)
Respiratory Disorder	4 (2)	5 (2)	1 (<1)	1 (<1)
Sinusitis	0 (0)	0 (0)	1 (<1)	2 (1)
Voice Alteration	0 (0)	0 (0)	0 (0)	1 (<1)
SKIN & APPENDAGES	17 (8)	18 (8)	16 (7)	16 (7)
Skin Carcinoma	0 (0)	1 (<1)	0 (0)	0 (0)
SPECIAL SENSES	69 (31)	70 (31)	13 (6)	14 (6)
Abnormal Vision	13 (6)	15 (7)	4 (2)	4 (2)
Deafness	0 (0)	1 (<1)	0 (0)	0 (0)
Glaucoma	0 (0)	1 (<1)	0 (0)	0 (0)
Partial Permanent Deafness	0 (0)	1 (<1)	0 (0)	0 (0)
UROGENITAL SYSTEM	36 (16)	42 (19)	48 (21)	54 (23)
Albuminuria	2 (1)	3 (1)	2 (1)	2 (1)
Gynecomastia	9 (4)	11 (5)	13 (6)	15 (7)
Hematuria	1 (<1)	3 (1)	4 (2)	4 (2)
Increased Urinary Frequency	0 (0)	0 (0)	1 (<1)	2 (1)
Papillary Kidney Necrosis	0 (0)	0 (0)	0 (0)	1 (<1)
Penis Disorder	0 (0)	1 (<1)	0 (0)	0 (0)
Urinary Retention	3 (1)	5 (2)	4 (2)	6 (3)

**Number (%) of Patients With Adverse Experiences Regardless of Relationship to Treatment
(Double-Blind Phase of Study No. FF/86/908/01): NDA 20-169 and Update**

BODY SYSTEM/Adverse Experience	Nilutamide + Orchiectomy (N=225)		Placebo + Orchiectomy (N=232)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
UROGENITAL SYSTEM (Cont'd)				
Urinary Tract Disorder	1 (<1)	3 (1)	6 (3)	6 (3)
Urinary Tract Infection	16 (7)	18 (8)	18 (8)	21 (10)
Urinary Urgency	0 (0)	1 (<1)	0 (0)	1 (<1)
Total Number of Patients With One or More Adverse Experiences	188 (84)	193 (86)	181 (78)	186 (80)

^a Data cutoff: 31 August 1989.

^b Data cutoff: 31 December 1992.

Study No. GHBA-606

The following table summarizes the incidence of the most frequent (5% or more of patients) adverse experiences during the double-blind part of Study No. GHBA-606 in both NDA 20-169 and the Safety Update. The adverse experiences are presented in decreasing order of occurrence for nilutamide patients in the original NDA. In the nilutamide group, the incidence did not increase for 26 of the 42 most frequent adverse experiences, increased by one or two patients for 12 of the adverse experiences, increased by three patients for two of the adverse experiences (one of which was death), and increased by five patients for one adverse experience, pain. Incidence decreased (because of recoding) for the remaining adverse experience, infection. Increases in incidences were comparable in placebo-treated patients.

Number (%) of Patients With the Most Frequently Reported Adverse Experiences in Study No. GHBA-606 (Double-Blind Phase)

Adverse Experience	Nilutamide+ Leuprolide (N=209)		Placebo+ Leuprolide (N=202)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
Hot Flushes	137 (66)	137 (66)	118 (58)	119 (59)
Impaired Adaptation to Darkness	118 (56)	118 (56)	11 (5)	11 (5)
Nausea	49 (23)	49 (23)	15 (7)	15 (7)
Pain	48 (23)	53 (25)	48 (24)	51 (25)
Constipation	40 (19)	40 (19)	30 (15)	32 (16)
Asthenia	38 (18)	38 (18)	38 (19)	41 (20)
Insomnia	31 (15)	32 (15)	32 (16)	32 (16)
Testicular Atrophy	31 (15)	33 (16)	21 (10)	23 (11)
Headache	27 (13)	27 (13)	19 (9)	19 (9)
SGOT Increased	26 (12)	27 (13)	28 (14)	28 (14)
Libido Decreased	23 (11)	23 (11)	9 (4)	9 (4)
Peripheral Edema	23 (11)	24 (11)	32 (16)	33 (16)
Dyspnea	22 (11)	22 (11)	12 (6)	13 (6)
Impotence	22 (11)	22 (11)	24 (12)	24 (12)
Infection*	22 (11)	8 (4)	26 (13)	8 (4)
Anorexia	20 (10)	21 (10)	12 (6)	13 (6)
Back Pain	20 (10)	23 (11)	30 (15)	30 (15)
Death	20 (10)	23 (11)	16 (8)	17 (8)
Dizziness	19 (9)	19 (9)	20 (10)	20 (10)
SGPT Increased	19 (9)	19 (9)	18 (9)	18 (9)
Abdominal Pain	18 (9)	19 (9)	11 (5)	11 (5)
Chromatopsia	18 (9)	18 (9)	0 (0)	0 (0)
Depression	18 (9)	18 (9)	14 (7)	15 (7)
Gynecomastia	18 (9)	18 (9)	20 (10)	22 (11)
Hypertension	16 (8)	16 (8)	18 (9)	20 (10)
Urinary Tract Infection	16 (8)	16 (8)	42 (21)	43 (21)
Anemia	15 (7)	16 (8)	12 (6)	12 (6)
Hematuria	15 (7)	16 (8)	14 (7)	15 (7)
Light Adaptation Impairment	15 (7)	15 (7)	2 (1)	2 (1)
Bone Pain	13 (6)	13 (6)	10 (5)	10 (5)
Dyspepsia	13 (6)	13 (6)	8 (4)	9 (4)
Flu Syndrome	12 (6)	13 (6)	4 (2)	5 (2)
Sweating	12 (6)	12 (6)	6 (3)	6 (3)

Number (%) of Patients With the Most Frequently Reported Adverse Experiences in Study No. GHBA-606 (Double-Blind Phase)

Adverse Experience	Nilutamide+Leuprolide (N=209)		Placebo+Leuprolide (N=202)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
Urinary Tract Disorder	12 (6)	14 (7)	14 (7)	15 (7)
Vomiting	12 (6)	12 (6)	8 (4)	8 (4)
Alopecia	11 (5)	11 (5)	1 (<1)	1 (<1)
Chest Pain	11 (5)	12 (6)	8 (4)	9 (4)
Dry Skin	11 (5)	11 (5)	5 (2)	5 (2)
Fever	11 (5)	11 (5)	13 (6)	13 (6)
Rash	11 (5)	11 (5)	8 (4)	8 (4)
Hypesthesia	10 (5)	10 (5)	4 (2)	4 (2)
Nocturia	10 (5)	11 (5)	10 (5)	10 (5)

* Infections were recoded more specifically to the Respiratory System.

^a Data cutoff: 28 February 1990.

^b Data cutoff: 17 March 1993.

The following table shows the incidence of specific adverse experience during the double-blind part of Study No. GHBA-606 that changed from the original NDA to the data cutoff (17 March 1993) for the safety update. As was the case with the other primary study, the increased incidence of a specific adverse experience usually reflects an increase of only one patient. The large increase in the incidence of upper respiratory infection in the respiratory system for both nilutamide and placebo patients can be almost entirely accounted for by a more specific recoding of infection in body as a whole to upper respiratory infection.

**Number (%) of Patients With Adverse Experiences Regardless of Relationship to Treatment
(Double-Blind Phase of Study No. GHBA-606): NDA 20-169 and Update**

BODY SYSTEM/Adverse Experience	Nilutamide+Leuprolide (N=209)		Placebo+Leuprolide (N=202)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
BODY AS A WHOLE	155 (74)	152 (73)	142 (70)	138 (68)
Abdominal Pain	18 (9)	19 (9)	11 (5)	11 (5)
Ascites	0 (0)	1 (<1)	0 (0)	0 (0)
Asthenia	38 (18)	38 (18)	38 (19)	41 (20)
Back Pain	20 (10)	23 (11)	30 (15)	30 (15)
Cellulitis	0 (0)	1 (<1)	6 (3)	6 (3)
Chest Pain	11 (5)	12 (6)	8 (4)	9 (4)
Death	20 (10)	23 (11)	16 (8)	17 (8)
Flu Syndrome	12 (6)	13 (6)	4 (2)	5 (2)
Hernia	6 (3)	7 (3)	4 (2)	5 (2)
Infection*	22 (11)	8 (4)	26 (13)	8 (4)
Injury	5 (2)	6 (3)	5 (2)	8 (4)
Neoplasm	1 (<1)	2 (1)	1 (<1)	1 (<1)
Pain	48 (23)	53 (25)	48 (24)	51 (25)
CARDIOVASCULAR SYSTEM	53 (25)	54 (26)	58 (29)	62 (31)
Atrial Fibrillation	0 (0)	1 (<1)	3 (1)	3 (1)
Congestive Heart Failure	4 (2)	4 (2)	4 (2)	5 (2)
Hypertension	16 (8)	16 (8)	18 (9)	20 (10)
Myocardial Infarct	5 (2)	6 (3)	7 (3)	8 (4)
Peripheral Vascular Disorder	1 (<1)	1 (<1)	1 (<1)	2 (1)
DIGESTIVE SYSTEM	125 (60)	126 (60)	83 (41)	88 (44)
Anorexia	20 (10)	21 (10)	12 (6)	13 (6)
Cholecystitis	0 (0)	0 (0)	1 (<1)	2 (1)
Colitis	0 (0)	0 (0)	0 (0)	1 (<1)
Constipation	40 (19)	40 (19)	30 (15)	32 (16)
Dyspepsia	13 (6)	13 (6)	8 (4)	9 (4)
Dysphagia	0 (0)	0 (0)	0 (0)	1 (<1)
Eructation	0 (0)	0 (0)	0 (0)	1 (<1)
Flatulence	4 (2)	5 (2)	5 (2)	5 (2)
Gastritis	1 (<1)	1 (<1)	3 (1)	4 (2)
Gastrointestinal Disorder	2 (1)	3 (1)	1 (<1)	1 (<1)
Rectal Hemorrhage	5 (2)	6 (3)	0 (0)	0 (0)
Sialoadenitis	0 (0)	0 (0)	0 (0)	1 (<1)
Tooth Caries	0 (0)	0 (0)	0 (0)	1 (<1)

**Number (%) of Patients With Adverse Experiences Regardless of Relationship to Treatment
(Double-Blind Phase of Study No. GHBA-606): NDA 20-169 and Update**

BODY SYSTEM/Adverse Experience	Nilutamide+Leuprolide (N=209)		Placebo+Leuprolide (N=202)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
ENDOCRINE SYSTEM	145 (69)	145 (69)	127 (63)	128 (63)
Hot Flushes	137 (66)	137 (66)	118 (58)	119 (59)
HEMIC & LYMPHATIC SYSTEM	42 (20)	45 (22)	37 (18)	37 (18)
Anemia	15 (7)	16 (8)	12 (6)	12 (6)
Haptoglobin Increased	4 (2)	6 (3)	10 (5)	10 (5)
Leukopenia	8 (4)	10 (5)	5 (2)	5 (2)
Lymphoma like Reaction	0 (0)	1 (<1)	0 (0)	0 (0)
Microcytic Anemia	0 (0)	1 (<1)	0 (0)	0 (0)
Monocytosis	0 (0)	1 (<1)	0 (0)	0 (0)
Thrombocythemia	2 (1)	2 (1)	2 (1)	3 (1)
Thrombocytopenia	4 (2)	5 (2)	2 (1)	2 (1)
METABOLIC & NUTRITIONAL SYSTEM	80 (38)	83 (40)	84 (42)	85 (42)
Alkaline Phosphatase Increased	6 (3)	7 (3)	6 (3)	7 (3)
Diabetes Mellitus	1 (<1)	2 (1)	2 (1)	2 (1)
GGT Increased	3 (1)	4 (2)	2 (1)	2 (1)
Hypercholesterolemia	0 (0)	0 (0)	0 (0)	1 (<1)
Hyperglycemia	7 (3)	8 (4)	12 (6)	12 (6)
Peripheral Edema	23 (11)	24 (11)	32 (16)	33 (16)
SGOT Increased	26 (12)	27 (13)	28 (14)	28 (14)
Weight Gain	3 (1)	4 (2)	2 (1)	2 (1)
MUSCULOSKELETAL SYSTEM	30 (14)	33 (16)	31 (15)	36 (18)
Arthritis	8 (4)	8 (4)	5 (2)	7 (3)
Myalgia	0 (0)	0 (0)	5 (2)	7 (3)
Pathological Fracture	4 (2)	7 (3)	6 (3)	7 (3)
NERVOUS SYSTEM	108 (52)	110 (53)	82 (41)	83 (41)
Agitation	2 (1)	3 (1)	1 (<1)	1 (<1)
Anxiety	5 (2)	5 (2)	4 (2)	5 (2)
Depression	18 (9)	18 (9)	14 (7)	15 (7)
Extrapyramidal Syndrome	1 (<1)	0 (0)	0 (0)	0 (0)
Insomnia	31 (15)	32 (15)	32 (16)	32 (16)
Nervousness	7 (3)	7 (3)	7 (3)	8 (4)
Neuropathy	1 (<1)	1 (<1)	0 (0)	1 (<1)

**Number (%) of Patients With Adverse Experiences Regardless of Relationship to Treatment
(Double-Blind Phase of Study No. GHBA-606): NDA 20-169 and Update**

BODY SYSTEM/Adverse Experience	Nilutamide+ Leuprolide (N=209)		Placebo+ Leuprolide (N=202)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
NERVOUS SYSTEM (Cont'd)				
Parkinsonism	0 (0)	1 (<1)	0 (0)	0 (0)
Sleep Disorder	1 (<1)	1 (<1)	0 (0)	1 (<1)
RESPIRATORY SYSTEM	54 (26)	69 (33)	51 (25)	67 (33)
Apnea	1 (<1)	2 (1)	1 (<1)	1 (<1)
Bronchitis	2 (1)	3 (1)	8 (4)	8 (4)
Dyspnea	22 (11)	22 (11)	12 (6)	13 (6)
Lung Disorder	9 (4)	8 (4)	7 (3)	7 (3)
Pharyngitis	2 (1)	2 (1)	6 (3)	7 (3)
Pneumonia	7 (3)	10 (5)	5 (2)	6 (3)
Upper Respiratory Infection	0 (0)	17 (8)	0 (0)	21 (10)
SKIN & APPENDAGES	50 (24)	50 (24)	44 (22)	46 (23)
Skin Benign Neoplasm	2 (1)	2 (1)	0 (0)	1 (<1)
Skin Discoloration	0 (0)	0 (0)	1 (<1)	2 (1)
Skin Disorder	5 (2)	5 (2)	7 (3)	6 (3)
Skin Melanoma	0 (0)	0 (0)	0 (0)	1 (<1)
Urticaria	0 (0)	0 (0)	0 (0)	1 (<1)
SPECIAL SENSES	144 (69)	144 (69)	47 (23)	47 (23)
Abnormal Vision	9 (4)	10 (5)	9 (4)	9 (4)
Ear Disorder	0 (0)	0 (0)	0 (0)	1 (<1)
Tinnitus	1 (<1)	2 (1)	4 (2)	4 (2)
UROGENITAL SYSTEM	103 (49)	106 (51)	105 (52)	112 (55)
Bladder Calculus	0 (0)	0 (0)	0 (0)	1 (<1)
Dysuria	0 (0)	1 (<1)	9 (4)	9 (4)
Gynecomastia	18 (9)	18 (9)	20 (10)	22 (11)
Hematuria	15 (7)	16 (8)	14 (7)	15 (7)
Nocturia	10 (5)	11 (5)	10 (5)	10 (5)
Pyuria	3 (1)	3 (1)	1 (<1)	2 (1)
Testicular Atrophy	31 (15)	33 (16)	21 (10)	23 (11)
Urinary Frequency	4 (2)	5 (2)	8 (4)	9 (4)
Urinary Incontinence	4 (2)	6 (3)	7 (3)	8 (4)

**Number (%) of Patients With Adverse Experiences Regardless of Relationship to Treatment
(Double-Blind Phase of Study No. GIIBA-606): NDA 20-169 and Update**

BODY SYSTEM/Adverse Experience	Nilutamide+Leuprolide (N=209)		Placebo+Leuprolide (N=202)	
	NDA 20-169 ^a	Safety Update ^b	NDA 20-169	Safety Update
UROGENITAL SYSTEM (Cont'd)				
Urinary Retention	2 (1)	2 (1)	12 (6)	13 (6)
Urinary Tract Disorder	12 (6)	14 (7)	14 (7)	15 (7)
Urinary Tract Infection	16 (8)	16 (8)	42 (21)	43 (21)
Total Number of Patients With One or More Adverse Experiences	208 (99.5)	208 (99.5)	199 (98.5)	199 (98.5)

* Infections were recoded more specifically to the Respiratory System.

^a Data cutoff: 28 February 1990.

^b Data cutoff: 17 March 1993.

Pooled Orchiectomy Studies

The following table summarizes the incidence of the most frequently reported adverse experience in the pooled 300 mg long-term orchiectomy studies reported in NDA 20-169. Two of the eight supportive studies are not represented here.

**Number (%) of Patients With the Most Frequently Reported
Adverse Experiences in Pooled Orchiectomy Studies^a
(NDA 20-169)**

Adverse Experience	Number (%) of Patients	
	Nilutamide 300 mg/day (N=335)	Placebo (N=326)
Hot Flushes	139 (42)	118 (36)
Impaired Adaptation to Darkness	75 (22)	16 (5)
Death	75 (22)	59 (18)
Impotence	59 (18)	60 (18)
Libido Decreased	49 (15)	54 (17)
Alcohol Intolerance	35 (10)	10 (3)
Nausea	35 (10)	13 (4)
Dizziness	28 (8)	12 (4)
Asthenia	22 (7)	12 (4)
Constipation	15 (5)	13 (4)
Gastrointestinal Pain	17 (5)	13 (4)
Vomiting	15 (5)	5 (2)
Chromatopsia	16 (5)	5 (2)

^a Studies: CDN/83/908/05, F/82/908/03 (300 mg), F/82/908/01, F/84/908/01, CH/85/908/05, and ZA/85/908/02.

The two remaining placebo-controlled studies performed in LHRH agonist-treated patients were evaluated individually for safety. In the placebo-controlled buserelin arm of Study No. F/82/908/01, 88% of nilutamide patients and 66% of placebo patients had adverse experiences ($p=0.015$). The most prevalent adverse experiences for nilutamide patients were hot flushes and impaired adaptation to darkness and for placebo patients were hot flushes and hypertension. A few cases of interstitial pneumonitis among nilutamide-treated patients resolved during continued nilutamide therapy.

In Study No. F/85/908/10, a 4-week placebo-controlled clinical pharmacology study, comparable proportions of nilutamide and placebo patients had one or more adverse experiences. The predominant adverse experiences were hot flushes, difficulty with light/dark adaptation, and sleeplessness for nilutamide patients and sleeplessness and lower limb pain for placebo patients.

C. DEATHS AND TREATMENT DISCONTINUATIONS BECAUSE OF ADVERSE EXPERIENCES

The following table summarizes the deaths that occurred in the 10 controlled studies.

Number (%) of Patients Who Died in Controlled Clinical Studies^a

Study Number	Nilutamide			Placebo		
	N	NDA 20-169	Safety Update	N	NDA 20-169	Safety Update
FF/86/908/01	225	42 (19)	56 (25)	232	28 (12)	33 (14)
GHBA-606	209	28 (13)	32 (15)	202	16 (8)	17 (8)
CDN/83/908/05	105	40 (38)	42 (40)	103	15 (15)	17 (17)
F/82/908/03						
150 mg	66	22 (33)	22 (33)	63	18 (29)	18 (29)
300 mg	62	23 (37)	23 (37)			
F/82/908/01	107	30 (28)	30 (28)	101	20 (20)	20 (20)
F/84/908/01	73	11 (15)	11 (15)	78	12 (15)	12 (15)
CH/85/908/05	26	5 (19)	5 (19)	25	4 (16)	4 (16)
ZA/85/908/02	6	2 (33)	2 (33)	5	1 (20)	1 (20)
FF/86/ANA/001	27	0 (0)	0 (0)	26	3 (12)	3 (12)
F/85/908/10	17	0 (0)	0 (0)	19	2 (11)	2 (11)
Total	923	203 (22)	223 (24)	854	119 (14)	127 (15)

^a Patients who discontinued nilutamide treatment for disease progression in Study Nos. FF/86/908/01, GHBA-606, and CDN/83/908/05 had the option to continue nilutamide in an open-label extension phase of the studies. Deaths occurring during the open-label phase are included in the nilutamide totals. Additionally, patients who died while receiving treatment with nilutamide beyond the 24-month period specified in the protocols for Study Nos. F/82/908/03, F/82/908/01, F/84/908/01, CH/85/908/05, and ZA/85/908/02 are also included in the totals.

The following table summarizes the treatment discontinuations because of adverse experiences in the 10 controlled studies.

Number (%) of Patients Who Had Treatment Discontinued Because of Adverse Experiences or Intercurrent Events Excluding Events Resulting in Death in Controlled Clinical Studies

Study Number	Nilutamide			Placebo		
	N	NDA 20-169	Safety Update	N	NDA 20-169	Safety Update
FF/86/908/01	225	24 (11)	28 (12)	232	11 (5)	13 (6)
GHBA-606	209	34 (16)	37 (18)	202	13 (6)	15 (7)
CDN/83/908/05	105	15 (14)	15 (14)	103	1 (1)	3 (3)
F/82/908/03						
150 mg	66	5 (8)	5 (8)	63	0 (0)	0 (0)
300 mg	62	7 (11)	7 (11)			
F/82/908/01	107	12 (11)	12 (11)	101	6 (6)	6 (6)
F/84/908/01	73	14 (19)	14 (19)	78	2 (3)	2 (3)
CH/85/908/05	26	8 (31)	8 (31)	25	2 (8)	2 (8)
ZA/85/908/02	6	1 (17)	1 (17)	5	1 (20)	1 (20)
FF/86/ANA/001	27	1 (4)	1 (4)	26	1 (4)	1 (4)
F/85/908/10	17	0 (0)	0 (0)	19	2 (11)	2 (11)
Total	923	121 (13)	128 (14)	854	39 (5)	45 (5)

D. LABORATORY DATA

Laboratory data were collected at baseline and at 6-month intervals throughout treatment. Hematological controls such as, RBC, WBC, hemoglobin, and hematocrit were done at 3-month intervals. The following tables summarize the cumulative number of patients in the two primary studies with selected laboratory test result values below, within, and above predefined limits in NDA 20-169 and in the updated data at any time during the study. Comparable numbers of nilutamide and placebo patients had changes from predefined limits from the original NDA to the time of the update.

**Number of Patients in Study No. FF/86/908/01 With Laboratory Values
Outside/Within Predefined Limits at Any Time During Treatment**

Laboratory Test	Nilutamide (N=225)						Placebo (N=232)					
	NDA 20-169 ^a			Safety Update ^b			NDA 20-169			Safety Update		
	B ^c	W	A	B	W	A	B	W	A	B	W	A
Hemoglobin	44	171	0	51	164	0	51	171	0	57	165	0
Hematocrit	65	147	0	68	144	0	53	164	0	62	155	0
RBC Count	65	126	0	71	120	0	63	137	0	70	130	0
SGOT (1)	0	196	15	0	193	18	0	213	8	0	213	8
(2)	0	156	40	0	151	45	0	182	24	0	179	27
SGPT (1)	0	182	22	0	180	24	0	205	8	0	205	8
(2)	0	143	44	0	140	46	0	170	27	0	168	29
Glucose	35	120	45	35	117	49	33	130	45	36	128	46

^a Data cutoff: 31 August 1989.

^b Data cutoff: 31 December 1992.

^c With reference to predefined limits: B=below, W=within, A=above.

SGOT/SGPT (1): increase above 2 x N if baseline missing or $\leq$ N or above 5 x N if baseline > N (N = upper limit of normal); SGOT/SGPT(2): increase to > 2 x baseline and > upper limit or normal.

**Number of Patients in Study No. GHBA-606 With Laboratory Values
Outside/Within Predefined Limits at Any Time During Treatment**

Laboratory Test	Nilutamide (N=209)						Placebo (N=202)					
	NDA 20-169 ^a			Safety Update ^b			NDA 20-169			Safety Update		
	B ^c	W	A	B	W	A	B	W	A	B	W	A
Hemoglobin	61	148	0	66	143	0	56	146	0	63	139	0
Hematocrit	144	65	0	148	61	0	160	42	0	162	40	0
RBC Count	95	114	0	100	109	0	92	110	0	95	107	0
SGOT	0	166	42	0	164	44	0	172	30	0	170	32
SGPT	0	151	37	0	150	39	0	155	28	0	155	28
Glucose	34	120	61	35	117	64	38	120	56	44	113	61

^a Data cutoff: 28 February 1990.

^b Data cutoff: 17 March 1993.

^c With reference to predefined limits: B=below, W=within, A=above.

E. OTHER SAFETY INFORMATION AND ANALYSIS OF SPECIFIC ADVERSE EVENTS

Summary of Nonclinical Data

Nilutamide is a relatively nontoxic compound with acute administration. In the fasted rat or mouse, the oral LD₅₀ was about 200 mg/kg. The most important metabolites of nilutamide were less toxic than the parent compound.

In repeated administration to rats and dogs, nilutamide was toxic at high doses. In the rat, 50 mg/kg was clinically tolerated for 3 months and caused only a slight depression of bodyweight gain in males after 6 months. This effect was accentuated in the 18-month study, particularly in the males at a dose of 45 mg/kg.

The dog was more sensitive to the compound; clinical tolerance for 6 months was seen at a dose level of 10 mg/kg.

Expected effects due to the pharmacologic activity of nilutamide were manifested dose-dependently in males, particularly by an antiandrogenic action on the prostate and the testes

in the rat and dog, and also on the seminal vesicles in the rat treated for 6 months and 18 months.

A common toxic effect seen in the two species tested, but at various dose levels, was reversible anemia. This normochromic anemia, although dose-dependent, always remained moderate in degree. Thus, at the maximum administered doses in the rat and the dog, which are 25 and 15 times, respectively, the human dose of 150 mg/day (based on a 70 kg person), the maximum decreases in the number of erythrocytes and hemoglobin levels were 25% and 16%, respectively, in rats at the dose of 50 mg/kg administered for 6 months, and 28% and 17% at the dose of 45 mg/kg administered for 18 months, while in dogs, the decreases were 24% and 20% at the dose of 30 mg/kg administered for 6 months, and 20% and 20% at the dose of 12 mg/kg administered for 12 months. Moreover, the values of the different hematologic parameters affected, although differing significantly from those of the controls, in general, remained within the limits of acceptable variation. The effect of nilutamide was more marked in females than males. In addition, it was noted in the studies in which several examinations were performed that the anemia did not worsen as the treatment progressed and, in the 3-month study in rats, this anemia was reversible since after a 4-week recovery period, all the hematologic parameters had returned to normal.

There was no patent explanation for the origin of this anemia. It is well known that androgens can cause hemoconcentration and stimulate erythropoiesis. An antiandrogen such as nilutamide might therefore increase the plasma volume, thereby reducing the hemoglobin level. A decrease in the level of serum proteins should then be observed, which did not occur in these studies. Furthermore, this hypothesis is not consistent with the observed increase in the reticulocyte count in the rat and dog, and the platelet count in the dog. As regards erythropoiesis, although it has been shown that some antiandrogens at high doses might antagonize the action of androgens, particularly in the production of erythropoietin by the kidney, no intrinsic anti-erythropoietic effect by these antiandrogens alone has been observed. Furthermore, it has been shown that nilutamide did not affect erythrocyte resistance to degradation in vitro.

On the basis of observed changes in hematologic parameters, it is not clear that the anemia observed is a hemolytic effect, because the reduction in hemoglobin levels persisted, while reticulocytosis regressed. Moreover, hyperbilirubinemia was observed only occasionally in the 6-month study in the rat, where it was very moderate (blood bilirubin values did not exceed the accepted normal limits for this parameter) and not dose-dependent. Similarly, bile pigments were not increased in the urine. Finally, it should be noted that nilutamide was shown not to reduce rat erythrocyte resistance to degradation with increasing doses of sodium chloride. Direct toxicity by the compound on the stem cells of the marrow also seems unlikely, given the discrepancy between the decrease in the red blood cell count, the stability of the leucocyte count, and the increase in the platelet count. To address some of the unanswered questions, a study was performed in the dog given nilutamide for eight weeks. The results confirmed that the observed anemia was probably not of central origin

and was probably not due to the antiandrogenic activity of the compound. Conversely, the anemia might be related to hemolysis. The red cell lifespan was moderately reduced in the treated animals, as was corpuscular volume. This hemolysis is presumably extravascular. Haptoglobin levels did not vary, and more pronounced hemosiderosis was noted in the myelograms of the treated animals. Levels of bilirubin did not increase under the effect of dosing.

Nilutamide demonstrated few effects on other organs. Thus, in the liver, it only occasionally caused an increase in organ weight in female rats receiving 50 mg/kg for 3 and 6 months, and a slight increase in serum alkaline phosphatase in dogs receiving 30 and 20 mg/kg from the 13th week onwards. There were no histologic alterations noted apart from hepatocytic hypertrophy in dogs sacrificed in the 12-month study. Lens opacities noted in the 78-week rat study were considered to be a finding common in aged rats since, the opacities were unilateral and occurred only at the end of the study. No drug-related lung histopathology was noted in either the 52-week dog study or the 78-week rat study.

In vitro and in vivo studies of the activity of nilutamide in the hepatic mono-oxygenase system showed that the observed effects were related to the antiandrogenic activity of the compound. In the rat kidney, only an increase in organ weight in females receiving 50 mg/kg for 6 months was demonstrated, with, from a histologic point of view and, particularly at the last dose in the same study, the presence in the tubular epithelial cells of brown pigments whose nature could not be determined.

In the dog 12-month study, deaths were observed with a dose-related incidence (time of onset, number of deaths) and were preceded by anorexia and body weight loss, leading to cachexia and dehydration. Anemia was not more marked in these animals than in the survivors, nor were laboratory investigation results more severely affected. Observations from a complementary 30-day dog study might indicate that high doses of nilutamide induce behavior changes such as severe hypotonia with lack of reactions to stimuli, progressive decrease in food consumption, and then anorexia leading to the death or premature sacrifice of the animals.

In conclusion, nilutamide was considered to be well tolerated in rats at a dose of 10 mg/kg (five times the human dose) administered for 3 months and 5 mg/kg (2.5 times the human dose) administered for 18 months. Conversely, nilutamide was less well tolerated in dogs, since the lowest dose administered, 3 mg/kg (1.5 times the human dose), caused very slight anemia for the first 13 weeks of the 6-month treatment, and the death of one of 12 dogs in Month 11 of treatment in the 12-month study.

However, it should be remembered that nilutamide is more active in the dog than in the rat. In fact, after 6 months of treatment, 3 mg/kg of nilutamide in the dog had the same effect on prostate weight as 50 mg/kg in the rat. In addition, plasma elimination of nilutamide is slightly slower in the dog than in the rat (half-lives of 9 and 7 hours, respectively).

Nilutamide showed no mutagenic effect in a variety of tests: four gene mutation tests, two chromosomal aberrations tests, and one DNA repair test. No effect of nilutamide was observed on growth of *E. coli*, in vitro. In the 18-month study in rats, there was an increase in the number of benign Leydig cell tumors of the testes at the high dose of 45 mg/kg, which may be attributed to the antiandrogenic activity of nilutamide, since these types of tumors have been observed with antiandrogens. Nilutamide showed no carcinogenic potential and no effect on the incidence of spontaneous tumors.

In reproduction studies, no effect of nilutamide was observed on the reproduction function of male or female rats, and no lethal teratogenic or growth-suppressive effects on fetuses were found. The "no effect" level of nilutamide in reproduction function for both sexes and in effects on fetuses was estimated to be 45 mg/kg.

Analysis of Dose-Response Information

Information on the relationship between the dose of nilutamide and safety is available from both animal and clinical studies. A summary of the most pertinent information follows.

In general, nilutamide has been well tolerated in animals, particularly in rats, with minimal evidence of toxic effects at doses of 4 or 2 mg/kg which are many times greater than the expected therapeutic dosage range for patients with prostate cancer. The preclinical studies, therefore, support the use of nilutamide with the expected therapeutic range.

Most clinical studies were performed using either a fixed dose of 300 mg/day or the recommended regimen of 300 mg/day for 1 month followed by 150 mg/day thereafter. Indications about the relationship between dose of nilutamide and type, frequency, and importance of clinical adverse experiences were obtained from two open studies (Study Nos. 8/78/2 and 9/79/1) and one controlled study (Study No. F/82/908/03). In the two open studies, doses ranging from 50 mg/day to 900 mg/day were used. Gastrointestinal distress, including nausea and vomiting, and malaise, headache, and dizziness, occurred in patients receiving daily nilutamide doses of 600 mg and 900 mg, which are above those that are being recommended in the NDA. In one controlled supportive study (Study No. F/82/908/03), patients who received nilutamide 300 mg/day developed more adverse experiences than patients receiving nilutamide 150 mg/day from the start of treatment or placebo. Statistically significant between-group differences in body system totals occurred for Body As a Whole ($p=0.005$) and Special Senses ($p=0.001$). For both categories, a dose effect was apparent. In the Body As a Whole category, the higher incidence of adverse experience in the nilutamide dose groups was mainly due to asthenia and alcohol intolerance in the 300 mg/day group. In the Special Senses category, the difference was due to the incidence of dark adaptation impairment (23%, 300 mg/day; 15%, 150 mg/day; 0%, placebo).

The most frequent adverse experience in Study No. F/82/908/03 was hot flushes, which was reported more often in the 300-mg/day group (42%) and in the 150-mg/day group (49%) than in the placebo group (37%). In all nilutamide studies, this has been the most frequently reported adverse experience and is most likely related to the desired antiandrogen effect. Among events found more frequently with nilutamide in other studies, gastrointestinal symptoms were in this study nonsignificantly more frequent in the nilutamide groups (16%, 300 mg/day, 22%, 150 mg/day) than in the placebo group (11%). The low incidence of nausea and vomiting was noteworthy, perhaps related to the formulation of the drug, given as capsules in this study and tablets in the other nilutamide studies. Adverse experiences in the respiratory system and the nervous system occurred with a slightly higher frequency in the nilutamide dose groups than in the placebo group.

In Study No. FF/86/908/01, one of the primary studies, an analysis of the dates of onset and resolution of adverse experiences of interest was conducted as an indirect approach to the relationship between dose and these adverse experiences. In this study, patients were randomized to orchiectomy plus nilutamide or orchiectomy plus placebo. The dose of nilutamide was 300 mg/day for the first 30 days and 150 mg/day thereafter. A patient visit occurred at the end of the first 30 days of treatment at which time the daily dose was reduced to 150 mg/day. The next patient visit occurred on study Day 90. Two hundred twenty-five patients were enrolled in the orchiectomy plus nilutamide group, and 232 were enrolled in the orchiectomy plus placebo group.

When a date of onset was reported, the majority (64% to 100%) of cases of nausea, alcohol intolerance, impairment of dark and light adaptation, disturbances of color vision, and dizziness occurred for the first time during the first month of treatment. For at least 18% to 82% of these patients, the symptoms had disappeared at the Month-3 visit, possibly because of the planned dose reduction from 300 mg/day to 150 mg/day after 1 month of treatment.

In Study No. GHBA-606, the other primary study, an analysis of the dates of onset and resolution of adverse experiences of interest was also conducted as an indirect approach to the relationship between dose and these adverse experiences. In this study, patients were randomized to leuprolide plus nilutamide or leuprolide plus placebo. The dose of nilutamide was 300 mg/day for the first 30 days and 150 mg/day thereafter. A patient visit occurred at the end of the first 30 days of treatment at which time the daily dose was reduced to 150 mg/day. The next patient visit occurred on study Day 90. Two hundred nine patients were enrolled in the leuprolide plus nilutamide group, and 202 were enrolled in the leuprolide plus placebo group.

With respect to these adverse experiences, in Study No. GHBA-606, the majority (73% to 86%) of cases with a reported date of onset began during the first 30 days of treatment when patients received 300 mg/day of nilutamide. With respect to visual abnormalities in Study No. GHBA-606 (dark adaptation impairment, disturbances in color vision, and light

adaptation impairment), at least 18% to 36% of symptoms had resolved at the Month-3 visit, possibly in relation to the dosage reduction after 1 month of treatment. The majority of cases of nausea and alcohol intolerance in Study No. GHBA-606 with a reported date of resolution occurred within the first 30 days and resolved during the first 90 days of treatment possibly in relationship to the planned dosage reduction to 150 mg/day at Day 30, or possibly owing to the development of tolerance to those adverse experiences (regardless of daily dose).

Laboratory safety tests were performed in the majority of controlled and uncontrolled clinical trials. There did not appear to be a strong relationship between the dose of nilutamide and any change from baseline in laboratory test results.

Drug Interaction Data

Data from four studies (Study Nos. CDN/83/908/05, F/82/908/03, F/82/908/01, and F/84/908/01) were reviewed to assess the potential for drug interactions between nilutamide and the concomitant use of anticoagulant, hypoglycemic, and antihypertensive medications. A total of 438 patients (248 nilutamide, 190 placebo) had their data included in this review.

Of the 16 patients (11 nilutamide, five placebo) receiving concomitant anticoagulant therapy, five (three nilutamide, two placebo) were noted to have wide variations in prothrombin time from baseline. The investigators never reported difficulties in adjusting patients' anticoagulant therapy. Of the 24 patients (eight nilutamide, 16 placebo) receiving concomitant hypoglycemic or insulin therapy, 13 (five nilutamide, eight placebo) had a greater than 3 mmol/L increase in blood glucose during treatment, while five patients had a greater than 3 mmol/L decrease in blood glucose during treatment. Of the 58 patients (33 nilutamide, 25 placebo) being treated for hypertension, 11 (seven nilutamide, four placebo) had an increase from baseline of 20 mm Hg in systolic blood pressure during treatment; eight patients (three nilutamide, five placebo) had at least one systolic blood pressure value lower than 20 mm Hg below baseline.

It has been shown that nilutamide inhibits in vitro the activity of certain hepatic microsomal enzyme systems and potentiates warfarin in vivo at high doses. It may therefore reduce the metabolism of compounds requiring these systems.

Consequently, drugs with a low therapeutic margin, such as oral anticoagulants, phenytoin, and theophylline, could have a delayed elimination and increases in their serum half-life, leading to a toxic level. The dosage of these drugs or others with a similar metabolism may need to be modified when administered concomitantly with nilutamide.

Relationship of Demographic Status to Safety

1. Adverse Experiences by Age

In Study No. FF/86/908/01, one of the primary studies, an analysis of the incidence of adverse experiences by age (<65 years vs. >65 years) was carried out. Of the 457 patients entered into the study, 225 (49%) received nilutamide. Of these 225 nilutamide patients, 47 (21%) were less than 65 years of age, and 178 (79%) were 65 years of age or older. The remaining 232 patients received placebo. Of these 232 placebo patients, 39 (17%) were less than 65 years of age, and 193 (83%) were 65 years of age or older.

A lower or comparable proportion of nilutamide patients in the older subgroup compared with the younger subgroup had adverse experiences in the Body As a Whole, Endocrine, Hemic and Lymphatic, Metabolic and Nutritional, Musculoskeletal, Nervous, Respiratory, Skin and Appendages, and Special Senses body systems. For the Cardiovascular, Digestive, and Urogenital body systems, the overall incidence of adverse experiences was higher in the older nilutamide patients than in the younger patients. In the placebo group, the overall incidence of adverse experiences was lower or comparable for older patients compared with younger patients for all body system categories except the Cardiovascular and Respiratory systems.

Although no statistical analysis was performed on the incidence of adverse experiences by age subgroup in this study, there does not appear to be any substantial treatment effect by age.

The second primary study, Study No. GHBA-606, was a double-blind study in 411 patients with metastatic prostate cancer to determine the efficacy and safety of nilutamide in combination with leuprolide. Of the 411 patients entered into the study, 209 (51%) received nilutamide 300 mg/day plus leuprolide 1 mg/day for 1 month followed by 150 mg/day of nilutamide plus the same dose of leuprolide until progression or death. Of these 209 nilutamide patients, 72 (34%) were less than 65 years of age, and 137 (66%) were 65 years of age or older. The remaining 202 (49%) patients received placebo plus leuprolide 1 mg/day until progression or death. Of these 202 placebo patients, 67 (33%) were less than 65 years of age, and 135 (67%) were 65 years of age or older.

A lower or comparable proportion of nilutamide patients in the older subgroup compared with the younger subgroup had adverse experiences in the Endocrine, Metabolic and Nutritional, Musculoskeletal, Nervous, Respiratory, Skin and Appendages, and Special Senses body systems. For the Body As a Whole, Cardiovascular, Digestive, Hemic and Lymphatic, and Urogenital body systems, the overall incidence of adverse experiences was higher in the older nilutamide patients than in the younger patients. In the placebo group, the overall incidence of adverse experiences was higher in the older patients than in the

younger patients for the Cardiovascular, Digestive, Respiratory, and Skin and Appendages systems.

Statistical analysis was performed on the incidence of individual adverse experiences for each age by treatment group by means of the Fisher's two-tailed test. A significantly higher proportion of younger than older nilutamide patients reported decreased libido ($p=0.009$), tenosynovitis ($p=0.040$), and urinary frequency ($p=0.013$). In the placebo group, a significantly higher proportion of younger than older patients reported pain ($p=0.001$), gastritis ($p=0.035$), myalgia ($p=0.042$), depression ($p=0.017$), and tinnitus ($p=0.011$). There were no statistically significant differences favoring younger patients in either treatment group.

In contrast with the results reported for Study No. FF/86/908/01, the incidence of hypertension, constipation, and anorexia was slightly lower in the older nilutamide group (7%, 18%, and 9%, respectively) than in the younger group (8%, 21%, and 10%, respectively).

Impaired dark adaptation and impaired light adaptation also occurred in lower proportions of older (53% and 7%, respectively) than younger (63% and 8%, respectively) nilutamide patients.

It does not appear from the results of Study No. GHBA-606 that nilutamide has a disproportionate effect on older compared with younger patients.

2. Adverse Experiences by Race

Of the 411 patients in one of the primary studies, Study No. GHBA-606, which was conducted at 38 centers in the United States, 319 (78%) were white, 80 (19%) were black, and 12 (3%) were of other races. The black population in this study is the largest racial subgroup of any controlled study in the nilutamide clinical program and was to determine if there is a treatment effect by race. Of the 319 white patients, 165 received nilutamide, and 154 received placebo. Of the 80 black patients, 37 received nilutamide, and 43 received placebo.

Statistical analysis on the incidence of adverse experiences by race was performed by means of a two-tailed Fisher's exact test.

In every body system except Metabolic and Nutritional, the overall incidence of adverse experiences in nilutamide patients was lower for black patients than for white patients. The difference was statistically significant ($p < .05$) for Body As a Whole, Cardiovascular, and Special Senses and was close to statistical significance for the Digestive System. For individual adverse experiences, a significantly higher proportion of black nilutamide patients than white nilutamide patients had abdominal pain and lymphocytosis, and a trend toward

a lower incidence in black patients was noted for anemia and insomnia. A notably but not significantly lower incidence of dark adaptation impairment occurred for black patients (46%) compared with white patients (60%), which contributed largely to the statistical difference in the Special Senses category. A trend toward a lower incidence in white patients was noted for hypercalcemia, increased GGT, and hyperphosphoremia.

Among placebo patients, the overall incidence of adverse experiences was lower for black patients than for white patients in six of the 12 body systems: Cardiovascular, Digestive, Endocrine, Skin and Appendages, Special Senses, and Urogenital. The only statistically significant difference in overall incidence by body system in the placebo group occurred for the Musculoskeletal System, in which the incidence of adverse experiences was significantly higher for black patients than white patients. For individual adverse experiences, a significantly higher proportion of black placebo patients than white placebo patients had sepsis, hyperphosphoremia, bone pain, hemoptysis, respiratory disorder, and nocturia, and a trend toward a higher incidence in black patients was noted for death and haptoglobin increased. A significantly higher proportion of white placebo patients than black placebo patients reported hot flushes, hematuria, and testicular atrophy.

In summary, the results of this well-controlled study show that nilutamide does not adversely affect the black subgroup of patients. To the contrary, most adverse experiences occurred in lower proportions of black patients than white patients. Whether this finding reflects a true racial difference or a social difference in reporting adverse experiences is not clear.

In Study No. J/87/908/02, conducted in Japan, eight possible or probable cases of interstitial pneumonitis occurred in 47 patients enrolled in the planned 12-week treatment. Comparison of the pharmacokinetic parameters and plasma concentrations of metabolites in the Japanese patients with those in European patients who had not developed respiratory adverse events did not explain the incidence of this adverse experience in the Japanese patients. Specific caution in treating Asiatic patients is recommended.

Other Potentially Important Pharmacologic Properties

1. Animal Studies

Action on the Central Nervous System

Nilutamide modified the behavior of the mouse or rat only at doses of 100 mg/kg (weak sedation, slight motor deficit in the rotarod test in the mouse) but exerted no anticonvulsant effect against electroshock or pentylenetetrazol in the mouse.

Nilutamide did not interact with serotonin or oxytremorine in the mouse. It accentuated reserpine-induced hypothermia from 100 mg/kg, but this was due to its intrinsic hypothermal effect.

In the rat, nilutamide had no effect on apomorphine-induced stereotypies, but it potentiated those induced by amphetamine dose-dependently from a dose of 1 mg/kg. This potentiation does not reflect a central effect of nilutamide, but can be compared to the potentiation of hexobarbital-induced sleep in the mouse, an effect that is proportional to the dose of nilutamide from 10 mg/kg but that is not found in barbitol-induced sleep. This potentiation is probably attributable to slowing of the hepatic metabolism of the drugs. A decrease in mono-oxygenase activity was also observed in the rat.

Action on the Cardiovascular System, the Autonomic Nervous System, and the Respiratory System After Intravenous Administration

In the anesthetized dog, nilutamide caused hemodynamic and respiratory modifications only at 10 mg/kg (hypotension followed by hypertension, polypnea, tachycardia, and transient ECG disturbances) but did not appreciably modify the blood pressure effects of adrenalin, noradrenalin, acetylcholine, and histamine. Similarly in the cat, nilutamide at intravenous doses of 1, 3, or 10 mg/kg, did not modify the response of the nictitating membrane to preganglionic or chemical stimulation.

Other Actions Following Oral Administration

Nilutamide exerted no effect on the rat gastrointestinal tract in single-dose administration at the high dose of 100 mg/kg. In the same species, nilutamide decreased urinary excretion of sodium and chloride at a dose of 10 mg/kg, whereas the urinary excretion of potassium was increased after 100 mg/kg. It had no effect on blood glucose levels or on prothrombin time, but it potentiated the anticoagulant action of warfarin from a dose of 10 mg/kg. Nilutamide, administered at 50 mg/kg/day for 10 days had no effect on carrageenan-induced pleurisy in the rat as measured by exudate volume and total leukocyte number in the pleural cavity.

Extensive animal studies have shown nilutamide to be a specific antiandrogen that does not interact with the progestin, estrogen, glucocorticoid, or mineralocorticoid receptors.

Lastly, at a dose of 100 mg/kg, nilutamide slightly decreased carrageenan-induced plantar edema and acetic acid-induced writhing movements in the mouse, probably as a result of its sedative effects. It demonstrated no analgesic effect in the hot plate test.

In Vitro Activities

At the high concentration of 10^{-4} M, nilutamide had no effect on the isolated guinea pig atrium and antagonized histamine-induced, serotonin-induced, and bradykinin-induced contractions but not those induced by acetylcholine in the guinea pig ileum. However, nilutamide did not antagonize adrenalin-induced contractions in the guinea pig seminal vesicle and did not modify ADP-induced or collagen-induced platelet aggregation.

2. Human Studies

Hormonal Effects

In Study No. FF/ANA/006, the effects of nilutamide on gonadotropin secretion in normal women and in those with polycystic ovarian disease were evaluated. Nilutamide, which interacts only with the androgen receptor, induced no significant change in the mean levels, frequency, or amplitude of the luteinizing hormone (LH) pulses or in LH and follicle-stimulating hormone responsiveness to gonadotropin-releasing hormone (GnRH) in women with polycystic ovarian disease (PCOD) and women with normal menstrual cycles. Plasma concentrations of estradiol (E_2), estrone (E_1), testosterone (T), dihydrotestosterone (DHT), androstenedione (A), dehydroepiandrosterone sulfate (DHAS) and urinary androstanediol glucuronide (3α -diol G) were not modified by nilutamide when compared with placebo cycles. Plasma sex hormone-binding globulin (SHBG) did not change in normal women but increased significantly in women with polycystic ovarian disease.

In another study (Study No. FF/86/305/ANA/005), basal levels of cortisol, 17-hydroxyprogesterone, 17-hydroxypregnenolone, A, DHEA, DHEA-S, T, DHT, pregnenolone, androstenediol, ACTH, plasma renin activity (PRA), and aldosterone were studied in 14 patients with Stage C or D prostate cancer receiving a combined treatment of castration and either an antiandrogen or placebo. Cortisol, aldosterone, PRA, and ACTH were unaffected by therapy. Forty-five days following castration, plasma levels of T and DHT fell in both groups. Whereas plasma cortisol and DHEA levels showed no significant changes after 45 days of treatment, basal values of DHEA-S dropped significantly for both groups. In addition, both groups showed significantly diminished post-castration basal levels of androstenediol ($p < 0.022$), androstenedione ($p < 0.02$), and 17-hydroxyprogesterone ($p < 0.007$). There were no significant inter-group variations in hormone levels, and there were no changes in either groups' response to stimulation by ACTH. These data obtained in a small number of castrated patients suggest that treatment of prostate cancer with nilutamide versus placebo does not produce a significant difference in hormone profile.

In Study No. F/82/908/03, 191 simultaneously orchiectomized patients with Stage D prostate cancer received nilutamide 300 mg/day, nilutamide 150 mg/day, or placebo; 159 of these patients were evaluable for efficacy. As expected, testosterone decreased and LH and FSH increased markedly in the three groups after castration. Adrenal androgen concentrations were decreased to a greater extent in both nilutamide treatment groups than in the placebo group. At most evaluation time points, the median androgen levels in the 300 mg/day group were decreased to a significantly ($p < 0.05$) greater extent than in the placebo group. The evaluation of other hormones assayed (estradiol, prolactin, and cortisol) was not significantly different in the three groups.

Use in Pregnancy

The indication for nilutamide is metastatic prostate cancer in combination with orchiectomy. Nevertheless, teratogenic studies were performed, and nilutamide was without effect on rat fetuses in oral doses up to 45 mg/kg.

Effect on Driving

No specific studies have been performed to date to evaluate the effects of nilutamide on driving performance or the ability to operate machinery. Because of nilutamide's potential to impair adaptation to darkness, it is advisable for patients who experience this effect to either refrain from driving at night or postpone driving until their eyesight has accommodated to the darkness and to avoid driving in tunnels during bright daylight. A study is planned to evaluate this effect.

Effects on Personality

Two adverse experiences of interest involving personality changes, and possibly related to nilutamide administration, were reported in Study GHBA-606 (nilutamide + leuprolide versus placebo + leuprolide). Patient No. a 58-year-old man, was hospitalized for an acute psychotic episode, which was manifested principally by manic symptoms that began approximately three weeks after he started nilutamide and leuprolide. The patient had no prior history of mania or other psychiatric disorder and no family history. A CAT scan of the head was negative for brain metastases. Ten days after he discontinued nilutamide, the patient's manic symptoms completely resolved; he was continued on daily leuprolide injections.

Patient No. an 80-year-old man, was hospitalized on Day 68 of the study because of notable personality changes and manic symptoms. The patient had no prior history of mania or other psychiatric disorder. Study medication was stopped for one week. A CAT scan demonstrated metastases to the skull but a normal brain. The patient had a history of chronic alcoholism but denied alcohol intake at the time of these events. He was treated with haloperidol and lorazepam, and his condition improved. Approximately 1 month after his study medication was restarted, the patient was reported to be calm and not confused. He continued in the study until Day 267, when he died of a cardiopulmonary arrest.

It should be noted that no other patients treated with nilutamide have reported an adverse experience involving manic symptoms or other personality changes considered possibly related to the study medication.

Long-Term Effects

Nilutamide has been administered to patients for periods of longer than 6 months and up to 5 years in both the controlled and uncontrolled studies. The rare occurrence of serious adverse experiences considered probably or possibly related to the study medication in patients who have been treated with nilutamide does not suggest a substantial risk with long-term exposure.

The types of adverse experiences most often considered possibly or probably related to nilutamide treatment (visual adverse events, transient increases in liver enzymes, interstitial pneumonitis) tend to occur within the first 6 months of treatment.

Withdrawal Effects

No specific studies have been performed to evaluate potential withdrawal effects of nilutamide, but on the basis of nilutamide's pharmacologic properties, a return to pretreatment levels of androgenic activity on prostate cancer cells would be expected after treatment withdrawal. As a result of this, the prostate cancer, whose growth and differentiation are dependent on the activity of circulating androgens, would be expected to progress.

3. Specific Adverse Experiences

Hematologic Adverse Experiences

The results from the primary studies (Nos. FF/86/908/01 and GHBA-606), and the pooled studies in orchiectomized and chemically castrated patients suggest that there is no significant difference between nilutamide and placebo with regard to deviations from predefined limits or mean changes from baseline in the hematologic variables of hemoglobin, hematocrit, or RBC count.

Two serious cases of anemia occurred in the clinical program of nilutamide. In Study No. CH/85/908/05, one nilutamide patient developed markedly elevated liver enzymes, which improved during continuation of treatment, and aplastic anemia after 5 months of treatment, which resulted in treatment discontinuation. In this patient, a bone marrow biopsy was more consistent with pancytopenia secondary to metastatic involvement of bone marrow. In Study No. NL/84/908/06 (an open clinical pharmacology study), one subject developed marked liver dysfunction during the study and severe bone marrow depression diagnosed 11 days after discontinuation. Evaluation of the available laboratory and histologic data did not reveal conclusive evidence that the adverse event was due to nilutamide nor was there conclusive evidence that there was another cause such as a microbial agent. However, the temporal relationship of the events was consistent with non-A non-B hepatitis and agranulocytosis.

As of February 1991, no cases of hemolytic anemia attributable to nilutamide had been observed in any of the clinical trials of nilutamide or had been spontaneously reported in France, where the drug has been marketed since November 1987. However, during postmarketing surveillance in France, two cases of aplastic anemia, for which a causal relationship to nilutamide could not be excluded, were reported among over 10,000 patients treated with nilutamide.

Effect on Liver Function

In double-blind, long-term studies of nilutamide (over 1 month in duration), among patients evaluable for transaminase measurements (the measurements were scheduled in all long-term studies), the percentages of patients with at least one on-drug SGOT or SGPT value above twice the upper limit of the normal range (2 N) were 8% (19/247) in the placebo group and 13% (37/295) in the nilutamide group ($p=0.065$). The percentages of patients with values above 5 N and 10 N were 0.8% and 0.4%, respectively, in the placebo group and 3.4% and 1.7%, respectively, in the nilutamide group. Three patients in the nilutamide group and none in the placebo group were withdrawn from the study because of transaminase elevation. In patients with normal or missing pretreatment values, there were more transient transaminase increases in the nilutamide group (7%) than in the placebo group (3%) ($p=0.056$). These transient increases occurred most often after 3 months of treatment, were most often between 2 N and 3 N (although values above 10 N were observed), and were not accompanied by symptoms. Return to normal most often took place within 6 months without discontinuation of treatment.

From over a total of 3,306 patients treated with nilutamide (3,201 in long-term therapeutic trials or compassionate use and 105 in short-term or clinical pharmacology studies), 31 liver-related adverse events were reported before 1 October 1987. Nilutamide was considered to be unrelated to seven of these events and unlikely related to 11. The relationship to study drug was considered possible in four patients and probable in six. Three cases were insufficiently documented. The incidence of possibly or probably related adverse events in long-term, therapeutic trials or compassionate use was therefore 0.4% (13/3,201) with a 95% confidence interval of 0.2% to 0.7%. In studies for which all case report forms were available for review, the incidence was 0.6% for double-blind studies and 0.9% for noncomparative studies. In the six patients having liver-related adverse experiences for whom the relationship with nilutamide was considered probable, the event was a hepatocellular injury in five and a mixed hepatitis in one, which occurred between 0.5 and 4 months after the beginning of treatment. Transaminases returned to normal within 3 months after cessation of treatment in patients for whom follow-up was long enough.

The results of both the primary study and the pooled studies were consistent with the review of the findings summarized above.

Among spontaneous notifications of adverse reactions reported to Roussel Uclaf for over 20,000 patients treated with the marketed drug, there were 10 cases of liver disorders considered possibly related to nilutamide.¹

Visual Adverse Experiences

The most common visual adverse experiences reported in patients treated with nilutamide are dark adaptation impairment and chromatopsia. These have been reported to occur in frequencies up to 57% and 9%, respectively (in primary Study No. GHBA-606), but most often at frequencies near approximately 20% and 5%. The great majority of these cases are reported to be mild in intensity and required no medical treatment. Some patients reported that wearing tinted glasses made the dark adaptation impairment more tolerable. In Study No. GHBA-606, almost half of these experiences resolved during the course of the study, possibly in relation to the planned dose reduction in the protocol from 300 mg/day to 150 mg/day after 1 month of treatment or possibly due to the development of tolerance to that adverse experience.

The time of onset of visual adverse experiences ranged from 1 to 365 days with a median of about 50 days in both the controlled and open trials. There was no statistically significant difference between the groups of patients with and without visual disorders in terms of their age, weight, general condition, or concurrent diseases. A statistically significant difference did exist ($p < 0.05$) in the frequency of visual disorders between the group of patients in the controlled trials without anemia at entry (32%) versus the group with anemia at entry (8%). Similarly, in the controlled trials, there was a statistically significant difference ($p < 0.02$) in the frequency of visual disorders in patients whose cancer regressed (34%) or stabilized (39%) compared with patients whose cancer progressed (14%). In both cases, however, the patients with anemia and the patients with disease progression had a much shorter follow-up period. Additionally, visual disorders were significantly associated ($p < 0.001$) with the incidence of hot flushes and alcohol intolerance.

All ophthalmological examinations, including visual acuity, visual field, color vision tests, etc., that were performed in patients remained normal or unchanged. The only abnormality was the lengthening of the photostress recovery time, which was always reversible upon treatment discontinuation.

The symptoms of patients and objective findings from several experiments conducted to elucidate the mechanism by which visual disorders occur point to a delayed regeneration of visual pigments after bleaching, thus impairing rod-mediated vision, and possibly also cone-mediated vision. This phenomenon is likely to be related to an interaction of nilutamide with

¹ Updated data as of March 1993. No increase in incidence has been noted. Report on Worldwide Spontaneous Notifications is in the Other Studies and Information Section of the Clinical Data Section.

Vitamin A carrier proteins or with the enzymes required for the formation of 11-cis-retinal. Experiments being conducted by Dr. B. Wiggert at the National Eye Institute to study the effect of nilutamide on 11-cis-retinal concentrations in the interphotoreceptor space in a toad eye-cup preparation may provide some explanation of the nilutamide effect on vision. A study on the effect of visual symptoms on driving ability is also planned.

Interstitial Pneumonitis

The development of interstitial pneumonitis in five patients enrolled in primary Study No. GHBA-606 resulted in a meeting with the FDA in February 1988, a "Warning" statement to be added to the Investigational Drug Brochure, and a protocol amendment for Study No. GHBA-606. The amendment excluded patients with pre-existing clinical or subclinical interstitial lung disease, as well as patients who were being treated with any medication known to be associated with interstitial lung disease; required chest X-ray and pulmonary function tests during pretreatment and at specified study months or more often if indicated in all newly enrolled patients and in those enrolled since 1 December 1987.

In the final report for Study No. GHBA-606, in which patients also received the LHRH agonist leuprolide, it was noted that interstitial lung disease occurred in seven (3%) of 209 nilutamide patients and one (1%) of 202 placebo patients. Of the seven cases in nilutamide patients, five were considered severe, one was considered mild, and one was considered moderate in intensity. Interstitial lung disease occurred in 2% of patients treated with orchiectomy and nilutamide, including 8/47 (17%) patients in an uncontrolled Japanese study of nilutamide (Study No. J/87/908/02). Because of the incidence of interstitial pneumonitis in this study, the pharmacokinetic parameters and plasma concentrations metabolites in the Japanese patients were compared with those in European subjects who had not developed respiratory adverse events. Differences in pharmacokinetics or metabolism in the two population did not seem to account for the difference in the incidence of respiratory adverse events.

In the clinical studies, interstitial pneumonitis was almost always reversible upon discontinuation of treatment and, in some cases, with corticosteroid administration or decreased dosage or both.

Since the beginning of the development of nilutamide, 72 cases of interstitial syndrome (interstitial lung disease) have been diagnosed in the population given nilutamide in either comparative or open trials or for compassionate use. Among them, 18 cases were considered unrelated to nilutamide, 42 cases were considered possibly related to nilutamide, and 12 cases insufficiently documented for causality assessment were added to the possibly

related cases for incidence. A review of all cases of interstitial pneumonitis that have occurred worldwide indicate that this adverse experience does not seem related to a hypersensitivity reaction. Idiosyncratic toxicity of nilutamide and/or of its metabolites on lung structures is therefore suspected. Metabolic studies are currently under way to identify the toxicity of nilutamide on lung cells.

Postmarketing Surveillance

Since nilutamide was first launched in France in 1987, more than half a million boxes of the drug have been sold, which represents substantial exposure to the agent. A patient requires two boxes for the first month and one box a month from the second month of treatment. Since the introduction of nilutamide, Roussel Uclaf's Pharmacovigilance Department has collected and reported on adverse experiences from spontaneous notification, from postmarketing studies (except for French phase IV studies, which are analyzed in a separate report), and from the literature. The data presented in these safety reports do not identify any areas of concern about the safety of nilutamide that have not already been incorporated into the product information.

F. CONCLUSIONS

The original NDA 20-169 for nilutamide summarized clinical trials in which over 2,261 subjects or patients have been treated with nilutamide to date. Among these subjects or patients were 2,168 patients with prostate cancer, including 682 patients who were treated with nilutamide 12 months or more. From the patients with prostate cancer in the NDA, it was concluded that nilutamide:

- Is generally well tolerated in this population of middle-aged and elderly men with metastatic prostate cancer.
- May be associated with interstitial lung disease in a small percentage of patients, and careful monitoring for this effect should be practiced. Interstitial lung disease was reported in 1.8% of patients treated with nilutamide and surgical castration and in 3% of patients receiving nilutamide with leuprolide (medical castration) in Study No. GHBA-606, a controlled double-blind study. Reported worldwide incidence is 1% to 2%. This disorder has almost always been reversible. A small uncontrolled Japanese study, No. J/87/908/02, reported a higher percentage of interstitial lung disease than studies conducted in Europe, Canada, and the United States.
- May be associated with visual disturbances, which occur in approximately 25% of orchiectomized patients receiving nilutamide and are described most often as impaired adaptation to darkness and occasionally as abnormal vision, photophobia, impaired

light adaptation or chromatopsia. These experiences very rarely required treatment discontinuation (1 to 2%) and are reversible upon treatment discontinuation. In one of the primary studies (Study No. FF/86/908/01), the most prevalent of the visual adverse experiences, dark adaptation impairment, was reported for 13% (29/225) of the nilutamide patients compared with 1% (3/232) of the placebo patients. No treatment was required in 28 of the 29 nilutamide patients, while the remaining patient required nonmedical treatment (tinted glasses). In Study No. GHBA-606, the other primary study, impaired dark adaptation was the most frequent adverse experience, occurring in 118 (57%) nilutamide patients and only 11 (5%) placebo patients. The delay in dark adaptation was reported to range from a few seconds to 30 minutes, with most patients reporting a delay lasting 5 minutes. Patients also reported that wearing tinted glasses helped the problem and that, in some cases, they avoided driving at night as a precautionary measure. Only 1% of patients discontinued treatment because of visual adverse experiences in this study.

- May be associated with elevations in liver function tests, which are generally transient. In orchiectomized patients, transaminase values above twice the upper limit of normal occurred in 7% to 13% of nilutamide patients and in 4% to 5% of placebo patients. The increases most often were transient and moderate (values below three times normal), and occurred within three months of nilutamide treatment. Markedly elevated values resulting in treatment withdrawal or hepatitis were reported in 1% of patients. With regard to the primary studies, in Study No. FF/86/908/01, SGOT and SGPT values were more than twice the upper limit of normal in two to three times as many nilutamide patients as placebo patients (7% and 11%, respectively, in the nilutamide group compared with 4% for both enzymes in the placebo group). Three patients (1.3%) in this study were withdrawn because of an increase in liver transaminases. In Study No. GHBA-606, transaminase values above twice the upper limit of normal occurred in 20% of nilutamide patients and 15% of placebo patients. One nilutamide patient was prematurely withdrawn from the double-blind phase of the study because of increased SGOT and SGPT.
- May occasionally cause alcohol intolerance, which has been reported in about 5% of nilutamide patients. In Study No. FF/86/908/01, 11 (4.9%) of the 225 patients receiving nilutamide compared with one (<1%) of the 232 patients receiving placebo had alcohol intolerance. This disorder might be related to the higher dose in the first month of the study (300 mg/day), since six patients had a resolution of this disorder during continued treatment. In Study No. GHBA-606, eight (4%) of the 209 patients receiving nilutamide compared with one (<1%) of the 202 patients receiving placebo had alcohol intolerance. In the pooled orchiectomy studies, in which a fixed dose of 300 mg/day was administered, the incidence of alcohol intolerance was 10% (35/335). However, in the 150 mg/day fixed-dose arm of one of the pooled studies (Study No. F/82/908/03), the incidence of alcohol intolerance was only 2% (1/65).

- May be associated with a greater incidence of impotence, reduction in libido, and hot flushes than orchiectomy alone as a result of the antiandrogenic activity of the compound. Infrequent decreases in hemoglobin, hematocrit, and red blood cell count may also be related to this effect. Gynecomastia is rare when nilutamide is combined with orchiectomy.
- Does not cause diarrhea.
- Infrequently causes nausea, which may occasionally require earlier dosage reduction, fractionation of the dose, or termination of treatment. It has been reported in about 9-10% of nilutamide patients (versus 4-6% of placebo patients). Although nausea is, in some cases, accompanied by vomiting, and severe enough to require treatment discontinuation, this usually occurs early in the course of treatment, when patients are receiving 300 mg/day. Patients on the 150 mg daily dosage are usually free of gastrointestinal symptoms. In one of the primary studies (Study No. FF/86/908/01), nausea and vomiting occurred at a slightly higher incidence in nilutamide patients (9% and 4%, respectively) than in placebo patients (6% and 3%, respectively). In Study No. GHBA-606, nausea occurred in 49 (23%) of nilutamide patients, compared with 15 (7%) of placebo patients. Nausea in combination with vomiting occurred in only nine (4%) nilutamide patients and 13 (6%) of placebo patients.

With regard to the primary studies, longer follow-up (34 to >40 months) did not modify the adverse event rates. No adverse experiences were seen with nilutamide in the Safety Update that had not occurred in the NDA analysis. It is important to note that even with the increasing length of exposure to the drug either during double-blind or open-label treatment, no interstitial lung disease or liver dysfunction occurred.

Since the submission of NDA 20-169 on 7 March 1994, no unexpected increase in the incidence of any specific adverse experience has occurred, and there has been no new or unusual adverse experience in this population. Laboratory data and postmarketing surveillance do not show any areas of concern about the safety of nilutamide that would warrant a change in the product information.

NILUTAMIDE FOR PROSTATE CANCER SUMMARY OF NDA

I. OVERVIEW OF CLINICAL DEVELOPMENT

A. PRODUCT DESCRIPTION

Nilutamide (RU 23908) is a potent, nonsteroidal antiandrogen that blocks, by competition, the binding of androgens with their receptors. (See Attachment 1 of this section for a general review of the drug.)

Since the growth and differentiation of prostate cancer cells is dependent on the presence of adequate concentrations of circulating androgens, the primary goal in the systemic treatment of metastatic prostate cancer is to suppress androgenic stimulation.

Bilateral orchiectomy (surgical castration) has been shown to have a beneficial effect on advanced prostatic cancer owing to the removal of the primary source of testosterone and its active metabolite dihydrotestosterone. Although helpful in patients where rapid response is crucial, bilateral orchiectomy has not yet been proven to prolong survival.

The administration of pharmacologic doses of estrogens (e.g., diethylstilbestrol) has been shown to be as effective as bilateral orchiectomy in reducing serum concentrations of testosterone as well as inducing remission of the disease. However, severe cardiovascular side effects limit the use of estrogens.

The use of luteinizing hormone-releasing hormone (LHRH) agonists has added a third option for treating advanced prostate cancer. However, chemical castration by means of the administration of an LHRH agonist is accompanied by an initial increase in luteinizing hormone and testosterone secretions, which could be responsible for a transient but potentially serious "flare" of the metastatic disease.

While these treatments are effective in the suppression of circulating androgens of testicular origin, they fail to suppress androgens of adrenal origin. It has been hypothesized that at least some of the recurrence seen after surgical or medical castration may result from the lack of suppression of active androgens of adrenal origin. By blocking the action of androgens at the cellular level, antiandrogens such as nilutamide neutralize the effect of androgens from all sources, and thus, theoretically, represent the ideal form of therapy. However, a pure antiandrogen as a single-drug therapy in a noncastrated individual through interruption of the negative feedback exerted by androgens at the hypothalamic-pituitary level, induces a secondary increase in gonadotropins and testosterone secretion which could overcome its antiandrogenic effects.

In preclinical studies in the castrated rat and castrated dog, nilutamide was shown to inhibit the increase in prostate and seminal vesicle weights induced by the administration of natural

or synthetic androgens. Studies in the noncastrated rat showed that nilutamide inhibited the negative feedback on the hypothalamic-pituitary axis, thereby inducing an increase in luteinizing hormone and testosterone levels. The concomitant administration of nilutamide with an LHRH agonist in the rat demonstrated an almost total antiandrogenic effect even when the rats were continuously perfused with adrenal androgens in amounts equivalent to those circulating in the human.

Nilutamide in combination with surgical (bilateral orchiectomy) or medical (LHRH agonist) castration therefore should be useful in the treatment of metastatic carcinoma (Stage D₂) of the prostate gland. A retrospective analysis of the data from the two large, well-controlled, primary studies identified baseline factors and clinical endpoints that were associated with a good response to nilutamide therapy (combined with surgical or medical castration). The predictive value of these factors will enable the prescribing physician to make informed decisions regarding the benefit of undertaking and continuing nilutamide therapy in a given patient versus the risk of adverse experiences. Additionally, the availability of nilutamide to the prescribing physician will provide a therapeutic alternative to flutamide for patients who cannot tolerate the gastrointestinal effects, particularly severe diarrhea, associated with flutamide administration.

In summary, the potential clinical benefits of nilutamide in combination with surgical (bilateral orchiectomy) or medical (LHRH agonist) castration for the treatment of metastatic carcinoma of the prostate gland, in an appropriate subgroup of patients, include the following:

- To provide a more complete androgenic blockade with combination therapy than with either treatment alone, and thereby improve the benefit of castration alone with regard to pain improvement, remission rate, time to progression, and survival.
- To offer the prescribing physician a basis for making informed decisions regarding treatment by the use of baseline factors and clinical endpoints.
- To offer an important new antiandrogen therapy to the patient population that would most benefit, as well as to provide an alternative to existing therapy.

The proposed package insert for nilutamide is located in Appendix A.

B. DEVELOPMENT OF CLINICAL PROGRAM

The overall clinical program for nilutamide was designed to evaluate the safety and efficacy of nilutamide (RU 23908) in combination with surgical or chemical (medical) castration in the treatment of prostate cancer. Clinical studies conducted in the United States and internationally have investigated the effects of nilutamide in combination with surgical or

chemical castration in patients previously treated and untreated with hormonal manipulation. Appendix B (Table of All Studies) identifies all the studies in the nilutamide clinical program.

The clinical data for nilutamide represent over 16 years of experience with the agent, from 1978 through 1993. Overall, during the development period, 2,168 patients with prostate cancer have been treated with nilutamide in combination with surgical or medical castration; 682 of these patients had been treated for 12 months or longer.

The overall clinical program for nilutamide consists of 20 clinical pharmacology studies, 10 double-blind, placebo-controlled studies (one was also a clinical pharmacology study), three uncontrolled studies, and seven studies in indications not included in the proposed labeling for nilutamide. In addition, 19 studies, including an EORTC study in hepatocellular cancer and four postmarketing studies, were ongoing at the time of data collection and will be reported at a later date.

Extensive animal studies have shown nilutamide to be a specific antiandrogen that does not interact with the progestin, estrogen, glucocorticoid, or mineralocorticoid receptors. Studies in rats showed that nilutamide in combination with an LHRH agonist was much more effective than either treatment alone in diminishing prostate or seminal vesicle weight.

In humans, the hormonal effects of nilutamide were studied in male transsexual volunteers who had never received hormonal therapy and were waiting for surgical castration (Study No. NL/84/908/06). The results of this study confirmed the antiandrogenic activity of nilutamide. On the basis of these and other encouraging results of clinical pharmacology studies, the Phase II-III clinical program was initiated to evaluate the safety and efficacy of nilutamide in combination with medical or surgical castration in the treatment of metastatic prostate cancer.

Preliminary results of a Phase II, open study conducted to evaluate the efficacy of nilutamide in combination with medical (LHRH agonist) or surgical (orchiectomy) castration showed a positive response in patients previously untreated (Study No. CDN/82/908/04) but not in patients previously treated by estrogen or castrated receiving nilutamide alone. These preliminary results support the hypothesis that first line treatment with complete androgen blockade is crucial to minimize the establishment of androgen-resistant cell clones. The results of this preliminary study were later confirmed by results from double-blind, placebo-controlled Study No. F/83/908/01-F/84/908/03 in patients who had relapsed after previous estrogen treatment. In this study, no benefit was noted in the group treated with orchiectomy plus nilutamide compared with the group treated with orchiectomy alone. Thus the selection of patients in the Phase III program was restricted to patients with Stage D₂ prostate cancer who had no previous hormonal treatment.

The primary studies in this clinical program were designed in accordance with the research principles set forth in the FDA's "General Guidelines for Clinical Trials" (September 1977). The major objective of the primary studies reported in this NDA submission was to demonstrate the safety and efficacy of nilutamide (RU 23908) in combination with surgical or medical castration in the treatment of Stage D₂ prostate cancer in patients who have had no previous hormonal manipulation. When these two primary studies started in 1986, the standard treatment for metastatic prostate cancer was castration, and no other antiandrogen at that time was proven to add efficacy to castration. The efficacy and safety of these combination treatments were compared with the efficacy and safety of surgical or medical castration and placebo, since hormonal ablation was the standard treatment for metastatic prostate cancer. The two large Phase III studies, Study No. FF/86/908/01 (nilutamide plus orchiectomy) and Study No. GHBA-606 (nilutamide plus leuprolide), were intended to support proposed labeling for castrated patients.

The selection of the optimal dose (maximal tolerated dose with clear antiandrogenic activity) for use in the Phase III program was based on data obtained from several studies. Results of an early dose-ranging study conducted with nilutamide 50 mg, 100 mg, 300 mg, and 600 mg per day in patients with advanced prostate cancer showed nilutamide to be well tolerated in doses of up to 300 mg per day (Study No. 8/78/2). Clinical pharmacokinetic studies showed that nilutamide is rapidly and completely absorbed after oral administration with a plasma elimination half-life of 43 hours in healthy volunteers and 56 hours in patients (Study No. 89/1523/CN). Steady state concentration is reached in about two weeks, with relatively minor variations in plasma concentration after each dose.

A double-blind, placebo-controlled study (Study No. F/82/908/03) comparing the efficacy and safety of nilutamide 150 mg and 300 mg and a placebo, administered as three daily doses in combination with orchiectomy, showed that nilutamide 300 mg had a more rapid effect than nilutamide 150 mg. Both doses resulted in similar efficacy after 6 months of treatment, and the lower dose appeared to be better tolerated. The higher initial dose makes it possible to reach more rapidly the concentrations obtained at steady state with a lower dose, which is essential when nilutamide is administered in combination with an LHRH agonist. Study No. F/85/908/01 showed that the safety and tolerability of nilutamide 300 mg administered once daily was similar to that of nilutamide 100 mg administered three times a day. On the basis of these data, the optimal dose to be used in the Phase III clinical trials was determined to be 300 mg, once daily, for the first month followed by 150 mg, once daily, thereafter. Investigators were given the option of reducing the dose to 150 mg, once daily, during the first month if the higher dose was poorly tolerated.

The results of two double-blind, placebo-controlled studies demonstrated that nilutamide was effective in inhibiting the potential adverse effects (increase or appearance of pain, increase in tumor markers) associated with the initiation of LHRH-agonist therapy (Study No. F/85/908/10 and the busarelin arm of Study No. F/82/908/01).

Four double-blind, placebo-controlled studies were conducted to evaluate the efficacy and safety of nilutamide in combination with bilateral orchiectomy in patients with Stage D₂ prostate cancer who have had no previous hormonal treatment. Three of these studies were conducted in France (Study Nos. F/82/908/03, F/82/908/01, and F/84/908/01) and one in Canada (Study No. CDN/83/908/05). Preliminary results of these four studies suggested a clinically significant improvement in the nilutamide-treated groups for most efficacy parameters. The results of Study No. CDN/83/908/05, which included the larger number of patients, showed a 30% increase in median survival time for patients receiving nilutamide (24.7 months) versus patients receiving placebo (19.2 months). Results of a smaller study conducted in Switzerland (Study No. CH/85/908/05) also showed a tendency toward increased survival for nilutamide patients.

The buserelin arms of two of these studies also assessed the efficacy and safety of nilutamide in combination with the LHRH agonist buserelin (Study Nos. F/82/908/01 and CDN/83/908/05). Although a limited number of patients were represented in the data, and although the group receiving buserelin plus nilutamide in Study No. CDN/83/908/05 was treated with open-label drugs, the median survival time for patients receiving nilutamide in combination with buserelin was similar to that seen for patients receiving nilutamide in combination with orchiectomy.

Efficacy Results

Primary Studies

On the basis of the encouraging results of the first analyses of the above studies, two large, Phase III, double-blind, placebo-controlled studies were initiated (Study Nos. FF/86/908/01 and GHBA-606). Study No. FF/86/908/01 was designed to compare the safety and efficacy of nilutamide in combination with orchiectomy with that of orchiectomy plus placebo in patients with Stage D₂ carcinoma of the prostate. Sixty-six investigators from 15 countries enrolled a total of 457 patients. The majority of patients were enrolled in European countries (primarily the Netherlands, the United Kingdom and France). Patients were also enrolled in South Africa, South America, the United States, and Canada. Seventy-five patients were North American, 42 (9%) from the United States and 33 (7%) from Canada. Study No. GHBA-606, conducted in the U.S., was designed to compare the safety and efficacy of nilutamide in combination with leuprolide with that of leuprolide plus placebo in patients with Stage D₂ carcinoma of the prostate. Thirty-eight investigators in the United States enrolled a total of 411 patients. The results of these two primary studies were to support the labeling claim for hormonally ablated patients.

In spite of similar designs and similar results on short-term criteria and response, the two studies led to apparently discordant results with regard to time to progression, a primary endpoint. In Study No. FF/86/908/01, there was a statistically significant difference

favoring nilutamide and orchiectomy, while in Study No. GHBA-606, there was no apparent benefit, in long-term criteria, of adding nilutamide to medical castration.

These findings led to the analysis of prognostic/surrogate endpoints of long-term outcome. Patients with baseline alkaline phosphatase (ALP) of no more than twice the upper limit of normal had the better chance for prolonged survival. In this subgroup of patients, those who early in the treatment period had normalized prostatic specific antigen (PSA) had significantly longer time to progression and survival. The positive results of nilutamide patients in this analysis in Study Nos. GHBA-606 and FF/86/908/01 allowed the reformatting of the NDA to produce a package suitable for filing under 21 CFR 314.101. The results of the surrogate marker analysis support the proposed labeling for this newly defined subgroup of castrated patients.

Study No. FF/86/908/01. Results obtained from Study No. FF/86/908/01 as of 31 August 1989 clearly demonstrate the superior efficacy of nilutamide in combination with orchiectomy over orchiectomy alone. Significantly more nilutamide patients than placebo patients had a complete or partial tumor regression at some time during the study (best response). Fewer objective progressions occurred in the nilutamide group than in the placebo group. Median time to progression was longer for nilutamide patients than placebo patients, and the progression-free survival was significantly better in the nilutamide group than in the placebo group. During the study, lower proportions of nilutamide patients than placebo patients died of prostate cancer or of any cause. The median survival time (any cause) was 5 months longer in the nilutamide group (28.3 months) than in the placebo group (23.2 months). The median cancer survival time was over 35 months in the nilutamide group and 27.5 months in the placebo group. The between-group difference in survival was not statistically significant for overall survival and was close to statistical significance for cancer-related survival. Overall, nilutamide patients had more significant improvement than placebo patients in metastatic related pain, bone scan isotope uptake, and laboratory indications of disease.

An analysis of tumor markers in Study No. FF/86/908/01 showed that early normalization of PSA values was highly correlated with increased median time to progression and survival ($p < 0.001$). In addition, PSA values were significantly more often normalized in patients receiving nilutamide ($p < 0.001$).

Study No. GHBA-606. On the basis of the results obtained in Study No. GHBA-606, nilutamide in combination with leuprolide appears to be a more effective treatment for metastatic prostate cancer than leuprolide alone. One of the primary measures of drug effectiveness - best response during treatment - showed that a significantly higher proportion of nilutamide patients than placebo patients achieved a complete or partial tumor regression at some time during the study. The data for two other primary measures of drug effectiveness - survival and time to objective progression - were not mature enough to detect significant differences between treatment groups. Fewer early progressions (on or before

Month 12) occurred in the nilutamide group than in the placebo group. However, only 45% of evaluable patients had objective / progressed as of the data cutoff point. The median time to progression was 25.0 months on nilutamide and 24.5 months on placebo, and the overall progression-free survival was not significantly different. Median survival time cannot be calculated because only 42% of the evaluable patients had died as of the data cutoff point. The significant improvement for the LHRH plus nilutamide group compared with the LHRH (placebo) group in the number of complete or partial tumor regressions and in the secondary efficacy parameters such as metastatic pain, performance status, bone scan isotope uptake, and laboratory indications of disease clearly show the efficacy of nilutamide.

The analysis of tumor markers in Study No. GHBA-606 showed that early normalization of PSA values was highly correlated with increased median time to progression and survival ($p < 0.001$). In addition, PSA values were significantly more often normalized in patients receiving nilutamide ($p < 0.001$).

Supportive Studies

A meta-analysis (presented in the Integrated Summary of Efficacy Data in the NDA) of all six long-term randomized, double-blind, placebo-controlled trials of nilutamide in orchiectomized, previously untreated patients with metastatic prostate cancer (Study Nos. CDN/83/908/05, F/82/908/03, F/82/908/01, F/84/908/01, CH/85/908/05, and ZA/85/908/02) further confirms the beneficial effect of nilutamide treatment with respect to response rate and improvement in individual efficacy parameters. Overall, in five of these studies that could be combined for this parameter, the proportion of nilutamide patients achieving complete or partial tumor regression at some time during the study was statistically significantly higher than that of placebo patients. At Month 6, significant differences in favor of nilutamide were also observed for bone pain, normalization of prostatic acid phosphatase, and normalization of alkaline phosphatase.

Safety Results

Primary Studies

Study No. FF/86/908/01. The most frequent adverse experience in Study No. FF/86/908/01 was hot flushes and visual disorders (impaired dark adaptation and abnormal vision), and respiratory disorders. Hot flushes and respiratory disorders occurred in comparable proportions of nilutamide and placebo patients. Increased SGOT and SGPT occurred at twice the incidence in nilutamide patients compared with placebo patients. Conversely, the incidence of anemia reported as an adverse experience in nilutamide patients was almost half that reported in placebo patients.

Study No. GHBA-606. The most prevalent adverse experience in Study No. GHBA-606, dark adaptation impairment, occurred at a much higher incidence in nilutamide patients than

seen in previous studies. Although this disorder was troublesome, it was often mild. The majority of nilutamide patients with dark adaptation impairment required no treatment, and the remaining patients required nonmedical treatment (wearing tinted glasses). This adverse effect may be dose-dependent and may decrease despite the continuation of treatment.

After a higher than expected rate of interstitial pneumonitis was noted in patients enrolled in Study No. GHBA-606, the Investigational Drug Brochure was amended in February 1988 to include a warning statement concerning this adverse experience. Additionally, the protocol for Study No. GHBA-606 was amended to exclude patients with pre-existing clinical or subclinical interstitial lung disease and those who were being treated with any medications known to be associated with interstitial lung disease; to require chest X-ray and pulmonary function tests during pretreatment and at study months 1, 2, 3, and 6 and more often as clinically indicated for all patients enrolled in the trial after 1 December 1987. Study No. FF/86/908/01 was not amended because enrollment in that trial had ended January 1988. In addition, periodic reports were submitted to the FDA summarizing all cases of interstitial pneumonitis, pneumonia, and other pulmonary adverse events reported in these two trials.

Supportive Studies

The six studies using 300 mg/day that were pooled for efficacy evaluation were also pooled for the evaluation of safety (661 patients): the most frequently reported adverse experiences were hot flushes, death, impotence, and decreased libido in comparable proportions of nilutamide and placebo patients and dark adaptation impairment in notably more nilutamide than placebo patients. Alcohol intolerance, nausea, dizziness, asthenia, and gastrointestinal symptoms were also among the most frequently reported adverse experiences in both nilutamide and placebo patients. Interstitial pneumonitis occurred in nilutamide patients but not in placebo patients.

The two remaining placebo-controlled studies performed in LHRH agonist-treated patients were evaluated individually for safety. In the placebo-controlled buserelin arm of Study No. F/82/908/01, 88% of nilutamide patients and 66% of placebo patients had adverse experiences ($p=0.015$). The most prevalent adverse experiences for nilutamide patients were hot flushes and impaired adaptation to darkness and for placebo patients were hot flushes and hypertension. A few cases of interstitial pneumonitis among nilutamide-treated patients resolved during continued nilutamide therapy.

In Study No. F/85/908/10, a 4-week placebo-controlled clinical pharmacology study, comparable proportions of nilutamide and placebo patients had one or more adverse experiences. The predominant adverse experiences were hot flushes, difficulty with light/dark adaptation, and sleeplessness for nilutamide patients and sleeplessness and lower limb pain for placebo patients.

Overall, after review of the data of the 2,168 patients with prostate cancer treated with nilutamide in the clinical program, it was concluded that nilutamide:

- Is generally well tolerated in this population of middle-aged and elderly men with metastatic prostate cancer.
- May be associated with interstitial lung disease in a small percentage of patients, and careful monitoring for this effect should be practiced. Interstitial lung disease has been reported in 1.8% of patients treated with orchiectomy and 3.5% of patients treated with LHRH agonist. The disorder has almost always been reversible after its discontinuation. The incidence was higher in a small uncontrolled Japanese study than in studies performed in Europe, Canada, and the United States.
- May be associated with visual disturbances, which occur in approximately 25% of orchiectomized patients receiving nilutamide and 57% of patients receiving leuprolide plus nilutamide in the large placebo-controlled primary study GHBA-606. The visual disturbances are described most often as impaired adaptation to darkness and occasionally as abnormal vision, photophobia, impaired light adaptation, or chromatopsia. These experiences very rarely required treatment discontinuation (1-2%) and are reversible either upon treatment discontinuation or, scheduled dose decrease or in many cases, during continued treatment.
- May be associated with transient increases in liver enzymes. In orchiectomized patients, increases in transaminases above twice the upper limit of normal occurred in 7% to 13% of nilutamide patients and in 4% to 5% of placebo patients. In the primary study with leuprolide (Study No. GHBA-606), 20% of nilutamide patients compared with 15% of placebo patients had transaminase values above predefined limits ($> 2 \times$ baseline or $>$ upper limit of normal). These increases most often were transient, stayed below three times normal values, and occurred after 3 months of treatment. Hepatitis was reported in less than 1% of patients.
- May occasionally cause alcohol intolerance, which has been reported in 4-5% of nilutamide patients.
- May cause nausea, occasionally requiring dosage reduction, divided doses, or termination of treatment. Nausea has been reported in about 9-10% of nilutamide patients in orchiectomy studies and in 25% of nilutamide patients in the primary study with leuprolide (Study No. GHBA-606) versus 4-6% of placebo patients. Although nausea is, in some cases, accompanied by vomiting and is severe enough to require treatment discontinuation, this usually occurs early in the course of treatment, when patients are receiving 300 mg/day. Patients on the 150 mg daily dosage are usually free of gastrointestinal symptoms.

- Does not cause diarrhea.
- May be associated with a greater incidence of hot flushes than surgical or medical castration alone as a result of the antiandrogenic activity of the compound.
- Limiting treatment to the retrospectively defined subgroup of patients whose baseline alkaline phosphatase is not more than twice the upper limit of normal likely to respond to nilutamide would significantly enhance the benefit to risk ratio of the drug.

Animal pharmacology studies have shown a slight decrease in the concentration of hepatic cytochrome P450 after repeated administration of antiandrogenic doses of nilutamide to rats, a decrease also seen following castration of rats. A study of antipyrine metabolism during nilutamide treatment was conducted in five patients (Study No. FF/86/ANA/305/04); however, the results of this drug interaction study were inconclusive because of the small number of patients. It is thus reasonable to caution that the concomitant administration of drugs with a low therapeutic margin, such as vitamin K antagonists, phenytoin, and theophylline, could have a delayed elimination and increases in their serum half-life, leading to an increase in blood levels. The dosage of these drugs or other drugs with a similar metabolism may need to be modified when the drugs are administered concomitantly with nilutamide.

Data from four supportive studies (Study Nos. CDN/83/908/05, F/82/908/03, F/82/908/01, and F/84/908/01) were reviewed to assess the potential for drug interactions between nilutamide and anticoagulant, hypoglycemic, and antihypertensive medications used concomitantly. On the basis of this very broad approach, no interaction between nilutamide and the concomitant use of anticoagulant, hypoglycemic, and antihypertensive medications was apparent.

C. FOREIGN MARKETING APPROVALS

Nilutamide (RU 23 908) has been approved for metastatic prostate cancer in combination with surgical or chemical castration (LHRH agonists) by the regulatory authorities in the following countries:

Foreign Marketing Approvals

COUNTRY	DATE OF APPROVAL
<u>EUROPEAN COUNTRIES</u>	
Belgium ^a	August 1990 ^b
Finland	December 1992 ^b
France	July 1986
Iceland	March 1991
Luxembourg ^a	January 1991 ^b
Netherlands	May 1990 ^b
Norway	December 1992 ^b
Portugal	November 1987
Sweden	December 1990 ^b
<u>EASTERN EUROPEAN COUNTRIES</u>	
Czechoslovakia	July 1990
Poland	October 1991
Russia	January 1992
Yugoslavia	January 1992
<u>AMERICAN COUNTRIES</u>	
Argentina	November 1989
Brazil	May 1989
Canada	December 1991 ^c
Chile	August 1991
Guatemala	December 1989
Peru	January 1990
Uruguay	May 1991
Venezuela	July 1990
Colombia	January 1990
Trinidad and Tobago	July 1992
<u>OTHERS</u>	
India	December 1992
New Zealand	April 1992
Egypt	August 1992
Iraq	March 1992
Morocco	December 1992

^a EEC Procedure, CPMP negative opinion in May 1989

^b Flare-Up

^c 300 mg daily in combination with surgical castration

Nilutamide has not been withdrawn from marketing in any country for any reason relating to safety or effectiveness. There are no significant safety or effectiveness problems.

D. CONCLUSIONS

The results of the studies in the clinical program for nilutamide demonstrate its efficacy in the treatment of metastatic prostate cancer in castrated patients. In two large multicenter double-blind, placebo-controlled studies (Study Nos. FF/86/908/01 and GHBA-606), nilutamide associated with castration was consistently and often significantly more effective than placebo in inducing tumor regression, reducing metastatic pain, and improving laboratory and radiographic evidence of disease, increasing significantly the rate of early PSA normalization mainly in the subset of patients with moderate increase $\leq 2N$ of alkaline phosphatase at baseline, thus enhancing their chance for longer time to progression and survival. The risk of visual disorders and interstitial pneumonitis, which occurred more frequently in nilutamide-treated patients than in placebo-treated patients is offset by the significant improvements in many disease parameters and the possible longer overall survival with nilutamide therapy. Additionally, the identification of a subgroup of patients more likely to respond to nilutamide therapy will enable the prescribing physician to make informed decisions regarding the benefit of undertaking and continuing nilutamide therapy in a given patient versus the risk of adverse experiences. Thus, an important new antiandrogen therapy could then be offered to the patient population that would most benefit.

Clin. Pharm./
Bio

JUN 20 1996

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 20-169

SUBMISSION DATE: 03/15/96

Nilutamide 50 mg tablets

BRAND NAME: Nilandron

SPONSOR: Roussel-UCLAF, France

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA Amendment No. 000AZ

Code: 1S (NME)

TITLE: "Review of Labeling and Additional Dissolution Data For Nilutamide Tablets"

BACKGROUND:

Nilutamide is an orally active nonsteroidal antiandrogen. NDA 20-169 (Nilandron; nilutamide 50 mg tablets) that was submitted by G. H. Besselaar Associates (on behalf of Roussel-UCLAF, France) on 03/07/94, was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II) dated 02/01/95. The NDA was found overall acceptable for meeting biopharmaceutic requirements. On 02/24/95, Nilandron was discussed in an Advisory Committee Meeting and it was recommended for approval by the committee members.

An Agency's "approvable" letter was sent to the sponsor on 03/07/95 for nilutamide tablets. In the letter, a food effect study for nilutamide was requested. However, several Biopharm's comments on Labeling (dated 02/01/95) were not communicated to the sponsor.

On 12/13/95, the study results of the food effect study No. ZA95/S08/12 were submitted to the Agency and reviewed by OCPB/DPE II on 02/29/96. The food effect study was found acceptable and the package insert (PI) was revised accordingly to incorporate information of food effect on nilutamide tablets after oral administration.

On 02/22/96, another Agency's letter was sent to the sponsor. Previous Biopharm's comments on Labeling (dated 02/01/95) were conveyed to the sponsor and the following dissolution method and specification were recommended:

USP Apparatus II (Paddle), 50 rpm
900 ml water at 37°C
Q = % in  min

SYNOPSIS:

On 03/15/96, the sponsor submitted an NDA Amendment No. 000AZ to the Agency for review. Included in the amendment were 1) a revised PI (03/96 version) and 2) additional dissolution information on nilutamide tablets using the Agency's recommended methodology.

For Labeling, the PI has been revised accordingly to include Biopharm's comments dated 02/01/95 and it is found appropriate. Please see the revised PI in Attachment 1 for details. However, it should be noted that currently, the Agency is attempting to standardize the content and presentation of the Pharmacokinetics (PK) subsection of the Clinical Pharmacology section of a PI. A template/format for the PK subsection was, therefore, sent to the firm by fax on 06/18/96.

The additional dissolution data were found acceptable and the specification of $Q = \text{[redacted]} \%$ in $\text{[redacted]} \text{ min}$ is found appropriate for meeting dissolution test requirement as stated in USP XXIII (1995). Please see the dissolution information in Attachment 2 for details. The sponsor, however, requested that their originally proposed dissolution specification ($Q = \text{[redacted]} \%$ in $\text{[redacted]} \text{ min}$) be used. It had been concluded in a previous bioreview dated 01/31/96 that $Q = \text{[redacted]} \%$ in $\text{[redacted]} \text{ min}$ is not discriminatory, i.e., greater than $\text{[redacted]} \%$ (mean) dissolved within $\text{[redacted]} \text{ min}$. Therefore, the sponsor's request is not acceptable.

Note: One batch (No. L20) had unusual and lower dissolution data (64% to 79%, $n=8$ out of 12 at 37°C with 80% relative humidity) during the 6-month stability testing. It is probably less of a concern since the tablets are to be stored under the recommended conditions, at room temperature (15 to 30°C) as indicated by the reviewing chemist of HFD-510.

RECOMMENDATION:

The Amendment No. 000AZ that was submitted on 03/15/96 under NDA 20-169 for Nilandron (nilutamide) 50 mg tablets by G. H. Eesselaar Associates (on behalf of Roussel-UCLAF, France) has been reviewed by OCPB/DPE II. The package insert (03/96 version) has been revised accordingly to incorporate previous Biopharm's comments (dated 02/01/95) and also the information of food effect on nilutamide tablets. The revised package insert (03/96 version) is acceptable provided that the sponsor incorporates the recommended changes that were sent to the sponsor by fax on 06/18/96. The sponsor should resubmit the updated package insert to the Agency for review.

For dissolution, the sponsor's request for specification of $Q = \text{[redacted]} \%$ in $\text{[redacted]} \text{ min}$ is not acceptable. OCPB/DPE II feels that 1) $Q = \text{[redacted]} \%$ in $\text{[redacted]} \text{ min}$ is not discriminatory and 2) $Q = \text{[redacted]} \%$ in $\text{[redacted]} \text{ min}$ is appropriate for meeting dissolution testing requirement as stated in USP XXIII (1995). Therefore, the following methodology and specification are recommended for Nilandron (nilutamide) 50 mg tablets:

USP Apparatus II (Paddle), 50 rpm
900 ml water at 37°C
Q = ~~88~~% in ~~15~~ min

This recommendation, the above dissolution methodology and specification as appropriate should be conveyed to the sponsor.

Tien-Mien Chen

06/18/96

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D. AD 06/19/96

FT initialed by Angelica Dorantes, Ph.D. *AD* 6/19/96

cc: NDA 20-169, HFD-510 (MO, CSO), HFD-870 (M. Chen, A. Dorantes, T. Chen), HFD-860 (Malinowski), HFD-880 (Fleischer), HFD-850 (Chron, Drug, Reviewer), HFD-340 (Viswanathan), FOI (HFD-205)

FEB 29 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-169

SUBMISSION DATE: 12/13/95

Nilutamide 50 mg tablets

BRAND NAME: Nilandron

SPONSOR: Roussel-UCLAF, France

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA Amendment (1S)

TITLE: "Review of A Food Effect Study for Nilandron tablets"

BACKGROUND:

Nilutamide is an orally active nonsteroidal antiandrogen. NDA 20-169 (Nilandron; nilutamide 50 mg tablets) that was submitted by G. H. Besselaar Associates (on behalf of Roussel-UCLAF, France) on 03/07/94, was reviewed by the Division of Pharmaceutical Evaluation II (HFD-870) in a bioreview dated 02/01/95. The NDA was found overall acceptable for meeting biopharmaceutics requirements. On 02/24/95, Nilandron was discussed in an Advisory Committee Meeting and it was recommended for approval by the committee members.

An Agency's "approvable" letter was sent to the sponsor on 03/07/95 for nilutamide tablets. In the letter, it is recommended that the effects of food on nilutamide bioavailability/pharmacokinetics be studied. On 04/13/95, the sponsor submitted protocol No. ZA/95/908/12 for a food study entitled, "Effect of Food on Bioavailability of Nilutamide After Single Dose Administration of 300 mg to Healthy Male Volunteers". The study protocol and its amendment (submitted on 05/24/95) were reviewed by HFD-870 on 05/11/95 and 06/23/95, respectively. The amended protocol was found acceptable and the food effect study was initiated on 06/22/95. Please see the bioreviews in HFD-870's drug review file for details.

NDA 28-169

3 OF 6

SUMMARY:

On 12/13/95, the sponsor submitted an amendment under NDA 20-169 for the study results of the food effect study No. ZA/95/908/12 for nilutamide tablets. Twelve (n = 12) healthy male volunteers received 6 x 50 mg nilutamide tablets either i) on an empty stomach (Treatment A; Reference) or ii) immediately after a high fat breakfast (Treatment B; Test) in an open, randomized, 2-way crossover design with a washout period of 3 weeks. The high fat food consisted of 2 fried eggs, 2 stripes of bacon, 85 g of hash brown potatoes, 2 slices of toast with butter, and 220 ml of whole milk.

Mean nilutamide serum levels are shown in Table 1 and Figure 1. The statistical results of the food effect on nilutamide PK are shown in Table 2. Based on log-transformed data, the ratios (Test vs. Reference) for nilutamide C_{max} , AUC_{0-168} , and $AUC_{0-\infty}$ values were all within 0.8 to 1.2. Therefore, no effects of a high fat breakfast on mean C_{max} and AUC values of nilutamide were found. No pharmacodynamic parameters were obtained in this study.

Mean serum levels and PK parameters of one of nilutamide metabolites analyzed, RU43866, are shown in Tables 3 and 4. No mean serum profiles for RU43866 were provided in this amendment. The study results show that based on log-transformed data, the ratios of Test vs. Reference for RU43866 C_{max} and AUC_{0-168} value were all within 0.8 to 1.2.

The to-be-marketed nilutamide 50 mg tablets were used in the study. The information on the batch No. and size of tablet production, content uniformity, date and site of manufacture, etc. is provided below:

Batch No.:	L28B
Batch Size:	1,426,923 tablets (a commercial size)
Content Uniformity:	97 ± 1.4% (n = 10)
Date of Manufacture:	April, 1993
Site of Manufacture:	Compiègne, France (for commercial product)

An HPLC method was used for the analyses of serum levels of nilutamide and RU43866 and the method was slightly modified from the previous one used in the original NDA. The modified HPLC method was properly validated and it is acceptable.

Please see the study report, the subject's demographic characteristics, individual PK parameters and raw data, and the results of statistical analyses in Appendix 1 for details. Appendix 2 contains information on the summary of assay method and its validation report, manufacture of the tablet batch, etc. Appendices 1 and 2 are being retained in HFD-870 and can be obtained upon request.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation II (HFD-870) has reviewed the results of a food effect study No. ZA/95/908/12 that was submitted on 12/13/95 under NDA 20-169 for Nilandron (nilutamide 50 mg tablets). The food effect study is acceptable and the firm's proposed labeling change to reflect the results obtained from the food effect study is appropriate, i.e., "Nilandron tablets can be taken with or without food".

COMMENTS: (Need not to be sent to the sponsor)

1. The dissolution information on the tablet batch used in the food effect study had been submitted previously on 08/15/95. It was reviewed on 01/31/96 and new dissolution specifications were proposed by the Agency.
2. In human, nilutamide is well absorbed and extensively metabolized after oral administration. At least 5 nilutamide metabolites have been identified. Metabolite RU43866 represents the major portion of the ¹⁴C-nilutamide recovered in urine. The pharmacokinetics and pharmacodynamics for the metabolites, however, have not been fully studied. Therefore, the food effect on the overall pharmacological activities of nilutamide is not known.



02/27/96

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D. AD 02/28/96

FT initialed by Angelica Dorantes, Ph.D. *Dorantes* 2/29/96

cc: NDA 20-169, HFD-510 (MO, CSO), HFD-870 (M. Chen, A. Dorantes, T. Chen), HFD-860 (Malinowski), HFD-880 (Fleischer), HFD-850 (Chron, Drug, Reviewer), HFD-340 (Viswanathan), FOI (HFD-205)

TABLE 1 MEAN ($\pm$ s.e.m.) PLASMA CONCENTRATIONS OF NILUTAMIDE (mg.l^{-1}) FOLLOWING A SINGLE ORAL DOSE OF 300 mg OF NILUTAMIDE ADMINISTERED ON AN EMPTY STOMACH OR AFTER A HIGH FAT BREAKFAST TO 12 HEALTHY VOLUNTEERS.

SAMPLING TIME (h)	TREATMENT A (on an empty stomach)	TREATMENT B (during a high fat breakfast)
0	LOQ	LOQ
0.25	0.189 ± 0.093 (b)	0.43 ± 0.13 (a)
0.50	0.71 ± 0.28	1.07 ± 0.25
0.75	1.15 ± 0.28	1.22 ± 0.25
1	1.68 ± 0.19	1.38 ± 0.24
1.5	2.13 ± 0.17	1.50 ± 0.22
2	2.08 ± 0.12	1.69 ± 0.19
3	2.105 ± 0.067	1.899 ± 0.097
4	1.923 ± 0.072	1.92 ± 0.10
6	1.531 ± 0.069	1.72 ± 0.11
8	1.441 ± 0.082	1.478 ± 0.084
12	1.341 ± 0.076	1.357 ± 0.091
24	1.108 ± 0.052	1.138 ± 0.050
48	0.770 ± 0.030	0.796 ± 0.037
72	0.524 ± 0.036	0.541 ± 0.035
120	0.245 ± 0.030	0.252 ± 0.029
168	0.124 ± 0.023	0.106 ± 0.023

LOQ: All the values were below the limit of quantification (0.020 mg.l^{-1})

(a): 1 out of 12 values below the limit of quantification

(b): 2 out of 12 values below the limit of quantification

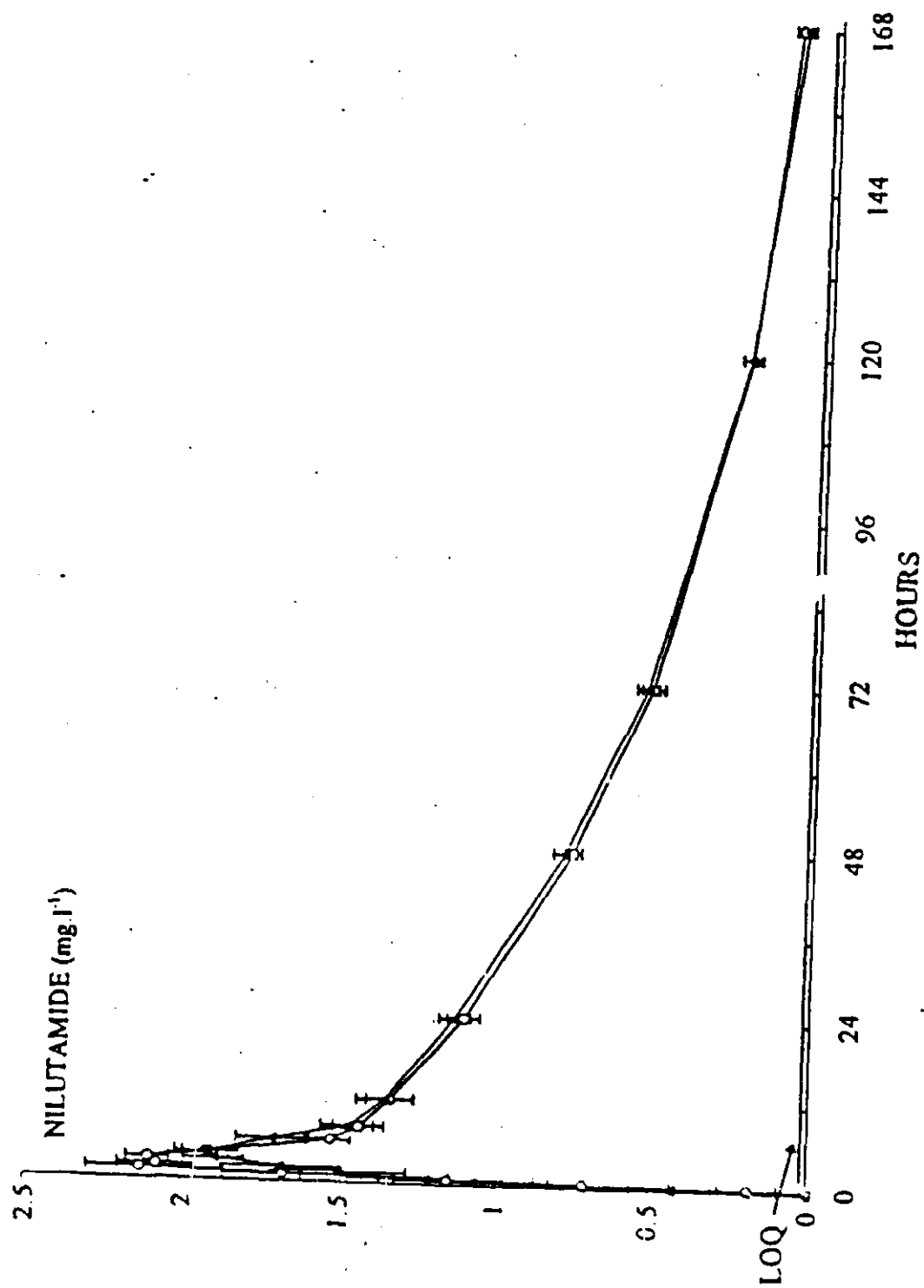


FIGURE 1: MEAN ($\pm$ s.e.m.) PLASMA CONCENTRATIONS OF NILUTAMIDE (mg.l⁻¹) FOLLOWING A SINGLE ORAL DOSE OF 300 mg OF NILUTAMIDE ADMINISTERED ON AN EMPTY STOMACH (-o-) OR AFTER A HIGH FAT BREAKFAST (-▲-) TO 12 HEALTHY VOLUNTEERS (linear plot)

TABLE 2 MEAN ($\pm$ s.e.m.) PLASMA PHARMACOKINETIC PARAMETERS OF NILUTAMIDE FOLLOWING A SINGLE ORAL DOSE OF 300 mg OF NILUTAMIDE ADMINISTERED ON AN EMPTY STOMACH OR AFTER A HIGH FAT BREAKFAST TO 12 HEALTHY VOLUNTEERS.

PARAMETER		TREATMENT A (on empty stomach)	TREATMENT B (during a high fat breakfast)	ANOVA (1)
Cmax (mg.l ⁻¹)	Mean	2.48 $\pm$ 0.11	2.14 $\pm$ 0.11	*
	PE	86 %		-
	90 % CI	78 - 94 %		-
Tmax (h)	Median [min-max]	2.25 [0.5 - 4]	3 [0.75 - 4]	NS
	PE (2)	0.50		-
	90 % CI	-0.75 - 1.5		-
AUC 0-168h (mg.l ⁻¹ .h)	Mean	98.9 $\pm$ 3.9	100.4 $\pm$ 4.3	NS
	PE	101 %		
	90 % CI	97 - 106 %		
AUC 0- ∞ (mg.l ⁻¹ .h)	Mean	108.7 $\pm$ 5.3	108.2 $\pm$ 5.3	NS
	PE	100 %		-
	90 % CI	94 - 106 %		-
t _{1/2} (h)	Mean	47.6 $\pm$ 4.5	46.1 $\pm$ 3.1	NS
	PE	99 %		-
	90 % CI	92 - 107 %		-

(1) ANOVA: treatment effect: NS : $p > 0.05$ - * : $0.01 < p \leq 0.05$

PE: Point estimates: ratio of geometric means or differences means of the test treatment (B) versus the reference treatment (A)

(2): Median of the differences in absolute units of the test treatment (B) versus the reference treatment (A)

CI : Confidence interval

TABLE 3: MEAN ($\pm$ s.e.m.) PLASMA CONCENTRATIONS OF RU 43866 (mg.l^{-1}) FOLLOWING A SINGLE ORAL DOSE OF 300 mg OF NILUTAMIDE ADMINISTERED ON AN EMPTY STOMACH OR AFTER A HIGH FAT BREAKFAST TO 12 HEALTHY VOLUNTEERS.

SAMPLING TIME (h)	TREATMENT A (on an empty stomach)	TREATMENT B (during a high fat breakfast)
0	LOQ	LOQ
0.25	LOQ	LOQ
0.50	LOQ	LOQ
0.75	LOQ	0.002 (h)
1	0.001 (i)	0.004 (g)
1.5	0.003 (g)	0.007 (f)
2	0.0094 ± 0.0030 (e)	0.0117 ± 0.0030 (c)
3	0.0196 ± 0.0023	0.0156 ± 0.0033 (b)
4	0.0321 ± 0.0053	0.0218 ± 0.0028
6	0.062 ± 0.013	0.0276 ± 0.0048
8	0.062 ± 0.011	0.0303 ± 0.0041
12	0.056 ± 0.010	0.0436 ± 0.0064
24	0.0614 ± 0.0088	0.0599 ± 0.0080
48	0.045 ± 0.010	0.0433 ± 0.0071
72	0.0294 ± 0.0066	0.0271 ± 0.0051 (a)
120	0.0127 ± 0.0024 (b)	0.0104 ± 0.0031 (d)
168	0.003 (g)	0.002 (i)

LOQ: All the values were below the limit of quantification (0.010 mg.l^{-1})

- (a): 1 out of 12 values below the limit of quantification
(b): 3 out of 12 values below the limit of quantification
(c): 4 out of 12 values below the limit of quantification
(d): 5 out of 12 values below the limit of quantification
(e): 6 out of 12 values below the limit of quantification
(f): 7 out of 12 values below the limit of quantification
(g): 9 out of 12 values below the limit of quantification
(h): 10 out of 12 values below the limit of quantification
(i): 11 out of 12 values below the limit of quantification

TABLE 4 MEAN ($\pm$ s.e.m.) PLASMA PHARMACOKINETIC PARAMETERS OF RU 43866 FOLLOWING A SINGLE ORAL DOSE OF 300 mg OF NILUTAMIDE ADMINISTERED ON AN EMPTY STOMACH OR AFTER A HIGH FAT BREAKFAST TO 12 HEALTHY VOLUNTEERS.

PARAMETER		TREATMENT A (on empty stomach)	TREATMENT B (during a high fat breakfast)	ANOVA (1)
C _{max} (mg.l ⁻¹)	Mean	0.075 $\pm$ 0.011	0.0600 $\pm$ 0.0080	NS
	PE	80 %		-
	90 % CI	64 - 99 %		-
T _{max} (h)	Median [min-max]	18 [6 - 24]	24 [24 - 48]	*
	PE (2)	9		-
	90 % CI	0 - 18		-
AUC 0-168h (mg.l ⁻¹ .h)	Mean	4.50 $\pm$ 0.81	3.83 $\pm$ 0.69	*
	PE	80 %		-
	90 % CI	69 - 94 %		-

(1) ANOVA: treatment effect: NS : $p > 0.05$ - * : $0.01 < p \leq 0.05$

PE: Point estimates: ratio of geometric means or differences means of the test treatment (B) versus the reference treatment (A)

(2) Median of the differences in absolute units of the test treatment (B) versus the reference treatment (A)

CI : Confidence interval

FEB 1 1996

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II**

Date: 02/01/96
To: Lana L. Pauls (CSO of HFD-510)
Through: Team Leader, Angelica Dorantes, Ph.D. (HFD-870) *ADorantes 2/1/96*
From: Tien-Mien Chen, Ph.D. (HFD-870)
RE: Revised Labeling for Nilandron (nilutamide tablets; NDA 20-169)

NDA 20-169 for nilutamide tablets (Nilandron) was reviewed by the Agency. On 03/07/95, an "approvable" letter including the Agency's requests/comments was sent to G. H. Besselaar Associates (on behalf of the sponsor, Roussel-UCLAF, France). On 08/15/95, the sponsor submitted their responses to the Agency including i) a proposed food effect study to be conducted and ii) a revised package insert for nilutamide tablets. The sponsor's 3 responses related to the Biopharm issues have been reviewed by the Division of Pharmaceutical Evaluation II (HFD-870) dated 01/31/96. This memo is an addendum to the bioreview dated 01/31/96 regarding the recommended labeling changes (Attachment 1).

In my previous bioreview dated 02/01/95, there were four labeling comments to be sent to the sponsor. However, none of Biopharm's labeling comments were included in HFD-510's "approvable" letter dated 03/07/95 for nilutamide tablets. In the "approvable" letter, HFD-510 recommended approval for the use of nilutamide tablets in combination with surgical castration only for treating male prostate cancer (Stage D₂). Therefore, Biopharm's Labeling Comment No. 4 presented in the previous bioreview dated 02/01/95 is less of a concern at this time.

A food effect study had been conducted and submitted to the Agency, but the study results have not been submitted to and reviewed by HFD-870. Thus, any changes in the "Dosage and Administration" subsection of the package insert could not be verified, therefore, the changes are not acceptable. Finally, HFD-870 recommends that other Biopharm's Labeling Comment Nos. 1 to 3 as shown below plus new Comment Nos. 4 and 5 be communicated to the sponsor.

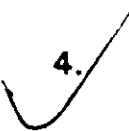
LABELING COMMENTS: (Need to be sent to the sponsor)

Please see the sponsor's revised version of package insert in Attachment 1 for details.

- 
1. The third paragraph (for Metabolism) in the subsection Pharmacokinetics under the Clinical Pharmacology section should be modified to include the following paragraph as appropriate.

2. The second sentence of the fourth paragraph (for Elimination) in the subsection Pharmacokinetics under the Clinical Pharmacology section should be modified to include the following sentences as appropriate.

- 
3. The fifth sentence of the fourth paragraph (for Elimination) in the subsection Pharmacokinetics under the Clinical Pharmacology section should be modified to include the following paragraph as appropriate.

- 
4. A sentence added by the sponsor itself to the paragraph for elimination in the subsection of Pharmacokinetics under the Clinical Pharmacology section is not needed and therefore, the added sentence should be deleted.

5. In the Dosage and Administration subsection, no changes should be made for dose administration as related to food intake until the results of the food effect study are

reviewed and the changes could be verified. Therefore, the second sentence should be modified as shown below:



02/01/96

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

cc: NDA 20-169, HFD-510 (MO, CSO), HFD-870 (M. Chen, A. Dorantes, T. Chen), HFD-860 (Malinowski), HFD-880 (Fleischer), HFD-850 (Chron, Drug, Reviewer), HFD-340 (Viswanathan), FOI (HFD-205)

JAN 31 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-169

SUBMISSION DATE: 08/15/95

Nilutamide 50 mg tablets

BRAND NAME: Nilandron

SPONSOR: Roussel-U'CLAF, France

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA Amendment (1S)

TITLE: "Sponsor's Responses To An Agency's Letter"

BACKGROUND:

Nilutamide is an orally active nonsteroidal antiandrogen. NDA 20-169 (Nilandron; nilutamide 50 mg tablets) that was submitted by G. H. Besselaar Associates (on behalf of Roussel-UCLAF, France) on 03/07/94, was reviewed by the Division of Pharmaceutical Evaluation II (HFD-870) in a bioreview dated 02/01/95. The sponsor wanted approval for a 50 mg tablet dosage form and for the use of nilutamide tablets in combination with i) surgical castration or ii) chemical castration using an LHRH agonist for treating male prostate cancer (Stage D₂). Nilandron was discussed at HFD-510's Advisory Committee Meeting that was held on 02/23-24/95. It was recommended for approval by the committee members.

An Agency's "approvable" letter was sent to the sponsor on 03/07/95 for nilutamide tablets. However, the letter only recommended approval for its use in combination with surgical castration for treating male prostate cancer (Stage D₂). In the Agency's letter, three comments/requests were communicated to the firm including a food effect study (Request No. 1). On 04/13/95, the sponsor submitted a protocol No. ZA/95/908/12 for a food study entitled, "Effect of Food on Bioavailability of Nilutamide After Single Dose Administration of 300 mg to Healthy Male Volunteers". The study protocol and its amendment (submitted on 05/24/95) were reviewed by HFD-870 on 05/11/95 and 06/23/95, respectively. The amended protocol was found acceptable and it was initiated on 06/22/95. An Agency's letter dated 06/02/95 was sent to the sponsor indicating that the approval for nilutamide (NDA 20-169) could be granted prior to the completion of the food effect study. Please see the above bioreviews and the Agency's letters in the drug review file for details.

SYNOPSIS:

On 08/15/85, the sponsor submitted their responses to the 3 requests/comments that were included in an Agency's letter dated 03/07/95. For Response No. 1, the sponsor indicated that the study report of the requested food effect study (No. ZA/95/908/12) was submitted to the Agency on 11/13/95, however it has not been sent to HFD-870 for consultation. Nevertheless, the bioreview for the food effect study report is not needed prior to the approval of the NDA as indicated in the Agency's letter dated 06/02/95.

Regarding the Agency's Request No. 2 (between-study analyses relating nilutamide plasma levels with efficacy and safety parameters), since the Agency only recommended approval for the use of nilutamide tablets in combination with surgical castration for treating male prostate cancer (Stage D₂), it is less of a concern. Therefore, no review for the sponsor's response is needed at this time.

Regarding the Agency's Request No. 3 [dissolution data using simulated intestinal fluid without enzymes (SIF, pH 7.50) for the clinical tested and bio-lots], the sponsor submitted the requested dissolution data using SIF as a medium for the 5 lots used in the clinical and bio- studies which were already 5 to 11 years old. Note: a shelf-life of 3 years is proposed for nilutamide tablets. The sponsor indicated that when using SIF as a medium with Q = 55% at 30 min, 4 tablets lots passed Stage 2 dissolution criteria and 1 lot passed Stage 3 (Table 1), whereas all lots passed Stage 2 after re-testing when using water as a medium with Q = 55% at 30 min (Table 2).

Table 1. SIF with Q = 55% at 30 min

Batch	Average on 12 tablets (dissolution percentage)	Number of tablets at Q 55% i.e., 55%
L16	98.2 % $\pm$ 3.0%	no tablet
L19A	99.7 % $\pm$ 2.4%	no tablet
JMP 21026-33	91.0 % $\pm$ 2.8%	no tablet
GW 20918-56	97.6 % $\pm$ 2.9%	no tablet
GW 20555-113	89.5 % $\pm$ 10.0%	1 tablet : 61.4 %

Table 2. Water with Q = 55% at 30 min

Batch	Average on 12 tablets (dissolution percentage)	Number of tablets at Q 55% i.e., 55%
L16	97.4 % $\pm$ 1.6%	no tablet
L19A	96.8 % $\pm$ 2.1%	no tablet
JMP 21026-33	90.6 % $\pm$ 2.5%	no tablet
GW 20918-56	96.0 % $\pm$ 2.9%	no tablet
GW 20555-113	91.8 % $\pm$ 2.6%	no tablet

The sponsor conducted further a statistical analysis for dissolution data. It was concluded by the sponsor that i) for SIF medium (pH 7.50), the statistical distribution was not normal, whereas it was for water medium and ii) the variances of the both groups were significantly different ($p < 0.05$). Therefore, the sponsor recommended that the originally proposed dissolution method and specifications using water as a medium be used. In addition, the sponsor indicated that they are in a registration process for nilutamide tablets using water as a dissolution medium in several countries.

In a telecon dated 01/17/96 with the sponsor (Ms. Carole Venetianer of G. H. Besselaar Associates), the sponsor was asked whether they have additional dissolution data using SIF for recently manufactured batch(es) of nilutamide tablets. On 01/23/96, the sponsor faxed additional dissolution data for a tablet batch No. L28B in water only. Lot No. L28B was the latest one that was manufactured in August of 93. It was used in the above mentioned food effect study. The results of dissolution testing for batch No. L28B are similar to those previously submitted using water as a medium, i.e., greater than % dissolved within min. Therefore, the proposed dissolution method using water as the medium is not really discriminatory. No dissolution information for batch No. L28B using SIF as a medium is available.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation II (HFD-870) has reviewed an NDA amendment dated 08/15/95 that was submitted under NDA 20-169 for nilutamide 50 mg tablets (Nilandron). Sponsor's Response No. 1 is appropriate but the bioreview of the study report is not needed prior to the approval of this NDA. Response No. 2 does not need to be reviewed at this time. For Response No. 3, the proposed dissolution method using water is acceptable, but the specifications need to be modified. HFD-870 recommended that the following dissolution method and specifications be used for the 50 mg nilutamide tablets on an interim basis and they should be sent to the sponsor.

USP Apparatus II (Paddle), 50 rpm
900 ml water at 37°C
Q = % in min


01/24/96
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D. AD 01/31/96

FT initialed by Angelica Dorantes, Ph.D.  2/1/96

cc: NDA 20-169, HFD-510 (MO, CSO), HFD-870 (M. Chen, A. Dorantes, T. Chen), HFD-360 (Malinowski), HFD-880 (Fleischer), HFD-850 (Chron, Drug, Reviewer), HFD-340 (Viswanathan), FOI (HFD-205)

JUN 23 1995

NDA: 20-169

SUBMISSION DATE: 05/24/95

Nilutamide 50 mg tablets

BRAND NAME: Nilandron

SPONSOR: Roussel-UCLAF, France

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA Supplement

TITLE: "Review of A Protocol Amendment for A Food Effect Study (No. ZA/95/980/12)"

BACKGROUND:

Nilutamide is an orally active nonsteroidal antiandrogen. The NDA 20-169 (Nilandron; nilutamide 50 mg tablets) that was submitted by Roussel-UCLAF, France on 03/07/94, has been reviewed by the Division of Biopharmaceutics (HFD-420) in a bioreview dated 02/01/95. The sponsor wanted approval for a 50 mg tablet dosage form and for the use of nilutamide tablets in combination with i) surgical castration or ii) chemical castration with an LHRH agonist for treating male prostate cancer (Stage D₂). The recommended dosing regimen for Nilandron is 6 x 50 mg tablets once a day (QD) for 30 days followed by 3 x 50 mg tablets QD. It is to be taken before breakfast with a glassful of water. Please see the bioreview in the HFD-420 drug review file for details. Nilandron was discussed at HFD-510's Advisory Committee Meeting that was held on 02/23-24/95.

The sponsor was sent an Agency "approvable" letter on 03/07/95 for nilutamide tablets. However, the letter only recommended approval for its use in combination with surgical castration for treating male prostate cancer (Stage D₂). Please see the Agency's letter dated 03/07/95 for details. In the Agency's letter, three comments/requests from Biopharm were sent to the firm. In a 04/13/95 response to one of Biopharm's requests, Roussel-UCLAF submitted a protocol for a proposed study entitled, "Effect of Food on Bioavailability of Nilutamide After Single Dose Administration of 300 mg to Healthy Male Volunteers (Study No. ZA/95/908/12)". The study protocol was reviewed by HFD-420 on 05/11/95 and three comments for the food effect study were sent to the firm in an Agency's letter dated 06/02/95. Please see the 06/02/95 letter for details.

SYNOPSIS:

The firm agreed to comply with the three comments that were sent to the firm in an Agency's letter dated 06/02/95 and has incorporated these comments into the study

protocol for the food effect study (No. ZA/95/908/12). Please see the firm's responses dated 05/24/95 in Appendix 1 (protocol amendment) for details. Note: The sponsor indicated that the study was initiated on 06/22/95.

RECOMMENDATION:

HFD-420 has reviewed the protocol amendment for a food effect study for nilutamide tablets that was submitted on 05/24/95 and finds it acceptable.

Tien-Mien Chen

06/19/95

Tien-Mien Chen, Ph.D.

Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt JPH 06/23/95

FT initialed by John Hunt J. Hunt 6/23/95

cc: NDA 20-169, HFD-510, Medical Officer (Fourcroy), CSO (Pauls), HFD-426 (Fleischer), HFD-427 (M. Chen, T. Chen), HFD-340 (Viswanathan), F, Chron, Drug, Reviewer, FOI (HFD-19).

Pauls
FEB 27 1995

NDA: 20-169

SUBMISSION DATE: 02/01/95
02/07/95

Nilutamide 50 mg tablets

BRAND NAME: Nilandron

SPONSOR: Roussel-UCLAF, France

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA Supplement

TITLE: "Review of Sponsor's Responses To The Agency's Requests"

BACKGROUND:

Nilutamide is an orally active nonsteroidal antiandrogen. It is a microcrystalline (no polymorphs) white to practically white powder and it is very slightly soluble in water. It is a new molecular entity with a molecular weight of 317.25.

Previously, the sponsor, Roussel-UCLAF, submitted NDA 20-169 (Nilandron; nilutamide 50 mg tablet) to the Agency for review on 06/14/91 but it was deemed not fileable. The sponsor resubmitted NDA 20-169 on 03/07/94 and it was filed on 05/06/94. The NDA has been reviewed by the Division of Biopharmaceutics (HFD-420) in a bioreview dated 02/01/95. Please see the bioreview in the HFD-420 drug review file for details.

During its bioreview, additional information regarding i) the solubility and pK_a of nilutamide drug substance and ii) the raw data of the pivotal studies on diskettes were requested. However, the sponsor indicated that no data for the pK_a were available because of very poor water solubility of nilutamide.

SYNOPSIS:

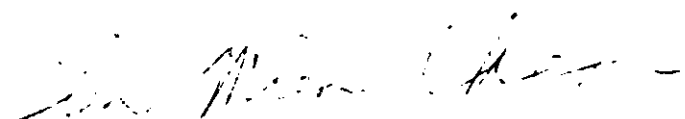
On 02/01 and 02/07/95, the sponsor of NDA 20-169 (Nilandron; nilutamide 50 mg tablet) submitted the requested information to the Agency for review, i.e., i) the solubility of nilutamide drug substance and ii) the raw data of the pivotal studies on diskettes.

Since the NDA bioreview has been completed and the requested information would not change HFD-420's recommendations/comments, it is therefore briefly reviewed. Please see the submitted information on the solubility of nilutamide drug substance in Attachment 1 for details. It is noted that the saturation solubility of nilutamide drug substance (≈ 0.040 mg/ml) is not appreciably changed with pH and/or ionic strength of the solutions tested.

Note: The NDA for nilutamide was one of two drugs discussed at HFD-510's Advisory Committee Meeting held on 02/23-24/95.

RECOMMENDATION:

On 02/01 and 02/07/95, the sponsor of NDA 20-169 (Nilandron; nilutamide 50 mg tablet) submitted additional information to the Agency for review. The information was previously requested by HFD-420 prior to the completion of its bioreview dated 02/01/95. The sponsor's responses are acceptable. Finally, several HFD-420 comments/recommendations that were presented in the 02/01/95 bioreview need to be communicated to the sponsor and they should be addressed appropriately by the sponsor.



02/27/95

Tien-Mien Chen, Ph.D.

Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt _____ JPH 02/27/95

FT initialed by John Hunt J. Hunt 2/27/95

cc: NDA 20-169, HFD-510, HFD-426 (Fleischer), HFD-427 (M. Chen, T. Chen), HFD-340 (Viswanathan), Chron, Drug, Reviewer, FOI (HFD-19).

FEB 1 1995

NDA: 20-169

SUBMISSION DATE: 03/07/94

Nilutamide 50 mg tablets

07/12/94

09/02/94

09/27/94

BRAND NAME: Anandron

10/24/94

12/05/94

01/18/95

SPONSOR: Roussel-UCLAF, France

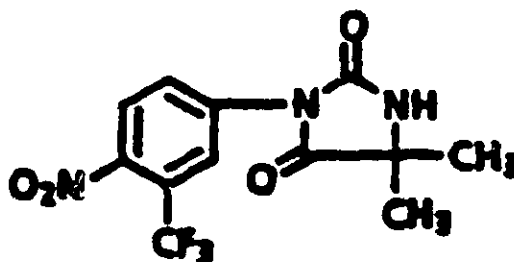
REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: New Drug Application (1 S) for an NME

TITLE: "Review of Human Pharmacokinetic and Bioavailability Studies Submitted to NDA 20-169 (Anandron; nilutamide 50 mg tablets)"

SYNOPSIS:

Nilutamide is an orally active nonsteroidal antiandrogen. It is a microcrystalline (no polymorphs) white to practically white powder with a molecular weight of 317.25 and is very slightly soluble in water. It is a new molecular entity, and its chemical structure is shown below:



Note: The sponsor indicated in a 09/27/94 supplement that the name, Anandron, may be changed to Nilandron.

Previously, the sponsor, Roussel-UCLAF, submitted NDA 20-169 (Anandron; nilutamide 50 mg tablet) to the Agency for review on 06/14/91 but it was deemed not fileable. Please see Background Section for details. The sponsor resubmitted NDA 20-169 on 03/07/94, and it was filed on 05/06/94.

Anandron is to be indicated for use in combination with surgical castration or chemical castration with an LHRH agonist for treating male prostate cancer (Stage D₂). The sponsor

wants approval for a 50 mg tablet dosage form. In its package insert (PI), the recommended dosing regimen is 6 x 50 mg tablets once a day (QD) for 30 days followed by 3 x 50 mg tablets QD. Anandron is to be taken before breakfast with a glassful of water. At the end of three months treatment, patients should be re-evaluated for the benefit/risk ratio for continued treatment.

There were 10 in vivo study reports submitted to the Human Pharmacokinetics Section of this NDA. Seven studies are considered to be pivotal pharmacokinetic (PK)/bioavailability (Bio) studies, i.e., Study No. 86/026/CN (relative bioavailability study), No. 90/2053/CN (single dose PK study), No. 87/380/CN (dose proportionality study), Nos. 87/526/CN and 89/1108/CN (multiple dose studies), and Nos. 87/508/CN and 89/1523/CN (human metabolism studies). Several tablet and capsule strengths/formulations had been developed and tested. The to-be-marketed tablet formulation, T2, was employed in both PK/Bio and clinical studies.

For three pivotal single dose studies, tablets were given on a fasting stomach (10 hr prior to dosing and 4 hr postdosing). The results show that i) under fasting conditions, the oral absorption of nilutamide is relatively rapid with a mean T_{max} around 2-3 hr, ii) the mean apparent terminal half-life ($T_{1/2}$) values for unchanged drug from different studies ranged from 40 to 50 hr, iii) the relative bioavailability (F_{rel}) in % for 1 x 100 mg capsule or 2 x 50 mg T1 tablets (not to-be-marketed) were around 160% as compared to a 100 mg dose of suspension under fasting conditions, and iv) 2 x 50 mg T1 tablets and 1 x 100 mg capsule demonstrated similar PK performance in normals. Further, an interstudy comparison shows that 2 x 50 mg T1 tablets and 2 x 50 mg T2 tablets have similar PK performance in normals. The results of the dose proportionality study show that the area under the curve ($AUC_{0-\infty}$) values and peak plasma drug levels (C_{max}) are proportional to dose (100, 200, and 300 mg) when given to normals. However, a further interstudy comparison shows that after a single dose of 6 x 50 mg, Japanese patients had a 44% higher mean $AUC_{0-\infty}$ value as compared to European normal volunteers. This could be due to the difference in mean body weight (BW); i.e., a higher mg/kg dose being given to Japanese (1.84 mg/kg) than to Europeans (1.24 mg/kg).

For the multiple dose studies (2 x 50 mg TID or 3 x 50 mg BID to patients), which were extracted from clinical trials, nilutamide as well as metabolite plasma levels were measured. Steady state was reported to be achieved within one month. For the 3 x 50 mg BID dosing regimen, the mean of average plasma levels at steady state (C_{ss}) for nilutamide was 6.78 $\mu\text{g/ml}$ ($n=8$). In the same study, compared also were steady-state AUC_{0-12} and $AUC_{0-\infty}$ obtained from the first dose of 3 x 50 mg. Mean steady-state AUC_{0-12} (81.4 $\mu\text{g-hr/ml}$, $n=8$) at Month 1 was about 110% higher compared to the single-dose $AUC_{0-\infty}$ (38.7 $\mu\text{g-hr/ml}$, $n=5$). The sponsor indicated that the higher steady-state AUC at Month 1 was due to a decrease in Clearance (CL) after chronic administration of nilutamide. This may be due to an inhibition of hepatic microsomal enzyme systems by nilutamide after multiple dosing.

Mean "one-point" plasma nilutamide levels at steady state which were used to monitor/check compliance of the drug administration were also reported. In one study where European patients were given 100 mg TID, mean "one-point" nilutamide plasma levels at steady state ranged from 6.45 $\mu\text{g/ml}$ (Month 1) to 6.05 $\mu\text{g/ml}$ (Month 12). However, the

values obtained from two additionally submitted pivotal clinical trials in which patients given 6 x 50 mg nilutamide QD for one month and 3 x 50 mg QD thereafter, were 3.84 to 5.66 $\mu\text{g/ml}$ for the 6 x 50 mg QD dosing (Month 1), and for 3 x 50 mg QD dosing the values were proportionally lower, 1.97 to 2.82 $\mu\text{g/ml}$. However, it was somewhat confounded by "undetectable" plasma nilutamide levels at steady state that were reported for some patients during hospital visits.

One multiple-dose study also demonstrated that Japanese patients who received either 2 x 75 mg QD (n = 7) or 4 x 75 mg QD (n = 7) had higher dose-normalized mean "one-point" plasma levels at steady state (8.88 $\mu\text{g/ml}$, n = 13) as compared European patients (6.51 $\mu\text{g/ml}$; n = 38) who received 2 x 50 mg TID. Seven out of 14 Japanese patients had higher incidence of toxicity/adverse effect, while none of 38 European patients had reported toxicity/adverse effect.

A ^{14}C -labelled tablet was used to study the metabolism of nilutamide in humans. Five metabolites were identified and the metabolic pathway was proposed. It was noted that i) fecal elimination was negligible ($\sim 3\%$ of the dose after 4 to 6 days), ii) nilutamide was extensively metabolized after oral administration, iii) urinary excretion of radioactivity was around 62% of total ^{14}C dose and only around 3 % was accounted for unchanged drug in urine after 5 days, iv) the mean $T_{1/2}$ value for at least one metabolite was 80 to 90 hr, v) the oxidation of a methyl group would create a chiral center; i.e., the formation of D- and L-isomers of metabolite(s), vi) one of the metabolites was studied and was shown to possess 25 to 50% of pharmacological activity as the parent drug, and vii) the D-isomer of the studied active metabolite showed a potency equal to or greater than the L-isomer. However, the PK of metabolites has not been fully studied.

For one PK study an analysis was conducted to study the relationship between some patients' nilutamide plasma levels and their elevated serum creatinine levels. Additionally, for each of the two pivotal clinical studies, analyses were conducted to assess the relationships between "steady state" plasma nilutamide levels and serum prostatic specific antigen (PSA), serum alkaline phosphatase (ALP), serum creatinine, serum SGOT, and serum SGPT levels as well as adverse reactions. Also carried out were analyses related to age, weight, and race. Seemingly, there were no apparent relationships found.

Dissolution data (using water as the medium) were submitted for tablets that were used in the PK/Bio studies. Upon request, additional dissolution data/profiles were submitted using simulated gastric and intestinal fluids (SGF and SIF) without enzymes. However, additional dissolution data are needed. Two in vitro protein binding studies demonstrated that the mean fraction bound (f_b) was 82% for the concentration range of $\mu\text{g/ml}$ (therapeutic range) studied.

Anandron is to be only indicated for treating male prostate cancer (Stage D₂). It is not intended for pediatric use. No food effect study on nilutamide was submitted. Finally, an HPLC method was used in most of the PK/Bio studies and it was found to be acceptable. A radioimmunoassay (RIA) method was also used to measure nilutamide levels in serum for one study and it was found to be somewhat reasonable, but complete crossreactivity data for all the metabolites were not provided.

RECOMMENDATION:

The Division of Biopharmaceutics (HFD-420) has reviewed NDA 20-169 for nilutamide (Anandron) that was submitted to the Agency on 03/07/94. HFD-420 feels that some additional information/data is needed for this product as is covered under General Comment Nos. 1 to 4 (page 18). Ideally, all this information/data should be obtained prior to the NDA's approval but if HFD-510 feels that it is not critical to have from an efficacy/safety perspective before the NDA is approved then, it could be obtained post-NDA approval. However, HFD-420 strongly feels that the information/data requested under Comment No. 4 should be submitted at this time. General Comment Nos. 1 to 4 (page 18) and the Labelling Comments (page 19) should be communicated to the sponsor.

Tien-Mien Chen

01/10/95

Tien-Mien Chen, Ph.D.

Pharmacokinetics Evaluation Branch II

Biopharm Day on 01/23/95 (Drs. Collins, Ludden, Fleischer, Chen, Gillespie and Hepp, and Mr. Hunt)

RD initialed by John Hunt JPH 01/20/95

FT initialed by John Hunt J. Hunt 2/1/95

cc: NDA 20-169, HFD-510, HFD-426 (Fleischer), HFD-427 (M. Chen, T. Chen), HFD-340 (Viswanathan), Chron, Drug, Reviewer, FOI (HFD-19).

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Appendix 1 (Study summaries):

Study No.	Descriptions	
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10. 86/366/CN	Long-term multiple dose study (100 mg TID or 150 mg BID) in patients using tablets	37

*. Pivotal study

Appendix 2:

Appendix 2 contains additional detailed data/information such as PI, assay validation reports for the methods used, individual raw data and the PK data/parameters, results of statistical and PK and/or PD analyses, dissolution data/profiles, the sponsor's responses, etc.. It is being retained in DB and can be obtained upon request.

I. **BACKGROUND:**

Originally, the sponsor, Roussel-UCLAF, submitted NDA 20-169 (Anandron; nilutamide 50 mg tablet) to the Agency for review on 06/14/91. Due to clinical issues the NDA was deemed not fileable after a 45-Day filing meeting that was held on 07/31/91. An FDA letter was sent to the firm on 08/14/91. As indicated in a previous bioreview dated 08/02/91, the NDA was, therefore, not formally reviewed by HFD-420.

Nilutamide is only slightly soluble in water. As indicated by the reviewing chemist of HFD-510, no information on the PKa or partition coefficient using n-octanol/water was provided for this drug.

II. **SUMMARY OF PHARMACOKINETICS, BIOAVAILABILITY, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.:**

1. **PHARMACOKINETICS:**

The mean and standard deviation of the mean (SD) for the PK parameters obtained from the single-dose studies are summarized below:

Table 1

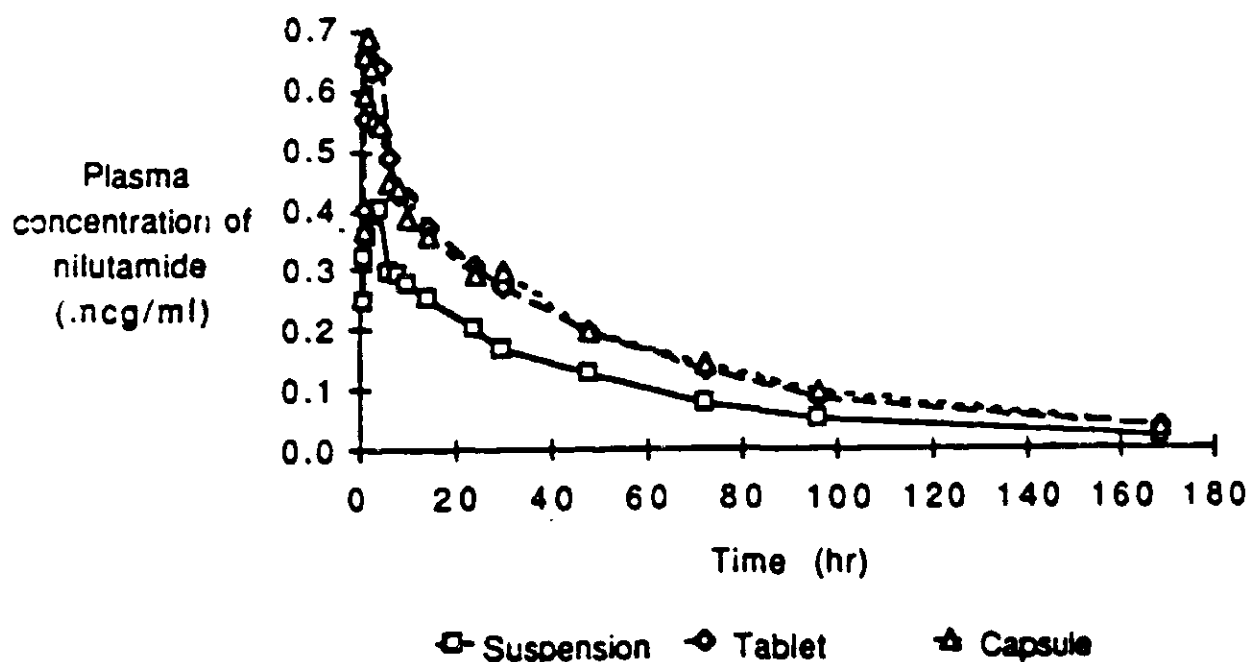
Mean PK Parameters Obtained From Single Doses of
Nilutamide in Normals and in Patients

Study No.	Dose (mg)	Dosage Form	T _{max} (hr)	C _{max} (µg/ml)	AUC* (µg·hr/ml)
86/026/CN [Normals] ^a (n = 12)	100	suspension	2.6 ^a ± 1.4	0.45 ± 0.14	16.3 ± 8.0
	2 x 50	T1 tablet ^a	1.9 ± 1.4	0.84 ± 0.17	26.4 ± 8.7
	1 x 100	capsule	1.9 ± 1.0	0.76 ± 0.38	25.6 ± 9.7
87/439/CN [Normals] (n = 12)	1 x 100	T5 tablet	1.9 ± 1.7	0.92 ± 0.38	27.4 ± 9.7
	2 x 50 ^b	T2 tablet	1.8 ± 1.4	0.81 ± 0.28	24.7 ± 9.4
88/763/CN [Normals] (n = 12)	1 x 150	T6 tablet	2.4 ± 1.4	1.42 ± 0.45	44.4 ± 8.0
	3 x 50	T2 tablet	3.1 ± 2.4	1.38 ± 0.35	47.7 ± 7.6
87/380/CN [Normals] (n = 12)	2 x 50 ^b	T2 tablet	1.8 ± 1.4	0.81 ± 0.28	24.7 ± 9.4
	4 x 50	T2 tablet	1.7 ± 1.0	1.58 ± 0.42	56.4 ± 17.
	6 x 50	T2 tablet	1.5 ± 1.0	2.32 ± 0.62	83.8 ± 26.
90/2053/CN [Patients] (n = 6)	6 x 50	T2 tablet	2.8 ± 2.8	2.58 ± 0.69	121 ± 27.

- a. AUCs were calculated by trapezoidal rule from time zero to the last time point when drug level was measurable (T_{last}).
- b. Normals represent normal healthy male volunteers, and patients represent male patients with prostatic cancer.
- c. For detailed tablet formulations used in each study please see Section of Formulation, Dosage, and Administration below.
- d. Mean ($\pm$ SD).
- e. These values were obtained from the same study.

The sponsor's calculations for the above PK parameters were spot checked and were found to be acceptable. The results obtained from the single dose studies show that mean T_{max} is around 2-3 hr under fasting conditions. Mean $T_{1/2}$ values for unchanged drug from different studies ranged from 40 to 50 hr (not shown here) indicating prolonged disposition kinetics for nilutamide in humans. The mean plasma nilutamide profile after single dose administration (Study No. 86/026/CN) is shown below in Figure 1.

Figure 1



An interstudy comparison for a single dose of 6 x 50 mg (Table 1) demonstrated the Japanese patients had an around 44% increase in mean $AUC_{0-\infty}$ value ($121 \mu\text{g}\cdot\text{hr}/\text{ml}$; Study No. 90/2053/CN) as compared to the normal European volunteers ($83.8 \mu\text{g}\cdot\text{hr}/\text{ml}$; Study No. 87/380/CN). This could be due to the difference in mean BW; i.e., higher mg/kg dose being given to Japanese ($1.84 \text{ mg}/\text{kg}$) than to Europeans ($1.24 \text{ mg}/\text{kg}$). However, the numbers of subjects used in these studies are considered to be small, and other factors which may contribute to the difference in PK may need further investigation.

Assuming that nilutamide was almost "completely" absorbed, the CL, $T_{1/2}$ for the apparent distribution phase after absorption, mean first-pass metabolism in %, and the volume of distribution at the terminal phase (V_d) values for nilutamide were "estimated" to be around 52 to 68 ml/min, 1.5 to 6 hr, 4%, and 185 to 270 liters, respectively.

For multiple-dose study No. 89/1523/CN (3 x 50 mg BID), data for 8 patients were reported. Steady state was reported to be achieved within one month and the mean ($\pm$ SD) steady-state AUC_{0-12} ($81.4 \pm 16.1 \mu\text{g-hr/ml}$) at Month 1 was about 110% higher compared to the AUC_{0-12} ($38.7 \pm 10.8 \mu\text{g-hr/ml}$; $n=5$) obtained from the first dose of 3 x 50 mg. The sponsor indicated that the higher steady-state AUC_{0-12} at Month 1 was due to a decrease in CL upon chronic administration of nilutamide. This could be due to metabolic enzyme inhibition, and it is seemingly consistent with a statement given in the Drug Interaction section of the package insert, i.e., nilutamide inhibits the activity of certain hepatic microsomal enzyme systems *in vitro*. From the same study, the mean ($\pm$ SD) C_{ss} for nilutamide, $6.78 \pm 1.34 \mu\text{g/ml}$ ($n=8$), was calculated by the sponsor as steady-state AUC_{0-12}/τ , where τ is the dosing interval (0 to τ hr).

Mean "one-point" plasma nilutamide levels at steady state, which were used to monitor/check compliance of the drug administration, were also reported (100 mg TID; Study No. 87/526/CN). They are summarized below:

Table 2 Mean "One-Point" Plasma Nilutamide Levels At Steady State

Treatment Time	Study No. 87/526/CN (100 mg TID)	
	Tablets ^a (2 x 50 mg)	Capsules (1 x 100 mg)
1 month	6.44 ^b [57] ^c ($\pm$ 2.58)	7.24 [33] ($\pm$ 3.65)
3 months	6.45 [44] ($\pm$ 3.14)	7.30 [31] ($\pm$ 3.95)
6 months	6.17 [25] ($\pm$ 2.84)	7.42 [27] ($\pm$ 2.71)
12 months	6.05 [10] ($\pm$ 1.97)	7.04 [12] ($\pm$ 2.69)

^a. Both T1 and T2 tablet formulations were used.

^b. Mean ($\pm$ SD).

^c. No. of patients.

The above mean "one-point" plasma nilutamide levels at steady state were close to the mean C_{ss} value reported for tablets, 6.78 $\mu\text{g/ml}$ (Study No. 89/1523/CN). Capsules seemingly had a slightly higher mean "one-point" plasma drug levels at steady-state than the tablets, however, they were not statistically significant ($p > 0.05$) at each month.

It was noted that after multiple-dose administration of nilutamide (Study No. 89/1108/CN) to Japanese ($2 \times 75 \text{ mg QD}$; $n = 7$, and $4 \times 75 \text{ mg QD}$; $n = 7$) and European patients ($2 \times 50 \text{ mg TID}$; $n = 38$) under different protocols, the Japanese patients seemingly had higher dose-normalized mean ($\pm \text{SD}$) "one-point" plasma nilutamide levels ($8.88 \pm 2.89 \mu\text{g/ml}$; $n = 13$) than the European patients ($6.51 \pm 2.75 \mu\text{g/ml}$; $n = 38$). Three out of the 7 Japanese patients who received $2 \times 75 \text{ mg}$ of nilutamide QD developed interstitial pneumonitis, and 4 out of another 7 Japanese patients who received $4 \times 75 \text{ mg QD}$ developed interstitial pneumonitis, whereas none of the 38 European subjects who received $2 \times 50 \text{ mg TID}$ developed interstitial pneumonitis. Note: In a discussion with the reviewing pharmacologist of HFD-510, she indicated that i) interstitial pneumonitis is considered as an adverse reaction, ii) it is dose and/or duration of treatment related, iii) it could be due to a formation of free radical during metabolism of nilutamide, however, the mechanism of the development of interstitial pneumonitis has not been clearly elucidated, and iv) interstitial pneumonitis is stated in the adverse reaction section of some drugs which share similar chemical structure as nilutamide, e.g. nitrofurantoin.

On 09/27/94, the sponsor submitted mean "one-point" plasma nilutamide levels at steady-state that were obtained from the two NDA's pivotal clinical trials, i.e., Nos. FF/86/908/01 (orchiectomized patients, $n = 129$) and GHBA 606 (Leuprolide-treated patients, $n = 134$). Both studies used the recommended dosing regimen i.e., $6 \times 50 \text{ mg QD}$ for 1 month followed by $3 \times 50 \text{ mg QD}$. However, during each hospital visit, the blood sampling time (one point only at the steady state) for each individual's nilutamide level was not clearly recorded and a few patients had "zero" nilutamide levels at steady state. The resulting mean "one-point" values at steady state were lower than those seen in Study No. 89/1523/CN (6.78 $\mu\text{g/ml}$ for the 300 mg daily dose). Mean "one-point" values at steady state at Month 3 were also proportionally lower for the 150 mg QD dose. These values are summarized below:

Table 3

Mean of One-Point Plasma Nilutamide Level At Steady State ($\mu\text{g/ml}$)

Month	Study No.	
	FF/86/908/01 (Orchiectomized)	GHBA 606 (Leuprolide-treated)
1*	3.84* [$n = 129$]*	5.66 [$n = 134$]

	($\pm$ 2.41)	($\pm$ 2.88)
3 ^a	2.23 [n = 126] ($\pm$ 1.29)	2.63 [n = 127] ($\pm$ 1.36)
6	2.05 [n = 105] ($\pm$ 1.34)	2.61 [n = 107] ($\pm$ 1.25)
12	2.02 [n = 64] ($\pm$ 1.27)	2.82 [n = 64] ($\pm$ 1.13)
18	1.95 [n = 28] ($\pm$ 1.25)	2.74 [n = 33] ($\pm$ 1.05)

- ^a. 300 mg QD for Month 1.
- ^b. Mean ($\pm$ SD) for parent drug level.
- ^c. No. of patients who had steady-state nilutamide level measured.
- ^d. 150 mg QD after Month 1.

2. BIOAVAILABILITY AND BIOEQUIVALENCE:

No PK data/parameters for an intravenous dose were available. From Study No. 86/026/CN, 2 x 50 mg T1 tablets and 1 x 100 mg capsule were 60% more bioavailable than an oral 100 mg suspension. From Study No. 89/1523/CN, 2 x 50 mg ¹⁴C tablets had only around 3 % of radioactivity excreted in feces after 5 days. This might suggest that absorption of the remainder of ¹⁴C radiolabelled dose, but it does not exclude GI metabolism and subsequent absorption of ¹⁴C radiolabelled metabolite(s).

An interstudy comparison of AUC values between study Nos. 86/026/CN and 87/439/CN for T1 and T2 tablets demonstrated that T2 and T1 tablets had similar PK performance in normal volunteers under fasting conditions. Please see Study No. 87/1108/CN in Appendix 1 for details.

3. DOSE PROPORTIONALITY:

Single doses of 100, 200, and 300 mg were given to 12 normal volunteers in a 3-way crossover study (No. 87/380/CN) using the 50 mg to-be-marketed T2 tablet formulation. The study results show that the AUC_{0-∞} and C_{max} values are proportional to the single doses given. The T_{max} values remained unchanged while the T_{1/2} values increased very slightly as dose increased. The mean plasma drug profiles are given in Figure 2, and the study results are summarized in Table 4. The findings from this single-dose study, however, did not exactly predict what the multiple dose findings were, i.e., after chronic administration of nilutamide, there was a decrease in CL and steady-state nilutamide plasma levels increased greater than what would be expected from the PK data obtained from the single-dose studies.

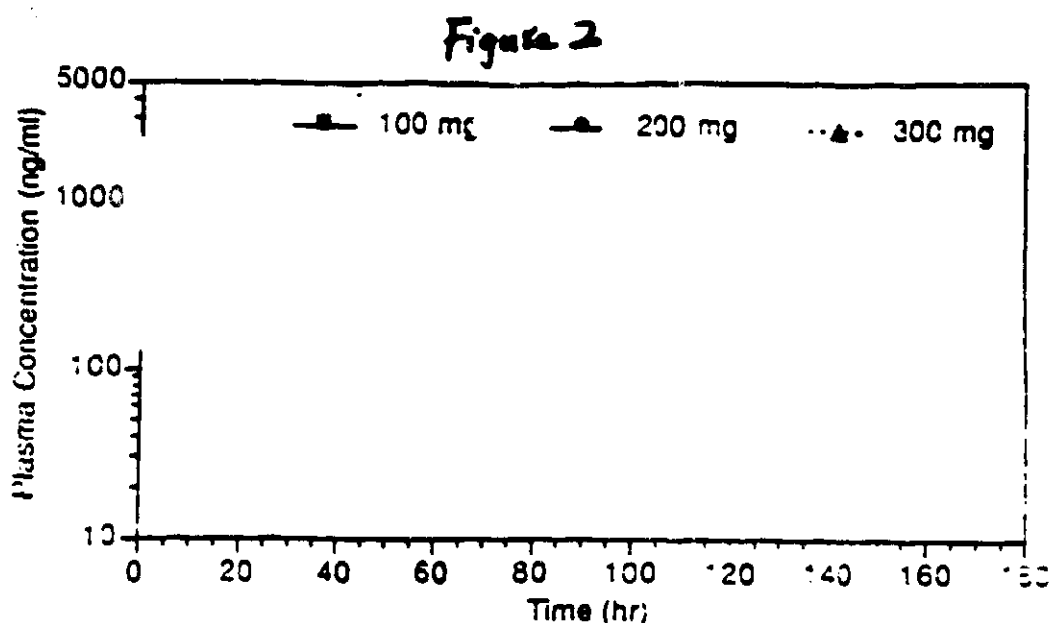


Table 4

Pharmacokinetic Parameters After a Single 100-mg, 200-mg, or 300-mg Dose of Nilutamide

Parameter	Nilutamide Dos		
	100 mg (2 x 50 mg)	200 mg (4 x 50 mg)	300 mg (6 x 50 mg)
AUC ($\mu\text{g} \cdot \text{hr}/\text{ml}$)	24.7* $\pm$ 9.4	56.4 $\pm$ 17.	83.8 $\pm$ 26.
AUC/Dose ($\text{ng} \cdot \text{hr}/\text{ml} \cdot \text{mg}$)	247 $\pm$ 94	282 $\pm$ 85	279 $\pm$ 84
Cmax ($\mu\text{g}/\text{ml}$)	0.81 $\pm$ 0.28	1.58 $\pm$ 0.42	2.32 $\pm$ 0.62
Cmax/Dose ($\text{ng}/\text{ml} \cdot \text{mg}$)	8.1 $\pm$ 2.8	7.92 $\pm$ 2.1	7.72 $\pm$ 2.1
Tmax (hr)	1.75 $\pm$ 1.4	1.71 $\pm$ 1.0	1.52 $\pm$ 1.0
t _{1/2} (hr)	41.2 $\pm$ 11.1	44.8 $\pm$ 12.5	48.9 $\pm$ 13.2

*. Mean $\pm$ SD.

4. METABOLISM:

A metabolism study using a ¹⁴C-labelled nilutamide tablet are summarized from 5 patients (Study No. 87/508/CN). Note: The ¹⁴C-labelled tablet formulation was not the same as the 50 mg to-be-marketed T2 tablet. The relative amounts of nilutamide and the five metabolites in the urine of individual patients were determined. The urine collected for 120 hrs post drug administration was extracted after enzymatic hydrolysis and the radioactivity was quantified in the different HPLC fractions collected. The results are provided below in Table 5.

Table 5

Nilutamide and Its Metabolites in the Urine After Administration of [^{14}C]Nilutamide to Patients

Compound	Subject No.					Mean $\pm$ SD
	1	2	3	4	5	
Nilutamide	2.5 ^a	2.8	5.6	2.8	2.6	3.3 $\pm$ 1.3
RU 45 018	1.6	5.3	n.d. ^b	1.2	1.2	2.3 $\pm$ 2.0
RU 43 866	11.1	12.3	10.3	8.1	12.6	10.9 $\pm$ 1.8
RU 48 166	3.5	2.9	5.2	2.2	4.8	3.7 $\pm$ 1.3
RU 48 275	3.7	6.5	5.1	3.2	5.1	4.7 $\pm$ 1.3
RU 48 276	1.2	2.6	4.8	2.6	2.7	2.8 $\pm$ 1.3
Total of 6 compounds	23.6	32.4	31.0	20.1	29.0	27.2 $\pm$ 5.2
Total [^{14}C] excreted	68.2	69.7	57.5	56.4	58.9	62.1 $\pm$ 6.3

^a. Percent of total ^{14}C dose administered.

^b. n.d.: not detectable.

Additionally, urine samples from a normal subject who received ^3H -labelled nilutamide were analyzed for tritium in the urinary water and for tritium associated with other molecules. The results showed a similar metabolic pattern.

In Study No. 89/1108/CN the plasma levels of 3 metabolites, RU 43866, RU 48275 and RU 48276, were also measured and the AUC ratios of metabolite/parent drug were calculated and shown below:

Metabolite	Mean AUC ratio for Metabolite/Parent Drug	
	European patients	Japanese patients
RU 43866	0.190 ($\pm$ 0.106) ^a	0.177 ($\pm$ 0.086)
RU 48275	0.0789 ($\pm$ 0.0371)	0.0485 ($\pm$ 0.0392)
RU 48276	0.0943 ($\pm$ 0.0514)	0.0193 ($\pm$ 0.106)

^a. Mean ($\pm$ SD).

In summary, it was noted that i) the drug was extensively metabolized after oral administration and only around 3 % radioactivity was recovered in urine as unchanged drug, ii) the mean $T_{1/2}$ value for total radioactivity/metabolites was 80-90

hr, iii) the oxidation of a methyl group would create an asymmetric center; i.e., the formation of D- and L-forms of metabolite(s), iv) one of the metabolites, RU 48275, was studied using an animal model androgen receptor and it was shown to possess 25 to 50% of pharmacological activity as the parent drug, however, it would probably not contribute significantly to the total pharmacological activity of the drug, and v) the D-isomer of the active metabolite, RU 48275, showed equal to or greater potency than the L-isomer. However, it should be noted that the PK and/or PD of the metabolites have not been fully studied.

Note: In vitro metabolism studies using human microsomal enzyme are reported in two published articles. The results indicate that "nilutamide inhibits hepatic cytochrome P-450 activity, and suggest that inhibition may actually occur after therapeutic doses of nilutamide in humans" [Babany et al: Biochemical Pharmacology, Vol. 38, No. 6, pp 941-947, 1989, and Hcrsmans et al: Xenobiotica, Vol. 21, No. 12, pp 1559-1570, 1991].

The metabolic pathway for nilutamide after oral administration was proposed as follows:

5. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS, ETC.:

Analyses evaluating nilutamide "steady state" plasma levels/pharmacodynamic (PD) parameters (i.e., serum PSA and ALP levels) were performed using the two pivotal clinical studies (Nos. FF/86/908/01 and GHBA 606). Also, analyses of "steady state" plasma nilutamide levels as related to renal function (i.e., serum creatinine levels) and hepatic function (i.e., serum SGOT and SGPT levels) were also performed. Lastly, analyses were carried out trying to relate drug levels with adverse reactions.

The sponsor indicated that for each study there were generally no relationships between i) "steady state" nilutamide plasma levels and serum PSA and ALP levels, ii) "steady state" nilutamide plasma levels and serum creatinine, SGOT and SGPT levels, and iii) "steady state" nilutamide plasma levels and adverse reactions. The sponsor's statements are generally correct, but the analyses may be somewhat confounded by the facts that i) the sampling times for each measured "steady state" nilutamide plasma level were not recorded, and ii) undetectable nilutamide levels at steady state were found in a few individuals. Please see Appendix 2 for details.

6. GENDER:

Anandron is to be only indicated for treating male patients with prostate cancer (Stage D₂).

7. PEDIATRICS:

Anandron is not intended for pediatric use.

8. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

Information on the composition of the formulations used in the studies is provided in Table 6. Further information on the manufacturing dates, sites, and batch sizes of tablets is provided in Appendix 2. Note: The ¹⁴C tablet formulation that was used in the human metabolism study (Study No. 86/026/CN) was not compositionally/proportionally the same as the T2 tablet.

9. DISSOLUTION METHOD AND SPECIFICATION:

The initial dissolution testing for the nilutamide 50 mg tablets that were manufactured at Romainville and used in the PK/Bio studies was performed using the USP II (paddle) method at 50 rpm with 900 ml water at 37°C as the dissolution medium.

Firm: Roussel Uclaf
 Drug: Nitutamide
 NDA

Table 6

DRUG FORMULATION DEVELOPMENT SUMMARY (Continued)

Ingredient	Formulations (Quantities in mg)									
	Tablets					Capsules				
	T1	T2*	T3	T4	T5	T6	C1	C2	C3	C4

50 mg 75 mg 100 mg 150 mg 50 mg 100 mg

✓ RU 23 908
 ✓ Corn starch
 ✓ Lactose

✓ Magnesium stearate
 ✓ Talc

Total

* Formulation T2 is the proposed commercial formulation. * C⁴ tablet Lot no. JL 20114-97 (Study NO 87/508/CN)

✓ Nitutamide 50.0 mg
 ✓ Maize starch mg
 ✓ Lactose mg
 ✓ Povidone (in water) mg
 ✓ Mg stearate mg
 ✓ Talc mg

01/18/95

Additional dissolution data using SGF and SIF media were submitted on 07/12/94 for a commercial batch that was manufactured at Compiègne (i.e., proposed manufacturing site for the to-be-marketed 50 mg tablets). The results are summarized in Table 7 (for SIF only).

Based upon the dissolution data in SGF and SIF, it is recommended that the following dissolution method be used for nilutamide 50 mg tablets.

USP Apparatus II (Paddle), 50 rpm
900 ml USP pH 7.5 simulated intestinal fluid (SIF) without enzymes at 37°C
Q = % in min

However, before this method and specification are finalized, dissolution profiles of biolots used in the PK studies and two pivotal clinical studies, Nos. FF/86/908/01 and GHBA 606, need to be provided.

10. SAMPLE COLLECTION:

Please see blood sample collection and treatment in details in the study reports in Appendix 1.

11. ASSAY:

An HPLC method was used for most of the studies and it was found acceptable. An RIA method was also used to measure serum nilutamide levels in Study No. 87/526/CN. Only two metabolites were tested for crossreactivity with nilutamide and it was very low (< 0.4%). Therefore, the RIA method was seemingly suitable for assay. Please see the assay validation reports submitted to the individual study (Appendix 2) for details.

12. DATA ANALYSIS:

Noncompartmental methods were used to calculate PK parameters, e.g., AUC_{0-t} , $AUC_{0-\infty}$, CL, Vd, etc. The C_{ss} for nilutamide was calculated as steady-state $AUC_{0-\tau}/\tau$, where τ is the dosing interval (0 to τ hr). Statistical analyses were also employed.

RESULTS

Dissolution in SIF

The table below provides results (as dissolved percentage) obtained on first 6 tablets (tb1 to tb6)

Time (min)	tb1	tb2	tb3	tb4	tb5	tb6	mean	CV
							7.6	24.5
							40.2	14.6
							71.2	6.3
							93.5	2.9
							97.8	3.2
							99.4	3.3

100.00

50.00

0.000

0.0

20.0

40.0

60.0

(min)

The table below provides results (as dissolved percentage) obtained on last 6 tablets (tb7 to tb12)

Time (min)	tb7	tb8	tb9	tb10	tb11	tb12	mean	CV
							8.2	24.5
							43.6	14.6
							72.2	6.3
							92.9	2.9
							95.8	3.2
							98.2	3.3

100.00

50.00

0.000

0.0

20.0

40.0

60.0

(min)

% dissolved

% dissolved

III. GENERAL COMMENTS: (Nos. 1 to 4 need to be sent to the sponsor)

1. In the package insert (PI), it is stated that Anandron is to be given "before breakfast with a glassful of water". Although the pivotal clinical studies administered the to-be-marketed Anandron tablet according to the PI's dosing recommendations (i.e., given before breakfast and using the recommended dosing regimen), no classical pharmacokinetic/bioavailability study was conducted to assess the effect of food on this tablet product. Therefore, a food effect study is desirable and for such a study at least twelve normal healthy subjects and a standard FDA high fat breakfast should be used. The Division of Biopharmaceutics should be contacted for discussing study design, etc.
2. In the PI the following is stated.

For each of the NDA's two pivotal clinical studies (i.e., Study FF/86/908/01 in surgically castrated patients and Study GHBA 606 in chemically castrated patients who were given concomitant 1 mg/day Leuprolide subcutaneous administration), data analyses within a study were carried out to determine if relationships exist between "steady state" nilutamide plasma levels and i) the "good prognostic factors" of plasma alkaline phosphatase (ALP) and prostate specific antigen (PSA), ii) plasma creatinine levels, iii) the liver transaminases SGOT and SGPT, and iv) adverse reaction. No between study analyses were conducted.

Particularly of concern is at least one adverse reaction. Example, from the Table given in the Adverse Reaction section of the PI, for the adverse reaction of impaired adaptation to darkness, it occurred in 13% of surgically castrated patients getting nilutamide versus 56% of chemically castrated patients getting concomitant nilutamide (Note: In patients that only received Leuprolide plus placebos the incidence was 5%). Therefore, between pivotal clinical study analyses need to be done relating nilutamide plasma levels and the different efficacy and safety parameters.

3. As noted in Comment No. 2 above, nilutamide can be given concomitantly with an LHRH agonist. No pharmacokinetic data were provided which assessed the possible effect of nilutamide on the disposition characteristics of the agonist leuprolide. Therefore, any information related to this should be provided. If there are stored plasma/serum samples from completed studies, analysis of them for leuprolide levels might be an option and/or obtaining samples from any ongoing studies.

4. It is proposed that the following dissolution method/specification be implemented for NDA 20-169:

USP Apparatus II (Paddle), 50 rpm

900 ml USP pH 7.5 simulated intestinal fluid (SIF) without enzymes at 37°C

Q = % in min

However, before this method is finalized, dissolution profiles (up to min) need to be provided for the biobatches (12 tablets per each batch) used in the human pharmacokinetic studies as well as the batches used in the two pivotal clinical studies, Nos. FF/86/908/01 and GHBA 606.

5. Study No. 87/380/CN demonstrated dose proportionality after single doses in normals while in multiple-dose study No. 86/366/CN, the patients' mean steady-state $AUC_{0-\infty}$ value (81.4 $\mu\text{g-hr/ml}$) was much higher (110% ↑) than the first dose mean $AUC_{0-\infty}$ value (38.7 $\mu\text{g-hr/ml}$). Note: In linear kinetics, steady-state $AUC_{0-\infty}$ and first dose $AUC_{0-\infty}$ values should be equivalent. It is reported that for this study findings there could be a decrease in clearance (CL) after chronic administration of nilutamide. It was noted further that the patients' CL decreased within the first month and then was reasonably steady for the rest of the treatment period which was reflected by the mean "steady state" plasma nilutamide values that were obtained from other studies. This is an indication of possible metabolic enzyme inhibition which has been documented in several published articles using human liver microsomes *in vitro* (Babany et al: Biochemical Pharmacology, Vol. 38, No. 6, pp 941-947, 1989, and Horsmans et al: Xenobiotica, Vol. 21, No. 12, pp 1559-1570, 1991).

IV. **LABELLING COMMENTS:** (Need to be sent to the sponsor)

1. The third paragraph (for Metabolism) in the subsection Pharmacokinetics under the Clinical Pharmacology section should be modified as follows:

2. The second sentence of the fourth paragraph (for Elimination) in the subsection Pharmacokinetics under the Clinical Pharmacology section should be modified as follows:

3. The fifth sentence of the fourth paragraph (for Elimination) in the subsection Pharmacokinetics under the Clinical Pharmacology section should be modified as follows:

4. After the last sentence of the first paragraph of the PI's Clinical Studies section, the following should be indicated.

Drugs & Aging 3 (1): 9-25, 1993
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 DRA1 161

Nilutamide

A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Prostate Cancer

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Summary

Synopsis

Nilutamide is a nonsteroidal antiandrogen with affinity for androgen receptors but not for progestogen, estrogen, or glucocorticoid receptors. Consequently, nilutamide blocks the action of androgens of adrenal and testicular origin which stimulate the growth of normal and cancerous prostatic tissue. Nilutamide has a long half-life which permits once-daily administration.

Nilutamide is usually given in combination with surgical or chemical castration using gonadotrophin-releasing hormone (GnRH) [luteinising hormone-releasing hormone (LHRH)] agonists. In castrated patients the addition of nilutamide improves objective response rates, bone pain, urinary symptoms, tumour markers and time to disease progression.

The tolerance of nilutamide is generally acceptable. Adverse effects are usually mild and reversible and consistent with androgen depletion. Unexpected but reversible adverse effects of nilutamide include delayed adaption to dark after exposure to bright light, transient increases in transaminases, and more severe but rare interstitial pneumonitis.

Thus, nilutamide is a welcome treatment option that may be particularly useful in patients to whom the convenience of once-daily administration is seen as a worthwhile benefit.

Pharmacodynamic Properties

Nilutamide is a nonsteroidal antiandrogen with weak affinity for androgen receptors. It is considered a 'pure' antiandrogen since it has limited affinity for progestogen and glucocorticoid receptors. Although nilutamide binds only weakly to androgen receptors *in vitro*, it produces sustained receptor antagonism *in vivo*. Evidence suggests that nilutamide inhibits the synthesis of androgens, in particular those of adrenal origin, in addition to its effects at the androgen receptor. Importantly, it does not impair the synthesis of glucocorticoids.

Binding of nilutamide to androgen receptors in the pituitary prevents the negative feedback effect of testosterone, increasing luteinising hormone release which, theoretically, stimulates further testosterone secretion. However, in humans testosterone levels plateau after a 2-fold increase. Further, this effect can be blocked by concomitant administration of a GnRH agonist.

In castrated mice inoculated with various androgen-dependent tumour cell lines, nilutamide reduces the incidence and development of tumours. In contrast, nilutamide, flutamide and cyproterone acetate stimulate androgen-dependent processes in specific androgen-dependent tumour cell models.

In rats, prostate weight decreases to a greater extent after combination treatment with nilutamide and a GnRH agonist than after a GnRH agonist alone. In human subjects undergoing gender transformation, it appears that nilutamide does not change prostate volume.

Pharmacokinetic Properties

Nilutamide is fully absorbed after oral administration, with peak plasma concentrations of 0.9 mg/L occurring within 3 hours of a single dose (150 or 200mg) in patients with prostate cancer. Mean plasma elimination half-life in patients with prostate cancer is 56 hours, suggesting that the drug can be given as a single daily dose, and steady-state plasma concentrations (4.4 to 8.5 mg/L according to the dose) are achieved within approximately 2 weeks.

Nilutamide is extensively metabolised, with one of the metabolites interacting with androgen receptors and the prostate of castrated rats, although its activity is much less than that of the parent compound. Plasma clearance of nilutamide appears to decrease with repeated administration.

Therapeutic Efficacy in Prostate Cancer

Placebo-controlled studies in orchiectomised patients with stage D (metastatic) prostate cancer have shown that nilutamide (150 or 300 mg/day) is significantly more effective than placebo in terms of objective responses. Subjective responses (based on bone pain relief and performance status) have also been observed in more nilutamide than placebo recipients. Above a time to

progression was significantly increased, so far there has been no significant difference in favour of nilutamide in improving survival, but only trends.

Nilutamide has also been compared with placebo in patients receiving the GnRH agonist buserelin, and has been shown to be effective in preventing the 'disease flare' associated with the initial increase in testosterone levels observed at the beginning of GnRH agonist therapy. Placebo-controlled studies have shown a significantly better objective response rate, improvement of bone pain and normalisation of tumour markers with a GnRH agonist plus nilutamide than with a GnRH agonist alone.

Nilutamide has been assessed as monotherapy only in a small number of previously untreated patients; an objective partial response rate of 38.5% was achieved.

Tolerability

Nilutamide has been relatively well tolerated in clinical trials. Nilutamide 150 to 300 mg/day produces a delayed adaptation to darkness in about 30% of patients. This is reversible on discontinuation of therapy, or perhaps even spontaneously. Hepatotoxicity and interstitial pneumonitis are rare but serious adverse events that have been reported in patients receiving nilutamide. Adverse events related to androgen deprivation, such as hot flushes, gynaecomastia and impotence, occur commonly with nilutamide, as they do with most drugs used in the treatment of prostatic cancer. Nausea, vomiting, and alcohol intolerance have commonly been observed during nilutamide treatment. Pruritus, dizziness and headache have been reported rarely.

Effects on sexual function are difficult to assess since the drug is recommended to be used in combination with castration. It is possible that nilutamide may interact with drugs metabolised by the cytochrome P-450 system but this has not been observed in clinical practice.

Dosage and Administration

Nilutamide is administered orally as a single daily dose of 300mg for 1 month, then 150 mg/day thereafter, in previously untreated patients, in combination with a GnRH agonist or orchiectomy.

1. Pharmacodynamic Properties

Nilutamide (fig. 1) is a nonsteroidal antiandrogen drug which, like flutamide (see review by Brogden & Chrisp 1991), is considered a 'pure' antiandrogen since its other hormonal effects are negligible. Nilutamide binds to the androgen receptor in target tissues and inhibits the binding of androgens (Moguilewsky et al. 1987).

1.1 Receptor Binding Affinity

Unlike the steroid antiandrogens such as cyproterone acetate and megestrol acetate which bind to androgen, progestin and glucocorticoid receptors (Moguilewsky et al. 1986), nilutamide binds specifically to the androgen receptor and does not interact with progestin or glucocorticoid receptors (Gaillard-Moguilewsky 1991) [table I]. *In vitro*

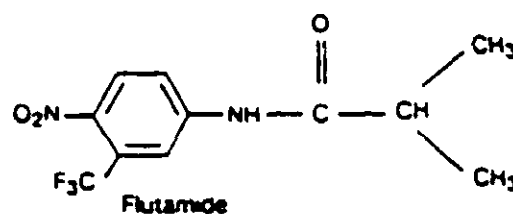
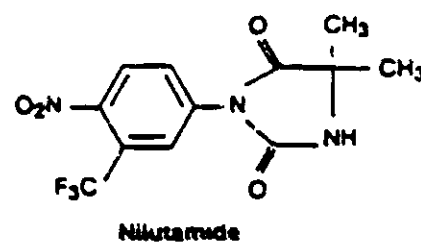


Fig. 1. Structural formulae of nilutamide and flutamide.

Table I. Receptor binding affinities (%) of steroidal and nonsteroidal antiandrogens for rat prostatic tissue *in vitro* (after Moguilewsky et al. 1986)

Antiandrogen	Receptor				
	androgen ^a	progestin ^b	estrogen ^c	gluco-corticoid ^d	mineralo-corticoid ^e
Nilutamide	4.5	< 0.1	< 0.1	< 0.1	< 0.1
Cyproterone acetate	20	60	< 0.1	5	1
Flutamide	0.3	< 0.1	< 0.1	< 0.1	< 0.1
Hydroxyflutamide	4.5	< 0.1	< 0.1	< 0.1	< 0.1
Megestrol acetate	39	120	< 0.1	50	3

a Binding affinity relative to testosterone (100%).

b Binding affinity relative to progesterone (100%).

c Binding affinity relative to estradiol (100%).

d Binding affinity relative to dexamethasone (100%).

e Binding affinity relative to aldosterone (100%).

studies in rat prostate have shown that nilutamide interacts only weakly with androgen receptors compared with testosterone, cyproterone acetate and megestrol acetate (table I) [Moguilewsky et al. 1986; Raynaud et al. 1979]. However, in contrast to the results of *in vitro* studies, when nilutamide 10 mg/kg was administered *in vivo* to rats, greater than 60% of cytosolic androgen binding sites were occupied during the first 16 hours (Raynaud et al. 1985). It was hypothesised that the receptor occupancy level of nilutamide was a function of its long half-life in tissue and plasma compartments (see section 2).

Evidence that nilutamide acts not only at peripheral androgen receptors, but also on the pituitary came from the observation that nilutamide 10 μ mol/L reversed testosterone- and 5 α -dihydrotestosterone-induced inhibition of gonadotrophin-releasing hormone (GnRH)-stimulated luteinising hormone (LH; menotropins) release *in vitro* (Raynaud et al. 1979). Administration of nilutamide 1 mg twice daily to rats increased the LH levels induced by GnRH approximately 4-fold (Raynaud et al. 1979).

In contrast to the antiandrogenic effects of nilutamide on target tissues, the drug may stimulate androgen-dependent processes. Steinsapir and co-workers (1991) demonstrated that in rat prostate, nilutamide, hydroxyflutamide and cyproterone

acetate blocked the accumulation of nuclear androgen receptors induced by testosterone. However, in the absence of testosterone, the antiandrogens acted as potent androgen agonists and increased nuclear, cytosolic and microsomal androgen receptor levels. Such effects have not been observed in humans.

1.2 Effects on Androgen-Dependent Tissues

Nilutamide dose dependently prevents the increase in prostate weight induced by testosterone propionate 50 μ g in castrated rats, but only partially counteracts endogenous androgen effects on prostate of intact rats (Raynaud et al. 1979). Similarly, in castrated rats implanted with testosterone pellets to ensure continuous release of testosterone, subcutaneous administration of nilutamide 20 mg/kg for 28 days reduced the ventral prostate weight by 95% and the seminal vesicle weight by 85% compared with control animals (Burton & Trachtenberg 1986; Dhar & Setty 1990).

In castrated rats, nilutamide is also able to inhibit the trophic effect on the prostate of adrenal androgens infused at levels equivalent to those observed in castrated men (Moguilewsky et al. 1987).

However, nilutamide did not alter testis weight in intact rats (Dhar & Setty 1990). The reductions in secondary sex organ weight induced by nilutam-

ide were greater than those achieved with megestrol acetate 20 mg/kg but less than those obtained after castration (Burton & Trachtenberg 1986).

In rats, the GnRH agonist buserelin 1 µg/kg/day administered subcutaneously produced a transient increase in prostate weight due to the increase of testosterone at the beginning of treatment (flare-up effect) then reduced testis and prostate weight, but not to the same extent as surgical castration (Moguilewsky & Tournemine 1988). Oral nilutamide 20 mg/kg/day, in combination with buserelin (Moguilewsky & Tournemine 1988) or with GnRH ethylamide 250 ng/day (Lefebvre et al. 1982), not only counteracted the treatment flare-up effect, but produced a substantial decrease in prostate weight (from > 300mg to < 50mg) in rats. It is thought that GnRH agonists inhibit Leydig cell function in rat testes, and that nilutamide may potentiate this effect.

Spermatogenesis was blocked after subcutaneous administration of nilutamide in doses in excess of 10 mg/day for 30 days in 20 to 50% of tubules in 9 of 16 rats (Dhar & Setty 1990). Nilutamide also produced hyperplasia of Leydig cells, and resulted in a post-implantation loss of embryos when treated male rats were mated with female rats (Dhar & Setty 1990).

In 16 male subjects undergoing androgen blockade with nilutamide 100 to 300 mg/day for 8 weeks for male to female gender reassignment, prostate volume was not changed (de Voogt et al. 1987).

1.3 Activity in Androgen-Dependent Tumour Cell Lines

In a human androgen-dependent tumour model, namely human breast tumour cells (T-47D cells) containing androgen receptors and transfected with an androgen-dependent gene (MMTV-CAT), nilutamide displayed no agonist activity but inhibited chloramphenicol acetyltransferase activity induced by dihydrotestosterone (Gaillard-Moguilewsky 1991). Nilutamide 0.5mg reduced the incidence and development of the androgen-dependent tumour SC 115 in mice. All intact mice

developed tumours within 14 days of inoculation with SC 115 compared with 70 days after inoculation for all castrated mice. The administration of nilutamide to castrated mice further delayed the development and reduced the incidence of tumours, so that 120 days after inoculation only 44% had tumours, although of similar size (Gaillard-Moguilewsky 1991; Moguilewsky et al. 1987).

The lymph node carcinoma of the prostate (LNCaP) cell line is androgen-dependent. The androgen R1881 at a concentration of 0.1 nmol/L stimulated the growth of LNCaP cells, as indicated by a 3- to 4-fold increase in DNA content (Schuurmans et al. 1990) and [³H]thymidine uptake (Wilding et al. 1989). Unexpectedly, similar increases in DNA content or [³H]thymidine uptake were produced by nilutamide, hydroxyflutamide and cyproterone acetate at concentrations of 30 to 200 nmol/L, but not by ICI 176334 or triamcinolone acetonide (Olea et al. 1990; Schuurmans et al. 1990; Veldscholte et al. 1992; Wilding et al. 1989). However, the androgen receptor of LNCaP cells is mutated in the steroid binding region. This mutation might be responsible for the ability of the antiandrogens to stimulate this cell line and may not be relevant for advanced metastatic cancer. Alternatively, it is also possible that advanced metastatic cancer may undergo a stage whereby stimulation by antiandrogens may occur.

1.4 Inhibition of Androgen Synthesis

In addition to its effects at the androgen receptor, nilutamide may also inhibit the synthesis of androgens. An *in vitro* study using microsomes from rat testis demonstrated that nilutamide at high concentrations (> 50 µmol/L) competitively inhibited the synthesis of the testicular microsomal enzymes 17α-hydroxylase and 17,20-lyase (Ayub & Levell 1987) as does hydroxyflutamide, the active metabolite of flutamide (see section 2). However, the prodrug flutamide and cyproterone acetate were competitive inhibitors only of 17,20-lyase.

Evidence for a role of nilutamide in the inhibition of androgen synthesis has been provided by

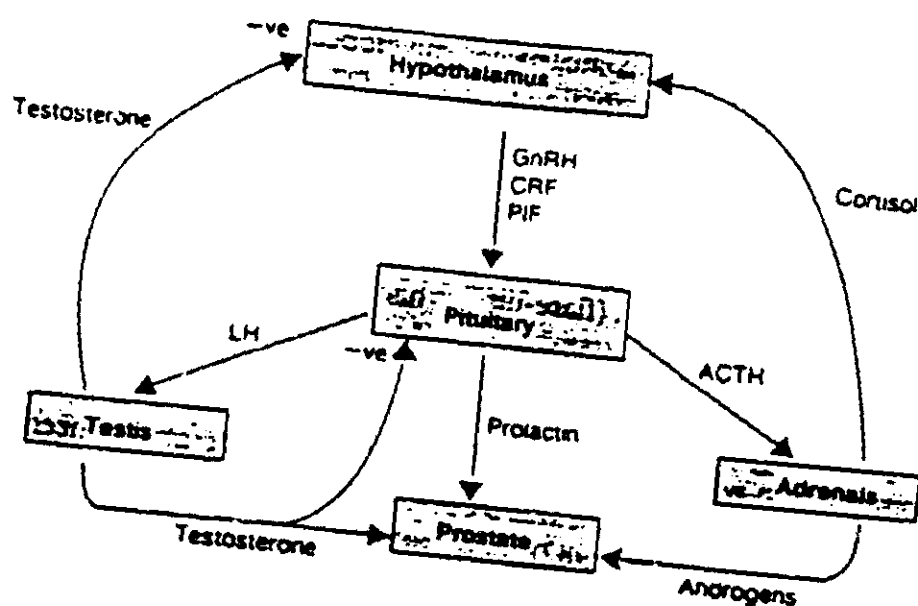


Fig. 2. Simplified hypothalamic-pituitary-adrenal-testicular axis: ACTH = adrenal corticotrophic hormone; CRF = corticotrophin-releasing factor; LH = luteinising hormone; PIF = prolactin-inhibiting factor; -ve = negative feedback.

long term studies in surgically castrated patients with histologically confirmed prostatic cancer. In castrated patients, nilutamide 150 to 300 mg/day in divided doses significantly reduced the levels of the adrenal androgen precursor steroids, dehydroepiandrosterone (DHEA) and DHEA sulfate, to 65 and 75%, respectively, of the levels achieved after castration alone (Bélanger et al. 1984; Fiet et al. 1990). In patients receiving a GnRH agonist and nilutamide, plasma levels of DHEA and DHEA sulfate were reduced to 64 and 45% of control (GnRH agonist alone) values (Labrie et al. 1984). A concomitant decrease in 17,20-desmolase activity has also been observed (Bélanger et al. 1984), suggesting that any inhibition of adrenal androgen synthesis occurs at the level of 17,20-desmolase activity. Cortisol levels were not significantly altered (Bélanger et al. 1984; Fiet et al. 1990). Further, there were no significant differences in plasma levels of LH, follicle-stimulating hormone (FSH), prolactin, testicular androgen or estradiol in patients receiving nilutamide or placebo (Fiet et al. 1990). Therefore, further evidence is required before definite conclusions can be made on whether nilutamide is capable of inhibiting adrenal androgen biosynthesis without affecting the biosynthesis of glucocorticoids.

1.5 Effects on Lipids

It is known that in men estrogens produce adverse cardiovascular effects, possibly through changes in lipoprotein profiles (Blackard et al. 1970), and that androgenic steroids decrease high density lipoprotein (HDL) levels. However, the effect of androgens on low density lipoproteins (LDL) remains to be determined. Complete androgen blockade using a GnRH agonist and an antiandrogen has made it possible to determine more precisely the effects of androgens on plasma lipoprotein profiles.

Moorjani and colleagues (1987) compared the plasma lipoprotein profiles of 17 patients with prostatic cancer receiving oral nilutamide 200 mg/day in combination with subcutaneous buserelin 500 µg/day with those of 62 matched elderly volunteers. No significant differences were observed between patients with prostatic cancer and controls before the institution of therapy. After 4 weeks of therapy, mean plasma testosterone levels had decreased to 12% of baseline levels (then ranged between 5 to 7% of baseline levels), dihydrotestosterone to 16% of baseline levels, and 17β-estradiol to 35% of baseline levels. In line with these decreases, after 16 weeks of treatment apolipoprotein

B (apo-B) levels in the very low density lipoprotein (VLDL) fraction decreased significantly to 74% of baseline levels, and in the LDL fraction increased significantly to 110% of baseline levels. There were significant increases in the concentration of cholesterol (117% of baseline) and apolipoprotein-A (113% of baseline) in the HDL fraction. At weeks 4 and 8 there were significant reductions in the ratios of total to HDL cholesterol and LDL to HDL cholesterol, although this decrease was no longer significant at weeks 12 and 16. Plasma phospholipid, triglyceride and apo-B levels did not change significantly. Total plasma cholesterol levels increased slowly, reaching statistical significance only at week 16 (6% above baseline level).

Long term studies will be required to confirm these favourable effects on plasma lipoproteins, and determine whether combination therapy with nilutamide and a GnRH agonist may translate into a better cardiovascular prognosis for patients with prostatic cancer.

1.6 Mechanism of Action

Various actions of nilutamide suggest it will have therapeutic efficacy in cancer of the prostate. The most important of these appears to be inhibition of the binding of androgens to the androgen receptors in the prostate (Gaillard-Moguilewsky 1991; Raynaud et al. 1979). Such binding stimulates the proliferation of prostatic cancer tissue.

Synthesis of adrenal androgens may also be inhibited by nilutamide (Ayub & Levell 1987). However, since the androgen receptors on the target tissue will be blocked by nilutamide, the relative contribution of any such action to the beneficial effects of nilutamide in patients with prostate cancer is likely to be small.

Nilutamide may exert a direct agonistic effect on GnRH receptors, potentiating the reduction in prostate and testis weight achieved with GnRH agonists (Lefebvre et al. 1982; Moguilewsky & Tournemine 1988). For this reason, the combination of nilutamide with a GnRH agonist has the potential for greater efficacy than a GnRH agonist alone. Additional benefits of nilutamide therapy are

the inhibition of the flare-up effects induced by the testosterone surge at the beginning of treatment with the GnRH agonist, and the inhibition of residual adrenal androgen activity.

An interesting action of nilutamide is the reduction in the incidence, and a delay in the appearance, of androgen-dependent tumours, such as SC 115 cells (Gaillard-Moguilewsky 1991). This opens up the possibility that nilutamide may have direct inhibitory effects on the tumour itself. However, in contrast to these findings, the androgen-sensitive human prostate tumour cells, LNCaP-FCG, showed a clearcut proliferative response to nilutamide and other antiandrogens *in vitro*. In addition, several investigators have failed to show a correlation between the proliferative potency of the antiandrogens and the relative binding affinities. Therefore, it is possible that the beneficial effects of antiandrogens, including nilutamide, may not be entirely due to a direct interaction with their preceived tumour target cell (Olea et al. 1990).

2. Pharmacokinetic Properties

The pharmacokinetic profile of nilutamide has been studied in small numbers of volunteers (single doses) and patients with advanced prostate cancer (single and multiple dosing). Plasma nilutamide concentrations have been assayed using high performance liquid chromatography, with a lower detection limit of 50 µg/L (Pendyala et al. 1988).

After administration of single oral doses of nilutamide 100, 200 or 300mg to healthy young volunteers, maximum plasma concentrations (C_{max}) of nilutamide were 0.8, 1.6 and 2.3 mg/L, respectively (table II). The mean time to C_{max} (t_{max}) was 1.6 hours (range 1.5 to 1.8 hours). The distribution phase was short, followed by a log-linear elimination phase (Tremblay et al. 1987).

A more detailed pharmacokinetic study by Pendyala et al. (1988) in 12 patients aged 57 to 82 (mean, 71) years with advanced prostate cancer (stage D) involved administration of a single dose of [^{14} C]nilutamide 150 or 200mg followed 4 or 8 days later by treatment with nilutamide 150mg twice daily for 2 to 7 weeks ($n = 11$). Pharmacokinetic

Table II. Pharmacokinetic parameters of single-dose oral nilutamide in volunteers and in patients with advanced prostate cancer (after Pendyala et al. 1988; Tremblay et al. 1987)

Nilutamide dose (mg)	Age (mean) [years]	C _{max} (mg/L)	t _{max} (h)	AUC _{0-∞} (mg/L · h)	t _{1/2} (h)
Volunteers (n = 12)	18-25				
100		0.8	1.8	25	43
200		1.6	1.5	56	45
300		2.3	1.5	64	49
Patients (n = 12)	57-82 (71)				
150		0.9	2.8	39	56

Abbreviations: AUC_{0-∞} = area under the concentration-time curve from 0 hours to infinity; C_{max} = maximum plasma concentration; t_{max} = time to C_{max}; t_{1/2} = plasma elimination half-life.

kinetic parameters after the single dose of [¹⁴C]nilutamide (table II) showed wide interpatient variability, with mean values of 0.9 mg/L for C_{max}, 2.8 h for t_{max}, 39 mg/L · h for the area under the concentration-time curve (AUC) and 56 h for the plasma elimination half-life (t_{1/2}). These results were generally similar to those in young volunteers (table II). Steady-state plasma nilutamide concentrations of 4.4 to 8.5 mg/L were achieved within about 2 weeks of initiating treatment.

The nitro group on the benzene ring of nilutamide is the main site of metabolic breakdown (fig. 3), and is reduced first to an hydroxylamine and then to an amino group. Only one of the subsequent metabolites, formed by oxidation of a methyl group attached to the imidazolidinedione ring, has been shown to have noticeable pharmacological activity, albeit less than that of nilutamide; it is therefore probable that unchanged nilutamide is the main active compound (Tournemine et al. 1987).

The plasma elimination half-life of nilutamide in patients with prostate cancer ranged from 23 to 87 (mean 56) hours (table II) [Pendyala et al. 1988], suggesting that nilutamide can be given as a single daily dose.

Excretion of radioactivity in the faeces after a single dose of [¹⁴C]nilutamide was negligible (1.4 to 7% of total dose recovered after 4 to 5 days) in 3 patients and recovery in the urine was high (61.6% total radioactivity recovered at 5 days, 0.8% as unchanged drug), indicating that nilutamide is well

absorbed from the gastrointestinal tract and extensively metabolised (Pendyala et al. 1988). Plasma clearance appears to decrease with repeated doses, since the AUC for 1 dosing interval (AUC_{0-12h}) was significantly higher than AUC_{0-∞} for a single dose.

3. Therapeutic Efficacy in Prostate Cancer

As the growth of prostate cancer is at least partially dependent on androgen stimulation, treatment has been aimed mainly at inhibiting testicular androgen secretion by orchiectomy or administration of estrogens and, more recently, GnRH agonists. However, none of these treatments has a significant effect on adrenal androgens, which may play a role in disease progression (Raynaud 1988). The rationale for using an antiandrogen, such as nilutamide, in combination with orchiectomy or a GnRH agonist is to block the effects of androgens of adrenal origin – the concept of complete androgen blockade. Nilutamide has also been administered in combination with a GnRH agonist to suppress the clinical consequences of the initial rise in androgen levels observed with the latter, manifested as a worsening of clinical symptoms (e.g. urinary obstruction, pain – 'disease flare').

Antiandrogens also act on the hypothalamus where testosterone normally inhibits the release of GnRH through a negative feedback mechanism. In

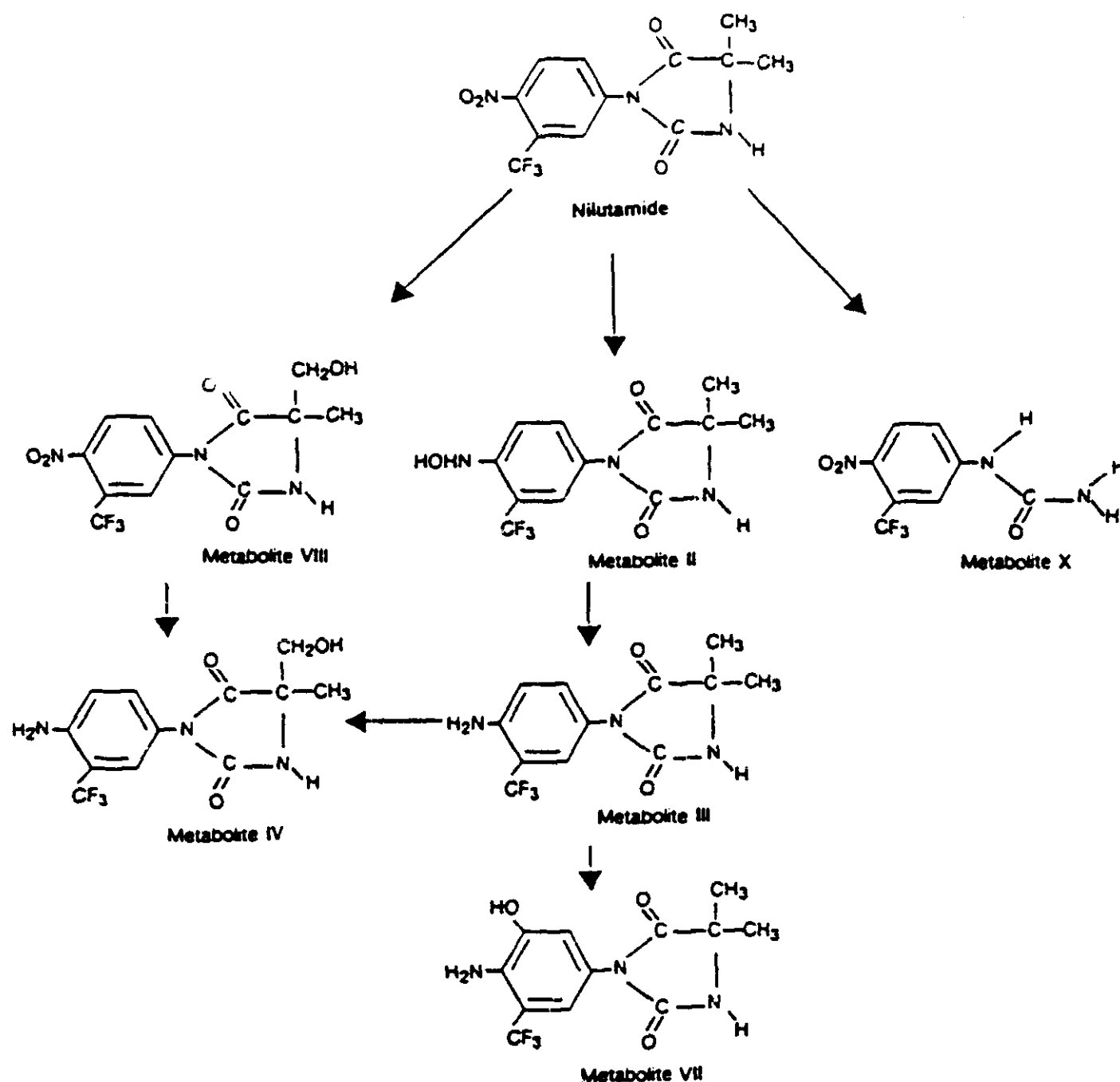


Fig. 3. Proposed metabolic pathway for nilutamide in humans. Metabolite VIII has some affinity for the androgen receptor, but its antiandrogen activity is less than that of nilutamide (after Creaven et al. 1991).

rats, nilutamide has been shown to produce an increase in plasma testosterone levels, which may eventually neutralise the effect of the drug (Raynaud et al. 1984). However, this may not be the case in humans. In 6 male volunteers undergoing male to female reassignment, serum testosterone levels rose steadily during 6 weeks of treatment with nilutamide 300 mg/day, after which no further changes occurred (Gooren et al. 1987). Similarly,

in previously untreated patients with prostate cancer receiving nilutamide monotherapy, a nonsignificant rise in serum testosterone levels was observed during the first month of therapy which plateaued thereafter (Decensi et al. 1991).

Because of these concerns, few data are available on the use of nilutamide alone in previously untreated patients, and most studies have investigated the efficacy of nilutamide in orchi-

ised patients, or in combination with a GnRH agonist. These trials have generally included previously untreated patients with stage C (nonmetastatic but extending beyond the prostate) or D (metastases present) prostate cancer. The design of each study was generally similar, but not all have utilised both objective [National Prostatic Cancer Project (NPCP)] and subjective response criteria. The most common subjective response criteria included bone pain and performance status [Eastern Cooperative Oncology Group (ECOG)] assessments.

Nilutamide was given orally in therapeutic trials.

3.1 Nilutamide Monotherapy

The efficacy of nilutamide monotherapy has been evaluated in an open multicentre study which included 26 patients with untreated metastatic prostate cancer, and 18 patients with metastatic disease and disease progression after orchiectomy or therapy with cyproterone acetate, a GnRH agonist, or estramustine. Respective objective partial response rates in untreated patients and those previously treated were 38.5 and 5.5%. Median progression-free survival and overall survival were 9 and 23 months, respectively, in the previously untreated group and 6 and 17 months in the treated group (Decensi et al. 1991). 47% of those who were sexually active before treatment claimed preservation of sexual function during nilutamide therapy, a factor which may be of importance for the quality of life of some patients. 13 previously untreated patients in whom disease progressed while receiving nilutamide were subsequently treated with a GnRH agonist (unspecified) ($n = 9$) or chemotherapy ($n = 4$). Five of the 9 GnRH agonist recipients achieved a partial response lasting 4 to 11 months. The small number of patients and the open trial design do not allow any clearcut conclusions to be drawn.

3.2 Combination Androgen Blockade

3.2.1 Nilutamide in Combination with Orchiectomy

In an open study performed in Japan (Akaza et al. 1991), an objective (complete plus partial) response rate of 85% was achieved among 40 patients

with stage C or D prostate cancer receiving nilutamide 150 or 300 mg/day after orchiectomy.

Several recently published randomised double-blind multicentre trials have compared nilutamide with placebo in patients with stage D prostate cancer who had undergone orchiectomy (table III). In all but one study, nilutamide in association with orchiectomy was significantly more effective than orchiectomy plus placebo in terms of objective responses. However, there has been no significant difference in favour of nilutamide in terms of improved survival, only trends.

These findings were confirmed in a meta-analysis of 7 double-blind studies comparing orchiectomy and nilutamide 300 mg/day with orchiectomy and placebo in 1056 evaluable patients (Bertagna et al. 1993). 50% of nilutamide recipients showed complete or partial disease regression compared with 33% of those receiving placebo ($p < 0.001$). Conversely, significantly fewer nilutamide than placebo recipients (21 vs 33%) showed disease progression within 6 months of orchiectomy. Bone pain improved in a significantly greater percentage of nilutamide vs placebo recipients (48 vs 34%) and the odds of progression (odds ratio 0.84) were significantly reduced in patients receiving nilutamide. The odds ratios for death from all causes (0.89) and from prostate cancer (0.90) were reduced in the nilutamide group, but the gain was not significant.

Relief of symptoms is an important goal in prostate cancer management. Brisset et al. (1987) reported that significantly more nilutamide (71 to 94%) than placebo recipients (44%) experienced bone pain relief. The percentage of patients with improved performance status was significantly higher among nilutamide recipients (80 to 100%) versus those receiving placebo (50%). There was also a trend in favour of greater improvements in these parameters among nilutamide recipients as noted by Namer et al. (1990), although the differences did not reach statistical significance. Bone pain improved in significantly more nilutamide recipients in the study by Béland et al. (1991) (fig. 4) and Janknegt et al. (1993); however, there were no significant differences in ECOG performance

Table III. Objective response rates (National Prostatic Cancer Project criteria) from multicentre, randomised, double-blind studies comparing nilutamide (N) with placebo (Pi) in surgically castrated patients

Reference	No. of patients	Treatment (mg/day)	Efficacy ^a				Survival		Comments
			CR	PR	SD	PD	overall (months)	progression-free rate (%)	
Beland et al (1991)	203	N 300 ^b	12	34	34	20	24	39	Follow-up 6-48 months N > PI response [*] N = PI survival
		PI	4	16	42	38	19	27	
Brisset et al. (1987)	195	N 150	61 ^c		20 ^d		22	42	Month 6 evaluation. N > PI response N = PI survival
		N 300	61 ^c		19 ^d		22	35	
		PI	33 ^c		34 ^d		24	40	
Janknegt et al. (1993)	457	N 300	41 ^c		22		28	Follow-up ≥ 18 months N > PI response ^{**} N = PI survival	
		PI	24 ^c		36		23		
Knönagel et al. (1989)	51	N 300	31 ^c		47 ^e		Follow-up 1 year N > PI response ^{***}		
		PI	10 ^c		15 ^e				
Namer et al. (1990)	125	N 300	2	67	22	9	Follow-up > 3 years N > PI response N = PI survival		
		PI	3	49	32	16			

a Percentage of patients with complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

b 100mg 3 times daily.

c Includes CR + PR or 'regression'.

d Defined as progression or nonresponders.

e Includes SD + PD.

Abbreviations and symbols: > indicates significantly greater efficacy than placebo; ≥ indicates tendency for greater efficacy; = indicates equivalent efficacy; * p = 0.001 for CR+PR; ** p < 0.001; *** p = 0.03 for PD.

status between the 2 groups. The subjective improvement rate was 89% for bone pain, 83% for dysuria and 46% for performance status in the study by Akaza et al. (1991).

3.2.2 Nilutamide in Combination with a GnRH Agonist

Several multicentre studies have evaluated the efficacy of nilutamide in combination with the GnRH agonist buserelin.

In 2 randomised double-blind multicentre studies involving a total of 84 evaluable patients receiving buserelin 500 µg/day, nilutamide 300 mg/day was significantly more effective than placebo in preventing the signs of 'disease flare' (Kuhn et

al. 1989; Navratil 1987). There was a 14% increase in disease regression in those receiving combination therapy, and although the difference was not significant, the mortality rate was lower in this group; after 12 months the progression-free rate was 63% in nilutamide plus buserelin recipients compared with 48% in those receiving buserelin plus placebo, with corresponding overall survival rates of 87 versus 80% (Navratil 1987).

Other studies of combination therapy have not included a placebo group but provide supportive data for the role of nilutamide in preventing 'disease flare' (Labrie et al. 1983, 1986; Navratil 1990). Labrie et al. (1983) reported data from various previously treated and untreated patients. 37 previ-

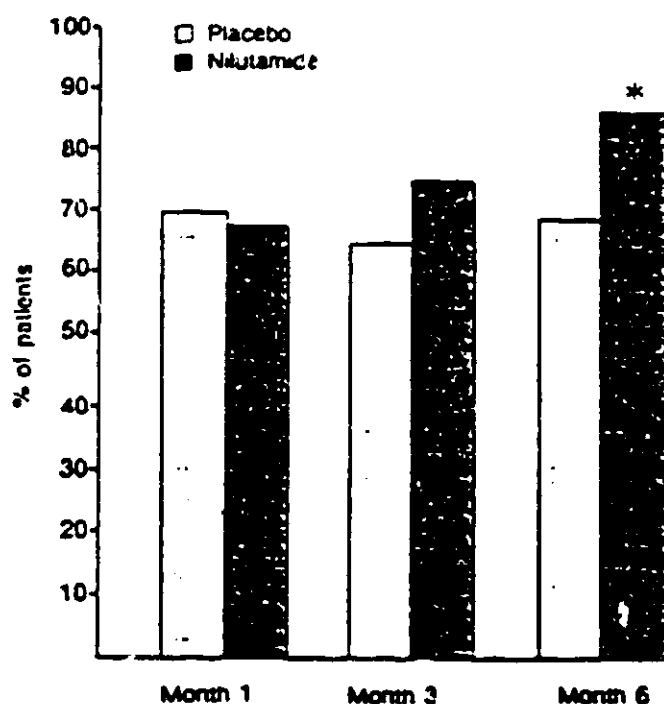


Fig. 4. Percentage of orchiectomised patients with improved bone pain during treatment with placebo or nilutamide 300 mg/day (data from Béland et al. 1991); * indicates $p < 0.05$ vs placebo.

ously untreated patients received buserelin plus nilutamide, 97% of whom showed a positive objective response (30 evaluable patients). The subjective response rate was 89%. However, the objective response rate was only 55% in 9 evaluable patients who had previously received diethylstilbestrol (stilboestrol), and was even lower (25%) in previously treated patients who had relapsed. Nevertheless, 'disease flare' was prevented.

Similar results were obtained in 15 patients receiving nilutamide and buserelin, where the objective and subjective (performance status) rates were both 86% (Migliari et al. 1991).

The efficacy of nilutamide in combination with leuprorelin has also been studied in a randomised, double-blind study (Crawford et al. 1990). 53% (90/169) of nilutamide recipients achieved a complete or partial response compared with 41% (67/164) of placebo recipients ($p = 0.015$). Patients receiving nilutamide also tended to have significantly greater improvements in metastatic pain and performance status. Median time to progression was slightly

longer (24.3 months) in patients receiving nilutamide, but the difference was not significant.

Thus, the combination of nilutamide with a GnRH agonist appears to offer a significant therapeutic advantage over therapy with a GnRH agonist alone.

3.3 Effect of Nilutamide on Tumour Markers

Measurement of prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) are often performed in studies when evaluating the response to therapy in patients with prostate cancer.

Several studies have shown greater improvements in one or both of these tumour markers in patients receiving nilutamide versus placebo following orchiectomy or in addition to a GnRH agonist (Béland et al. 1991; Brisset et al. 1987; Crawford et al. 1990; Janknegt et al. 1993; Namer et al. 1990; Navratil 1987). In a meta-analysis of 7 double-blind trials comparing orchiectomy and nilutamide with orchiectomy and placebo, PAP levels normalised in 66% of nilutamide versus 53% of placebo recipients ($p = 0.002$) whose pretreatment levels were abnormal (Bertagna et al. 1993).

PSA was reported to be a better disease progression indicator than PAP in patients receiving leuprorelin and flutamide: detection of recurrence was not significantly improved when PAP was measured as well (Dupont et al. 1991). Arai et al. (1990) examined the prognostic value of PSA in patients with prostate cancer who had undergone orchiectomy or who were receiving endocrine therapy. They found that the PSA level before treatment did not predict disease outcome; however, patients with a more rapid decrease in PSA had a longer progression-free interval. These patients could be identified after only 1 month's therapy. Determination of PSA therefore appears to be a good marker of response to therapy and for indicating disease progression (Arai et al. 1990; Dupont et al. 1991).

4. Tolerability

In surgically castrated patients nilutamide up to 300 mg/day and placebo have been associated with a similar incidence of general adverse events in

clinical trials, except for visual disturbances. Similarly, there does not appear to be a significant increase in the incidence of adverse events when nilutamide is added to a GnRH agonist (Kuhn et al. 1989).

Delayed adaptation to darkness after exposure to bright light (mean 9 min compared with an upper normal limit of 1.3 min) has been reported in 20 to 65% of patients who received nilutamide 150 to 300 mg/day (Béland et al. 1991; Boccardo et al. 1991; Briset et al. 1987; Harnois et al. 1986; Janknegt et al. 1993; Namer et al. 1990). In a meta-analysis of 7 double-blind placebo-controlled trials, visual disturbances occurred in 30% of nilutamide recipients compared with 6% of placebo recipients (data on file, Roussel Uclaf). Ophthalmological studies have shown an altered darkness adaptation curve in some patients, but no anatomical changes in the retina have been observed. In all patients, the delayed adaptation to darkness reversed on discontinuation of therapy, dosage reduction and in some patients spontaneously despite continued therapy. In a group of 15 patients evaluated after 6 months of uninterrupted therapy with nilutamide, the impairment in the dark adaptation objectively measured with Goldmann adaptometry was no longer significant (Migliari et al. 1991).

Hot flushes developed in 77% of nilutamide recipients who had been surgically castrated. This was not significantly different to the frequency (67%) in placebo recipients (Béland et al. 1991; Janknegt et al. 1993). Similarly, in patients receiving buserelin 500 µg/day, the frequency of hot flushes was not significantly different in those also given placebo (2 of 24) or nilutamide (4 of 22) [Navratil et al. 1987]. Decensi and co-workers (1991) reported hot flushes in 53% of patients receiving nilutamide monotherapy.

Although overt gynaecomastia has not been observed with the combination of nilutamide and a GnRH agonist, in one study 3 of 15 patients had breast swelling and pain (Migliari et al. 1991). Decensi et al. (1991) reported gynaecomastia in 44% of patients receiving nilutamide monotherapy.

Hepatotoxicity has been reported rarely with nilutamide. Transient reversible increases in trans-

aminase levels have been observed in 8% of patients in the first 3 months of treatment, while hepatitis has been reported in < 1% of patients (Béland et al. 1991; Boccardo et al. 1991; Decensi et al. 1991; Namer et al. 1990). Jaundice and pruritus resolved within 1 week and laboratory tests returned to normal within 6 weeks after discontinuation of nilutamide 150 mg/day in a 69-year-old man (Hannmel et al. 1991).

Nilutamide undergoes reduction in the liver by NADPH-cytochrome P-450 to the nitro anion free radical, which in the presence of oxygen can be regenerated into nilutamide, producing a superoxide anion. In rat hepatocytes, this redox cycling of nilutamide produces oxidative stress (Berson et al. 1991; Fau et al. 1991). Whether oxidative stress, secondary to nilutamide metabolism, is responsible for the hepatotoxicity seen in humans remains to be determined.

Interstitial lung disease has been reported in less than 2% of nilutamide recipients (Béland et al. 1991; Pfitzenmeyer et al. 1991) and may progress to pulmonary fibrosis (Seigneur et al. 1988) but is reversible on prompt treatment discontinuation (Jonville et al. 1992; Pfitzenmeyer et al. 1992). In addition, a Japanese study was discontinued because of interstitial pneumonia in 6 (12.8%) patients after the administration of nilutamide 150 to 300mg (Akaza et al. 1991). Nilutamide was confirmed as the causative factor by dechallenge and subsequent rechallenge in a 79-year-old man who developed interstitial pneumonitis after treatment with nilutamide for 42 days (cumulative dose 16.5g) [Akoun et al. 1990]. In isolated rat lung and lung microsomes, nilutamide has been shown to be metabolised (reduced) [Berger et al. 1992; Camus et al. 1991], via processes similar to those which occur in the liver. Pulmonary toxicity may result from these metabolic processes, although this requires confirmation in further studies.

The simultaneous development of liver and lung toxicity was observed in a 69-year-old man with prostate cancer receiving combination therapy with oral nilutamide 200 mg/day and subcutaneous GnRH ethylamide 500 µg/day, reducing to 250µg every other day (Gomez et al. 1992). After discon-

tinuing nilutamide, pulmonary and liver function tests improved.

Mild to moderate gastrointestinal adverse events, namely nausea and vomiting, have been reported in approximately 30% of patients receiving nilutamide, but these usually diminish after the first few weeks of treatment (Béland et al. 1991; Boccardo et al. 1991; Decensi et al. 1991; Namer et al. 1990). Treatment has rarely been stopped because of gastrointestinal adverse events (Boccardo et al. 1991; Decensi et al. 1991; Namer et al. 1990). Endoscopy in 15 patients who had received nilutamide therapy for 6 months did not reveal any change in the pre-existing pathology, such as hiatus hernia or gastritis, even in patients who subsequently complained of nausea and abdominal discomfort (Migliari et al. 1991).

Alcohol intolerance resulting in a disulfiram-like reaction during nilutamide therapy has been reported in up to 20% of patients (Béland et al. 1991; Boccardo et al. 1991; Brisset et al. 1987; Decensi et al. 1991).

Pruritus, dizziness and headache have been reported occasionally with nilutamide (Béland et al. 1991). One case of exfoliative dermatitis requiring treatment withdrawal has been reported (Migliari et al. 1991).

In a report of an attempted suicide, a 79-year-old man ingested 13g of nilutamide, i.e. 43 times the therapeutic dose (Rouger-Barbier et al. 1989). He underwent gastric lavage. Moderate vomiting and diarrhoea were noted in the first 12 hours. No alterations in laboratory parameters or chest x-ray were observed.

Since nilutamide is metabolised by the cytochrome P-450 system, and may also directly inhibit cytochrome P-450 activity at therapeutic doses, the metabolism of other drugs may be altered. Indeed, in rats nilutamide increased hexobarbital sleeping time and the anticoagulant effect of warfarin (Babany et al. 1989). However, no similar effects have been reported in clinical trials to date.

Nilutamide produced favourable effects on plasma lipid profiles (see section 1.5), giving it a potential advantage over other endocrine therapies

which may produce adverse effects on the plasma lipid profile (Blackard et al. 1970).

Overall, nilutamide appears to be a reasonably well tolerated drug in most patients, even in overdose. The profile of adverse events is similar to that observed with flutamide except for visual disturbances and, rarely, pneumonitis with nilutamide, and severe diarrhoea with flutamide.

5. Dosage and Administration

Nilutamide 300 mg/day for the first month then 150 mg/day orally has been used in the treatment of prostatic cancer in untreated patients in combination with orchiectomy or a GnRH agonist. Although initially used in divided doses (every 8 hours), the half-life of nilutamide (mean 56 hours) is long enough to allow once-daily dosing. Indeed, nilutamide has been shown to be effective and acceptably tolerated as a single daily dose, which is important for compliance, particularly in the elderly population in whom the drug is most likely to be used. It will be important to discuss with individual patients any problems they may be experiencing when taking nilutamide, or indeed any antiandrogen, in order to prevent noncompliance, which may lead to disease progression. In addition, physicians should be alert to the possibility that hepatotoxicity or interstitial pneumonitis may develop.

6. Place of Nilutamide in Therapy

Since the observation by Huggins and Hodges (1941) that androgens promote the growth of both normal and cancerous prostatic tissue, much effort has gone into eliminating the source of androgens in patients with prostatic cancer. This has been achieved predominantly through surgical castration or chemically with the use of estrogens. However, estrogens are associated with a number of adverse reactions, such as cardiovascular complications, making them unsuitable for long term therapy, while surgical castration is often associated with significant psychological trauma and permanent loss of sexual potency.

More recently, the GnRH agonists have been shown to produce reductions in serum testosterone levels equivalent to those achieved with castration (e.g. Leuprolide Study Group 1984) without the adverse effects associated with estrogens. GnRH agonists act at the pituitary level to inhibit the release of LH through 'down-regulation' of GnRH receptors (fig. 2). However, before this down-regulation is achieved, an initial 'flare' of testosterone levels and consequently of disease activity occurs (Chrisp & Sorkin 1991; Filicori & Flamigni 1988; Fraser 1984).

Despite the initial success of the above treatment regimens, many patients with prostatic tumours relapse (Resnick & Grayhack 1975). A possible explanation for this is the presence of circulating androgens of adrenal origin, which are not affected by the above treatments (Labrie et al. 1984). Nilutamide, by acting at the androgen receptor, blocks the effects of androgens on the prostate and hence has the potential to limit the adverse prostatic effects caused by the testosterone 'flare' associated with the initial use of GnRH agonists and that caused by adrenal androgens. However, in addition to acting at target tissues, nilutamide blocks androgen receptors in the pituitary, thereby inhibiting the negative feedback effect of testosterone. It has been hypothesised that the unopposed production of testosterone may eventually cause disease progression. For these reasons, nilutamide is given in combination with a GnRH agonist or surgical castration. Nevertheless, there have been few trials of nilutamide monotherapy. In one such trial, nilutamide produced partial responses in 38.5 and 5.5% of previously untreated and treated patients, respectively. A potential advantage of nilutamide monotherapy over chemical or surgical castration is the maintenance of sexual function in just under half of the patients. However, this trial was not double-blind or placebo-controlled, and only involved a small number of patients.

In combination with surgical castration, nilutamide has produced objective (complete + partial) response rates of up to 85%; improvements in bone pain, urinary obstruction, performance status

and tumour markers have also been reported. High response rates (up to 97%) have been observed in patients receiving the combination of nilutamide and a GnRH agonist. Response rates have generally been significantly higher in patients receiving nilutamide after orchiectomy or with a GnRH agonist compared with those undergoing orchiectomy or receiving a GnRH agonist alone. A trend in favour of improved survival with the addition of nilutamide has also been suggested, although improvements have not achieved statistical significance.

Nilutamide was generally well tolerated. Most of the adverse events reported were consistent with those reported with other endocrine therapies. However, nilutamide produces a reversible delayed adaptation to darkness after exposure to bright light in about 30% of patients. The plasma lipid profile is favourably affected by nilutamide. Interstitial lung disease is a very rare adverse event which must lead to discontinuation of treatment for subsequent reversal of toxicity.

Because of its long plasma elimination half-life (56 hours), nilutamide offers the convenience of once-daily dosing, and the subsequent benefits for compliance that this brings. This is particularly important in the elderly population in whom the drug is most likely to be used.

Thus, treatment with castration in combination with an antiandrogen appears to offer significant advantages in terms of initial response over either agent alone. But, direct comparisons of nilutamide and flutamide in combination with a GnRH agonist or orchiectomy are required.

However, in the absence of such comparisons, nilutamide appears to be associated with both advantages (long half-life) and disadvantages (visual adverse reactions in some patients) over flutamide. For those patients for whom compliance is a problem, as in the elderly population, the use of nilutamide in combination with orchiectomy would seem an attractive option.

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NILUTAMIDE FOR PROSTATE CANCER SUMMARY OF NDA

IV. DESCRIPTION OF CLINICAL PROGRAM

A. OVERVIEW

The controlled clinical trials of nilutamide in combination with surgical or medical castration reported in this NDA comprise 10 double-blind, placebo-controlled, parallel-group studies (Study Nos. FF/86/908/01, GHBA-606, CDN/83/908/05, F/82/908/03, F/82/908/01, F/84/908/01, CH/85/908/05, ZA/85/908/02, FF/86/ANA/001, and F/85/908/10). These studies were conducted to evaluate the efficacy and safety of nilutamide in combination with surgical (bilateral orchiectomy) or medical (LHRH agonist) castration in the treatment of patients with metastatic prostate cancer who were previously untreated. Study No. F/82/908/01 also evaluated the effects of nilutamide in combination with diethylstilbestrol. Study No. F/85/908/10 is also a clinical pharmacology study in that it evaluated the antiandrogenic effects of nilutamide in counteracting the peak of testosterone induced during the early phase of LHRH-agonist administration and on hormonal parameters.

Study Nos. FF/86/908/01 and GHBA-606 were designed to study best objective response, time to progression, and survival as the main efficacy criteria. These are the primary adequate and well-controlled studies. Seven of the eight other studies were designed to study best objective response as the main efficacy criterion. Study No. F/85/908/10 was a 1-month study designed to evaluate the efficacy of nilutamide in inhibiting the adverse effects observed at the start of treatment of prostatic cancer with an LHRH agonist (buserelin). These eight studies are supportive adequate and well-controlled studies.

Two other double-blind, placebo-controlled studies were conducted to evaluate the effects of nilutamide in combination with orchiectomy in the treatment of patients with Stage C or D prostate cancer in whom hormonal therapy had failed (Study Nos. F/83/908/01 and F/84/908/03). Data from these two studies were combined for analyses because of the similarity of the protocols and case report forms. The results of the combined data showed that in previously treated patients, nilutamide (300 mg/day) in combination with orchiectomy provided no additional benefit compared with that of orchiectomy alone.

The proposed labeling in this NDA submission is therefore limited to nilutamide in combination with surgical or medical castration in previously untreated patients with metastatic prostate cancer. The focus of this efficacy summary will be on the 10 studies conducted to evaluate the effects of nilutamide in combination with bilateral orchiectomy or medical castration with an LHRH agonist in patients with metastatic prostate cancer who were previously untreated. Some design features of these 10 controlled studies are shown in the following table.

Design Features of the Ten Double-Blind, Placebo-Controlled Studies

Study No.	Treatment	Duration (Double-Blind Period)
Primary Studies		
FF/86/908/01	Nilutamide 300 mg ^a + orchiectomy vs. Placebo + orchiectomy	18 months ^b
GHBA-606	Nilutamide 300 mg ^a + leuprolide vs. Placebo + leuprolide	18 months ^b
Supportive Studies		
CDN/83/908/05	Nilutamide 300 mg + orchiectomy vs. Placebo + orchiectomy Nilutamide 300 mg + buserelin (open)	24 months ^b
F/82/908/03	Nilutamide 150 mg + orchiectomy vs. Nilutamide 300 mg + orchiectomy vs. Placebo + orchiectomy	24 months ^b
F/82/908/01	Nilutamide 300 mg + orchiectomy vs. Placebo + orchiectomy Nilutamide 300 mg + buserelin vs. Placebo + buserelin Nilutamide 300 mg + DES ^c vs. Placebo + DES	24 months ^b
F/84/908/01	Nilutamide 300 mg + orchiectomy vs. Placebo + orchiectomy	24 months ^b
CH/85/908/05	Nilutamide 300 mg + orchiectomy vs. Placebo + orchiectomy	24 months ^b
ZA/85/908/02	Nilutamide 300 mg + orchiectomy vs. Placebo + orchiectomy	24 months ^b
FF/86/ANA/001	Nilutamide 300 mg ^a + orchiectomy vs. Placebo + orchiectomy	6 months
F/85/908/10	Nilutamide 300 mg + buserelin vs. Placebo + buserelin	28 days

^a Nilutamide 300 mg/day for 1 month, then 150 mg/day thereafter.

^b Or until progression or death.

^c Diethylstilbestrol

B. PRIMARY STUDIES

Study Nos. FF/86/908/01 and GHBA-606 were double-blind, parallel-group, placebo-controlled, randomized studies conducted to evaluate the efficacy and safety of nilutamide in combination with orchiectomy (in Study FF/86/908/01) or leuprolide (in Study GHBA-606) and the long-term safety and tolerance of nilutamide in the treatment of prostate carcinoma (Stage D₂). In Study FF/86/908/01, starting on the day after orchiectomy, patients received either nilutamide (300 mg/day p.o. for 1 month followed by 150 mg/day p.o. thereafter) or placebo p.o.; patients who did not objectively progress and who did not have significant adverse experiences during the first 18 months continued the double-blind medication until objective disease progression, the occurrence of an adverse experience, or any other event necessitating withdrawal from the study. Patients whose disease progressed

while receiving nilutamide could continue nilutamide (150 mg/day, p.o.) on an open-label basis following study discontinuation, while patients who had been receiving placebo were not permitted to receive nilutamide. Enrollment dates were June 1986 through February 1988; and cutoff date for data collection was 31 August 1989. In Study No. GHBA-606, patients received 18 months of treatment with either nilutamide (300 mg/day for the first month followed by 150 mg/day thereafter) plus leuprolide 1 mg/day subcutaneously or placebo plus leuprolide 1 mg/day. Patients who did not objectively progress (responders) and who did not have significant adverse experiences or toxicity during the first 18 months were permitted to continue the double-blind medication for an extended period. If objective progression occurred during the double-blind period, patients who had been receiving nilutamide were permitted to continue nilutamide on an open-label basis, while patients who had been receiving placebo were not permitted to receive nilutamide. Enrollment dates were September 1986 through June 1988; and the cutoff date for data collection was 28 February 1990.

Patients in both primary studies were evaluated for efficacy and safety at routine intervals as indicated in the following flowcharts of study events.

Flowchart of Study Events (FF/86/908/01)

		Part A					Part B ^a
Study Month	0	1	3	6	12	18 ^e	
Visit Number	1	2	3	4	5	6	
Written Informed Consent	x ^c						
Medical History	x ^c						
Physical Examination							
Full	x ^c			x	x	x	x
Abbreviated		x	x				
Biopsy	x ^c						
Pain Assessment	x	x	x	x	x	x	x
Performance Status	x	x	x	x	x	x	x
Radiologic Evaluations							
IVP/Nephrogram ^b	x ^c		x ^h	x ^{d,e}	x ^{d,e}	x ^{d,e}	x ^{d,e}
Chest X-Ray	x ^c		x ^h	x	x	x	x
Bone Scan	x ^c		x ^h	x	x	x	x
Ultrasound ^c	x ^c		x ^h	x	x	x	x
X-Ray ^f	x ^c		x ^h	x	x	x	x
Cat Scan ^c	x ^c		x ^h	x	x	x	x
Lymphography ^c	x ^c		x ^h	x	x	x	x
Laboratory Evaluations							
Hematology ⁱ	x ^c	x	x	x	x	x	x
Prothrombin Time	x ^c	x	x	x	x	x	x
Blood Chemistries	x ^c	x	x	x	x	x	x
Urinalysis	x ^c	x	x	x	x	x	x
Prostate Acid Phosphatase/PSA	x ^c	x	x	x	x	x	x
Testosterone	x ^c						
Overall Evaluation (NPCP)			x ^h	x	x	x	x
Global Evaluations	x	x	x	x	x	x	x
Dispense Medication	x	x	x	x	x	x ^j	x ^j

^a Extended treatment, patients evaluated at 6-month intervals.

^b Another appropriate technique (e.g., ultrasound) may be substituted if patient allergic to injection dye or if other technique preferred.

^c May be performed within 4 weeks prior to Visit 1.

^d To be performed if previously abnormal or to evaluate suspected new structural abnormalities.

^e If required to evaluate metastatic involvement.

^f Two or three representative sites in which bone scan is positive are to be followed throughout the study. X-ray may also be used to characterize possible new areas of metastatic involvement.

^g If patient discontinued prematurely, all these assessments must be completed.

^h Evaluation performed only if subjective progression (modified NPCP criteria) has occurred and it is necessary to determine whether objective progression (modified NPCP criteria) has occurred.

ⁱ Additional blood samples for hematology are to be obtained at Months 9 and 15, as well as every three months during Part B and the open-label phase.

^j To be dispensed only if the patient is continuing in the study.

Flowchart of Study Events (GHBA-606)

Study Month Visit Number	0 1	Part A					Part B ^a
		1 2	3 3	6 4	12 5	18 ^b 6	
Written Informed Consent	x ^c						
Medical History	x ^c						
Physical Examination							
Full	x ^c			x	x	x	
Abbreviated		x	x				x
Biopsy	x ^c						
Pain Assessment	x	x	x	x	x	x	x
Performance Status	x	x	x	x	x	x	x
Radiologic Evaluations							
IVP/Nephrogram ^b	x ^c		x ^b	x ^{d,e}	x ^{d,e}	x ^{d,e}	x ^{d,e}
Chest X-Ray	x ^c		x ^b	x	x	x	x
Bone Scan	x ^c		x ^b	x	x	x	x
Ultrasound ^e	x ^c		x ^b	x	x	x	x
X-Ray ^f	x ^c		x ^b	x	x	x	x
Cat Scan ^e	x ^c		x ^b	x	x	x	x
Lymphography ^e	x ^c		x ^b	x	x	x	x
Laboratory Evaluations							
Hematology ⁱ	x ^c	x	x	x	x	x	x
Prothrombin Time	x ^c	x		x	x	x	x
Blood Chemistries	x ^c	x	x	x	x	x	x
Urinalysis	x ^c	x	x	x	x	x	x
Acid Phosphatase/PSA/ Testosterone/Nilutamide	x ^c	x	x	x	x	x	x
Overall Evaluation (modified NPCP)			x ^b	x	x	x	x
Global Evaluations	x	x	x	x	x	x	x
Dispense Medication	x	x	x	x	x	x ^j	x ^j

^a Extended treatment, patients evaluated at 6-month intervals.

^b Another appropriate technique (e.g., ultrasound) may be substituted if patient allergic to injection dye or if other technique preferred.

^c May be performed within 4 weeks prior to Visit 1.

^d To be performed if previously abnormal or to evaluate suspected new structural abnormalities.

^e If required to evaluate metastatic involvement.

^f Two or three representative sites in which bone scan is positive are to be followed throughout the study. X-ray may also be used to characterize possible new areas of metastatic involvement.

^g If patient discontinued prematurely, all these assessments must be completed.

^h Evaluation performed only if subjective progression (modified NPCP criteria) has occurred and it is necessary to determine whether objective progression (modified NPCP criteria) has occurred.

ⁱ Additional blood samples for hematology are to be obtained at Months 9 and 15, as well as every three months during Part B and the open-label phase.

^j To be dispensed only if the patient is continuing in the study.

The following table summarizes the demographic and pretreatment characteristics of patients in the primary studies.

**Demographic and Pretreatment Disease Characteristics
(Evaluable Patients in Primary Studies)**

Characteristics	Number (%) of Patients	
	FF/86/908/01	GHBA-606
Age (years)	N=423	N=390
< 50	()	4 (1)
50-59	25 (6)	53 (14)
60-69	128 (30)	177 (45)
70-79	205 (48)	138 (35)
≥ 80	64 (15)	18 (5)
[Mean]	[71.5]	[67.0]
[Range]		
Race	N=423	N=390
White	385 (91)	304 (78)
Black	15 (4)	75 (19)
Other	23 (5)	11 (3)
Duration of Stage D₂ Diagnosis (months)	N=423	N=423
[Mean]	[1.8]	[1.8]
[Range]		
Metastatic Related Pain	N=422	N=390
No Pain	150 (36)	153 (39)
Pain	272 (64)	237 (61)
Karnofsky Performance Status	N=422	N=390
Normal (80-100)	271 (64)	333 (85)
Impaired (10-70)	151 (36)	56 (14)
Prostatic Acid Phosphatase*	N=265	N=305
Normal	61 (23)	48 (16)
Elevated	204 (77)	257 (84)
Prostate Specific Antigen*	N=267	N=267
Normal	8 (3)	4 (1)
Elevated	259 (97)	263 (99)
Alkaline Phosphatase	N=418	N=379
Normal	139 (33)	195 (51)
Elevated	279 (67)	184 (49)

Note: Percentages may not sum to 100% because of rounding.

* Central Laboratory Evaluation

In Study No. FF/86/908/01, 457 patients with a primary diagnosis of previously untreated metastatic prostate carcinoma (Stage D₂) were enrolled; 225 patients were randomized to orchiectomy and nilutamide and 232 were randomized to orchiectomy and placebo. A total of 350 patients discontinued from the double-blind phase of the study, 199 (85 nilutamide, 114 placebo) because of objective progression, 28 (13 nilutamide, 15 placebo) because of subjective progression, 55 (35 nilutamide, 20 placebo) because of adverse experiences including intercurrent events, and 68 (35 nilutamide, 33 placebo) because of other reasons. Two hundred seven of the 225 (92%) nilutamide patients and 216 of the 232 (93%) placebo patients were judged evaluable for efficacy analysis.

In Study No. GHBA-606, 411 patients with a primary diagnosis of previously untreated metastatic prostate carcinoma (Stage D₂) were enrolled in the study. In the double-blind phase, 209 patients were randomized to receive the combination of nilutamide and leuprolide, and 202 were randomized to receive placebo plus leuprolide. A total of 292 patients discontinued from the double-blind phase of the study, 153 because of objective progression of disease (73 nilutamide, 80 placebo), 37 because of subjective progression (20 nilutamide, 17 placebo), 65 because of adverse experiences including intercurrent events (41 nilutamide, 24 placebo), and 37 because of other reasons (18 nilutamide, 19 placebo). One hundred ninety-seven (94%) of the 209 nilutamide patients and 193 (96%) of the 202 placebo patients were judged evaluable for the efficacy analysis.

C. SUPPORTIVE STUDIES

The remaining eight controlled clinical studies had different dosing schedules from the primary studies but similar flowchart of study events and provide support for the efficacy and safety conclusions reached in the primary studies. Six of the eight supportive studies were randomized, double-blind, placebo-controlled trials of nilutamide in combination with orchiectomy in patients with metastatic prostate cancer who were previously untreated and were included in a meta-analysis for efficacy (Study Nos. CDN/83/908/05, F/82/908/03, F/82/908/01, F/84/908/01, CH/85/908/05, and ZA/85/908/02). Because of the small number of patients, Study No. ZA/85/908/02 was not included in the analysis of short-term endpoints such as bone pain and tumor markers and was pooled with Study CH/85/908/05 in the analysis of long-term endpoints (progression-free and overall survival). The two nilutamide groups of Study F/82/908/03 (150 mg/day and 300 mg/day) were pooled. Study No. F/85/908/10 was not included because it was a 1-month study. Study No. FF/86/ANA/001 was not included because the selection of patients was different (patients with metastatic related pain) and the duration of follow-up was shorter (6 months). The analysis was restricted to proven Stage D prostate cancer patients. In addition, patients who had received a previous hormonal treatment for their cancer and those who had started nilutamide more than 3 months after orchiectomy were excluded.

D. OPEN-LABEL STUDIES

Four uncontrolled clinical studies (Study Nos. FF/305/ANA/02, J/87/908/02, and I/86/908/02 and the open-label buserelin arm of Study No. CDN/83/908/05) were conducted to evaluate the efficacy and safety of nilutamide in combination with orchiectomy in the treatment of patients with Stage C or D prostate cancer.

Study No. FF/305/ANA/02 evaluated the tolerance and efficacy of nilutamide (300 mg/day in three divided doses for 1 month, then 150 mg/day for the following 5 months) in 621 patients with metastatic prostate cancer who had been surgically castrated and who may have had previous hormonal therapy. Efficacy was analyzed in a subpopulation of 175 patients with Stage D prostate cancer who had never received previous hormonal therapy.

In Study No. J/87/908/02, 34 patients with metastatic prostate cancer who had no previous hormonal therapy were orchiectomized and treated with nilutamide 75 mg/day, 150 mg/day, or 300 mg/day for 12 weeks. In this study the overall efficacy was assessed as complete response, partial response, no change, stable disease, and progressive disease, according to the evaluation criteria proposed by Shimazaki group.

Study No. I/86/908/02 evaluated the safety and the clinical efficacy of nilutamide plus buserelin therapy. Nilutamide was administered at a daily oral dosage of 300 mg (six 50-mg tablets before breakfast) during the first month and 150 mg (three 50-mg tablets before breakfast) thereafter. The nilutamide administration was initiated 3 days before the combined treatment with buserelin to avoid the possibility of a flare-up reaction, which could be caused by an initial rise in patients' testosterone levels. The buserelin dosage was 500 µg TID subcutaneously for the first 7 days, then 400 µg TID intranasally thereafter. Fifteen patients with previously untreated, biopsy-proven advanced prostate cancer (Stage D) were enrolled.

In Study No. CDN/83/908/05, 46 patients with metastatic prostate cancer, previously untreated, who had refused surgical castration, were treated with nilutamide 300 mg/day and buserelin 500 µg/day subcutaneously for 30 days and 250 µg/day thereafter. The treatment duration was 24 months or until progression of the disease or death. Assessments for these patients were the same as for patients included in the randomized comparative arms of the study. Five patients were excluded from the efficacy analysis because of incorrect staging and previous hormonotherapy.

Results of the efficacy and safety analyses are presented in sections V (efficacy) and VI (safety).

Pharm/Tax

NDA 20-169

NILANDRON (ANANDRON, NILUTAMIDE)

SPONSORS: ROUSSEL UCLAF
Paris, France

G.H. BESSELAAR ASSOCIATES
Princeton, New Jersey

RECOMMENDATION -

Nilandron produces fatal liver toxicity in dogs and interstitial lung disease in rats at dose levels which produce plasma drug exposures (AUC) less than or equal to AUC exposures obtained in men on therapeutic doses. The preclinical toxicity studies do not support the safety of the therapeutic dose levels and, therefore, the NDA is non-approvable for Pharmacology/Toxicology.

Jeri El-Hage 2/5/95
Jeri El-Hage, Ph.D.

A Jordan
2/6

cc: NDA 20-169, HFD-510 NDA, HFD-502
HFD-510/ A Jordan/ J El-Hage/ *J. Fourcroy*
NDA 20-169

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NDA 20-169

February 3, 1995

Sponsor: Roussel-UCLAF, Paris, France
G.H. Besselaar Associates, Princeton, NJ 08540

Filing Date: April 15, 1994

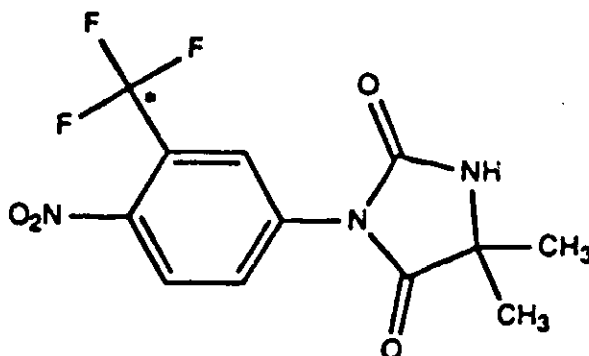
NDA Review of Pharmacology and Toxicology Data

Drug: Nilutamide (RU 23908)

Chemical name: 5, 5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione

Tradename: Nilandron (U.S.); Anandron (elsewhere worldwide)

Structure:



MW = 317.25

M.F. = $C_{12}H_{10}F_3N_3O_4$

Related IND:

Category: Nonsteroidal anti-androgen

Indication: Stage D 2 metastatic prostate cancer

Formulation: 50 mg tablet containing the following inactive ingredients- corn starch, lactose, providone, docusate sodium, magnesium stearate and talc.

Dose: 300 mg/day for 30 days followed by a 150 mg/day maintenance dose

Nilutamide (RU 23908) is a non-steroidal antiandrogen that competitively binds with androgen receptors. Its mechanism of action is binding and sequestration of androgen receptors preventing the binding of endogenous androgens and nuclear translocation of the hormone-receptor complex. Nilutamide is proposed for use in combination with surgical or medical (leuprolide) castration to prevent androgenic stimulation of prostate cancer by adrenal androgens.

Nilutamide (RU 23,908) is a non-steroidal antiandrogen active on the target organs of the androgens, namely, the prostate, seminal vesicles and the hypothalamic-pituitary axis.

- Nilutamide binds weakly and transiently with androgen cytosol receptors. The relative binding affinities of the antiandrogens for cytosolic steroid receptors are presented in Table 1 attached.

TABLE 1. RBAs of antiandrogens for the cytosol receptors of steroid hormones.

Incubation time at 0°C	AR*		PR	GR	MR	ER
	30min	24h	2h	4h	1h	2h
Cyproterone acetate	20	8	60	5	1	<0.1
Megestrol acetate	36	5	152	50	3	<0.1
Medroxyprogesterone acetate	54	40	125	70	6	<0.1
Chlormadinone acetate	35	5	175	38	1	<0.1
Flutamide	0.3	<0.1	<0.1	<0.1	<0.1	<0.1
Hydroxyflutamide	4.5	0.5	<0.1	<0.1	<0.1	<0.1
Anandron	4.5	0.5	<0.1	<0.1	<0.1	<0.1

* AR, PR, GR, MR and ER : androgen (rat prostate), progestin (rabbit uterus), glucocorticoid (rat thymus), mineralocorticoid (rat kidney) and estrogen (mouse uterus) receptors, respectively. The RBAs were measured as described previously (Ojasoo and Raynaud, 1978). The RBAs of testosterone, progesterone, dexamethasone, aldosterone and estradiol for AR, PR, GR, MR and ER were taken to be equal to 100.

TABLE 2. RBA of Anandron for AR in prostate cytosol from different species.

	Rat	Hamster	Dog	Man
RBA*	1.4 ± 0.3	10 ± 1	24 ± 5	9 ± 3
(n=)	(10)	(2)	(5)	(4)

* The RBA of Anandron was measured after incubation of prostate cytosol for 2 hr at 0°C with (3H) testosterone (for rat, hamster and dog) or with (3H) RU 1881 (human BPH) in the presence or absence of increasing concentrations of testosterone or of Anandron. (3H) RU 1881 (in the presence of a 100-fold excess of triamcinolone acetonide) was used as androgen ligand in the human prostate cytosol since it is not trapped by sex binding protein which can be present at varying concentrations in the different human samples tested. The RBA of Anandron was compared to that of testosterone taken as the reference hormone whatever the radioligand used (RBA of testosterone = 100).

- Nilutamide does not interact with estrogen, progesterone, glucocorticoid or mineralocorticoid receptors, and thus has no estrogenic, progestogenic, antiprogesterone, glucocorticoid, or antiglucocorticoid activity.
- Nilutamide is a weak inhibitor (20%) of human prostatic 5 α -reductase.
- Nilutamide does not bind to sex binding protein or transcortin.
- Nilutamide antagonizes the inhibitory effects of androgens on LHRH-induced LH release in the rat. In rats and in men, an increase in testosterone concentrations are observed after nilutamide treatment. Therefore, it is important to suppress increases in plasma testosterone by surgical or chemical castration.
- Nilutamide only partially inhibits (< 50%) the trophic effects of endogenous androgens regardless of dose or duration of treatment.
- The general pharmacologic effects of Nilutamide on the CNS, ANS, cardiovascular, respiratory, and gastrointestinal systems are summarized in Table 3.
- Of the four major Nilutamide metabolites RU 43,866, RU 45,018, RU 48,166 and RU 48,275, only RU 48,275 interacted with androgen receptors and produced dose-related antiandrogenic effects (only 20% as potent as parent compound).

Effects on Mono-oxygenase Activities

Data in rats, mice and humans suggest Nilutamide at the therapeutic dose produces inhibition of hepatic cytochrome P 450 activity. For example, hepatic cytochrome P450 activity was decreased by 50% in male rats dosed with nilutamide at concentrations $\geq$ 5 mg/kg/day. There were no drug effects on adrenal microsomal activity. Incubation of human liver microsomes with 110 μ M nilutamide (expected tissue concentration) inhibited hexobarbital hydroxylase (85%), benzphetamine N-demethylase (40%), benzo(a)pyrene hydroxylase (35%) and 7 ethoxycoumarin O-deethylase (25%) activities. Mice dosed with 15 and 30 μ mol/kg, ip nilutamide (comparable to therapeutic dose) displayed inhibition of hexobarbital hydroxylase.

Interaction of RU 23908 with "Retinol Binding Proteins"

Thirty to fifty percent of subjects treated with nilandron display dark adaptation disorders comparable to those found in hypovitaminosis A. The interactions of the antiandrogens nilutamide, flutamide and hydroxyflutamide and the androgen RU 181 with human prostate and serum retinoid binding proteins (RBP) were examined. At 10 and 20 μ M concentrations Nilutamide did not affect retinal binding to cellular (prostate) or plasma RBP.

Effects on Alcohol and Aldehyde Dehydrogenase

Alcohol intolerance has been reported in nilutamide-treated subjects. RU 23908 (10^{-6} to 10^{-3} M) had no effect on in vitro alcohol or aldehyde dehydrogenase activities.

TABLE 3

RU 23908
GENERAL PHARMACOLOGY

SUMMARY

RU 23908 was administered orally at 3-10-30-100 mg/kg (exceptionally <3 and > 100 mg/kg) and intravenously at 1-3-10 mg/kg.

1. CENTRAL NERVOUS SYSTEM

1-1 Spontaneous behaviour in mice and rats (p.o.)	<30 mg/kg no effect 100 mg/kg weak sedation 300-1000 mg/kg sedation and in some cases paralysis, dyspnea
Rectal temperature	>100 mg/kg : slight hypothermia
Lethality after 24h	300 mg/kg mice 6/10 Rats 1/6 1000 mg/kg mice 10/10
1-2 Rotarod test (p.o.)	100 mg/kg : very weak motor deficit
1-3 Anticonvulsant activity in mice	
Electroshock (p.o.)	} no effect
Pentylentetrazol (p.o.)	
1-4 Potentiation of barbiturate-induced sleeping time in mice (p.o.)	Barbital : not affected Hexobarbital : dose-dependent prolongation of sleeping time.
1-5 Interaction with 5-HTP in mice (p.o.)	no serotonergic effect
1-6 Antagonism of oxotremorine activity in mice (p.o.)	central or peripheral cholinergic effect : no antagonism hypothermia : slight potentiation (100 mg/kg)
1-7 Antagonism of reserpine-induced hypothermia in mice (p.o.)	no antagonism slight potentiation (100 mg/kg)
1-8 Amphetamine-induced stereotyped behaviour in rats (p.o.)	dose-dependent potentiation up to 0.3 mg/kg
1-9 Food consumption in dogs (p.o.)	not affected

2 CARDIOVASCULAR AND RESPIRATORY SYSTEMS

- 2-1 Haemodynamic and respiratory effect in anaesthetized dogs (i.v.)
 - 1-3 mg/kg : no abnormal changes
 - 10 mg/kg : SBP hypotension then hypertension - heart and respiratory rates : augmentation
 - ECG : some reversible alterations
- 2-2 Interaction with the pressor effects of mediators in anaesthetized dogs (i.v.)
 - vs adrenaline and noradrenaline virtually no influence
 - vs acetylcholine and histamine weak inhibition
- 2-3 Isolated guinea-pig atria
 - no chronotropic and no inotropic effect
 - isoprenaline responses : not affected

3 AUTONOMIC NERVOUS SYSTEM

- 3-1 Isolated guinea pig ileum
 - $1 \times 10^{-4}M$ non specific antagonism
 - 66-78% vs histamine, serotonin
 - bradykinin
 - 25% vs acetyl choline.
- 3-2 Isolated guinea pig seminal vesicle
 - $1 \times 10^{-4}M$: no adrenolytic effect

4 ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY

- 4-1 Acetic acid-induced writhing syndrome in mice (p.o.)
 - 3-10-30 mg/kg : no inhibition
 - 100 mg/kg inhibition 67%
- 4-2 Hot plate test in mice (p.o.)
 - no analgesic effect
- 4-3 Carrageenin-induced paw oedema in rats (p.o.)
 - 100 mg/kg : weak anti-inflammatory effect

5 GASTRO-INTESTINAL TRACT

5-1 Gastric secretion in pylorus ligated rats (p.o.) volume : no modification
pH : weak augmentation (100 mg/kg)

5-2 Gastric emptying in rats (p.o.) no effect

5-3 Gastro-intestinal propulsion in rats (p.o.) no effect

6 URINARY EXCRETION IN RATS (p.o.) 3 mg/kg : not affected
10-30-100 mg/kg : Na⁺, Cl⁻ decreased
100 mg/kg : K⁺ increased

7 BLOOD GLUCOSE LEVELS IN RATS (p.o.) no abnormal changes

8 BLOOD CLOTTING TIME TEST IN RATS (p.o.)
intrinsic effect no modification
interaction with warfarin dose dependent prolongation of prothrombine time

9 PLATELETS AGGREGATION IN VITRO IN RABBITS

ADP-induced aggregation no effect
Collagen-induced aggregation

Assessment of Nilutamide-induced Toxicity in Rat Hepatocytes In vitro

Nilutamide and flutamide (20, 40, 60, 80 and 100 ug/ml) were incubated with rat hepatocytes for 8 or 24 hours and effects on the release of intracellular enzymes (LDH, SGOT, SGPT) were monitored. Nilutamide was cytotoxic after 24 hours of incubation, with increased LDH at concentrations ≥ 60 ug/ml and increased SGOT at ≥ 80 ug/ml. Moderate rises in LDH only were observed after ≥ 80 ug/ml nilutamide for 8 hours. Flutamide produced an increase in all enzymes at 8 and 24 hours at concentrations ≥ 60 ug/ml.

Generation of Free Radicals during the Reductive Metabolism of the Nitroaromatic Compound, Nilutamide (J of Pharm Exp Ther. 257(2): 714, 1991)

Nilutamide is reduced by microsomal NADPH-cytochrome P-450 reductase into nitro-anion free radicals. In the presence of oxygen this nitro anion free radical undergoes redox cycling with oxygen, forming reactive oxygen species. Therefore, nitro-anion free radicals are capable of generating toxic reactive species under both anaerobic and aerobic conditions. The hepatic and pulmonary adverse effects of nilutamide are reminiscent of adverse effects observed with other nitroaromatic compounds (eg, nitrofurantoin). Flutamide does not form nitro-anion free radicals or superoxide anions.

Nilutamide Inhibition of Mephenytoin 4-hydroxylation in Male Rats and Human Liver Microsomes (Xenobiotica 21:12, 1559, 1991)

Nilutamide at the concentration expected in the human liver with therapeutic dosing, namely 100uM, inhibited mephenytoin hydroxylase by 40% in liver microsomes from untreated males and dexamethasone-treated rats of both sexes. Administration of Nilandron to rats (20 mg/kg, ip, bid) reproduces the plasma concentrations observed in humans receiving the therapeutic dose of Nilandron, and decreased the 24 hour urinary excretion of mephenytoin by 60%. Nilutamide (100uM) markedly inhibits mephenytoin 4-hydroxylase activity in human liver microsomes in vitro. Since therapeutic concentrations inhibit mephenytoin 4-hydroxylase activity in male rats and human liver microsomes, inhibition is likely to occur in men receiving nilutamide therapy for prostate cancer.

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

ADME data are summarized below. Individual studies are reviewed in the Pharmacology reviews which are appended.

Absorption

Nilutamide is well absorbed in all species. Oral absorption is 100% in rats and 98% in dogs. In dogs, 70% of absorbed radioactivity is attributable to nilutamide, demonstrating moderate presystemic metabolism. In man, only 3% of a radioactive dose is excreted in the feces, due to either lack of absorption or biliary excretion. In man, the proportion of absorbed radioactivity attributable to parent compound is unknown.

Distribution

The tissue distribution of total radioactivity was studied in the rat after multiple dosing with 20 mg/kg/day for 12 days. The data are summarized in Table IV (taken from NDA Vol 2.15). The tissue concentrations of radioactivity in the brain, lungs, prostate and eyes were roughly equivalent to plasma concentrations. Concentrations of radioactivity in the kidneys, liver and adrenal glands were significantly higher (2, 3 and 4 fold higher, respectively) than plasma levels.

TABLE IV: PLASMA ($\mu\text{g eq.ml}^{-1}$) AND TISSUE ($\mu\text{g eq.g}^{-1}$) CONCENTRATIONS OF TOTAL RADIOACTIVITY AFTER REPEATED ORAL ADMINISTRATION OF 20 mg.kg⁻¹ OF ¹⁴C-RU 23908 TWICE DAILY FOR 12 DAYS IN THE MALE RAT (mean $\pm$ standard error of the mean, n = 5).

	Day 1	Day 2	Day 4	Day 8	Day 12	ANOVA	TUKEY's test
PLASMA	11.4 ± 0.2	21.0 ± 1.4	22.2 ± 1.4	23.2 ± 1.7	24.8 ± 3.0	p = 0.0003	<u>1 2 4 8 12</u>
BRAIN	17.6 ± 1.8	25.0 ± 3.5	22.5 ± 1.6	21.5 ± 2.4	23.4 ± 3.7	NS	
LIVER	36.4 ± 1.6	55.8 ± 1.7	55.9 ± 3.4	52.7 ± 7.1	68.5 ± 6.4	p = 0.002	<u>1 8 2 4 12</u>
LUNGS	21.0 ± 1.2	31.7 ± 3.2	29.1 ± 1.0	28.8 ± 3.5	34.3 ± 3.4	p = 0.03	<u>1 3 4 2 12</u>
PROSTATE	15.5 ± 2.3	25.8 ± 1.6	29.1 ± 1.3	29.4 ± 3.5	32.6 ⁱⁱⁱ ± 3.6	p = 0.001	<u>1 2 4 8 12</u>
KIDNEYS	23.4 ± 1.0	42.4 ± 2.4	42.2 ± 3.9	41.2 ± 3.5	45.2 ± 3.7	p = 0.0005	<u>1 8 4 2 12</u>
ADRENALS	51.0 ± 8.5	80 ± 30	86.8 ± 9.2	82.3 ± 2.8	102 ± 13	NS	
EYES	10.2 ± 2.6	14.0 ± 1.1	15.0 ± 0.5	15.8 ± 1.3	20.9 ± 3.0	p = 0.0002	<u>1 2 4 8 12</u>

ⁱⁱⁱ n = 4
NS non-significant

Brain, ~~liver~~, Prostate, Eyes $\approx$ Plasma Conc
Liver, Lungs, Kidney, Adrenal 2-4 X Plasma Conc.

TUKEY's test: the means corresponding to each day are classified in ascending order.

Those underscored with the same line do not differ significantly.

RU 23,908 + RU 43,866 make up 75-90% of total radioactivity
RU 23,908 $\rightarrow$ RU 43,866 changed to
- 40 -
000041

Metabolism

The pathways involved in nilutamide metabolism are depicted in Table F taken directly from the NDA. The relative importance of the various metabolites in rat and dog are presented in Table 5.

In the rat 24 hours after a single 10 mg/kg oral dose, 22% of radioactivity in the plasma is attributable to parent drug (RU 23908, I) and 37% of radioactivity is present as the major metabolite RU 43,866 (III). In the dog 24 hours after a single 10 mg/kg oral dose, 28% of circulating radioactivity is due to parent drug with the major metabolites being VI (16% of radioactivity), VIII (RU 48,275, 12%), and III (RU 43,866, 8%). In men receiving therapeutic doses of 150 or 300 mg/day, the majority of the radioactivity in the plasma at steady state is attributable to the parent compound (75%). In man, the major metabolites present in plasma are RU 43,866 (III), RU 48,275 (VIII) and RU 48,276 (X). The half-life of nilandron in men is long and variable. (T_{1/2} of parent drug is 1-3.6 days; T_{1/2} of total radioactivity is 1.5-6 days). Time to reach steady state is 10-20 days (mean = 14 days).

A comparison of the pharmacokinetics of nilandron in different species is provided in the table below. The drug is metabolized more rapidly in rats and dogs than in men. The plasma half-life of nilandron is 5 hours in rats, 9 hours in dogs and 45-56 hours in man. Half-life of the metabolites are also different between species (T_{1/2} for total radioactivity = 11 hours in the rat; 53 hours in dogs after single doses). The differences in drug metabolism between species results in very different drug exposures for comparable mg/kg doses. For a comparable 5 mg/kg dose, AUC exposures in men are 4 times higher than those achieved in dogs and 8 times higher those observed in rats.

Plasma protein binding - Approximately 80% of plasma nilutamide is protein bound in all species.

TABLE 1
PHARMACOKINETICS PARAMETERS OF NILUTAMIDE (RU 23908)

<u>Species</u>	<u>Dose/Duration</u>	<u>C_{max}</u> (ug/ml)	<u>T_{max}</u> (hrs)	<u>AUC 0-24</u> (ug.hr/ml)	<u>T_{1/2}</u> (hrs)
RAT	10mkd, 1 day	2.95	2	30.9	4
	15 days	3.75	1.5	44.8	4.8
DOG	10mkd, 1 day	3.39	8	50.8	3.6
	15 days	5.2	4	80.2	9.1
MAN	150mg/d, 1 d (2.5 mkd)	.90	2.8	38.6	59.1
	300mg/d, 21 days (5 mkd)	C _{ss} = 6.5		162	45

Excretion

Excretion of nilutamide is primarily urinary in all species. Nilutamide is extensively metabolized prior to excretion with only a small percentage of radioactivity excreted in the urine as parent compound.

Species	Dose/route	<u>% of Radioactivity Excreted</u>		Clp (ml/hr/kg)
		Urinary	Fecal	
Rat	10/mg/kg, iv			150 (parent) 86 (radioact)
Dog	10 mg/kg, iv	69%	25-30%	127 (parent) 31 (radioact)
Man	150mg/day	78%		

TOXICOLOGY DATA

The toxicology data presented in the NDA has been previously reviewed (see Pharmacology reviews # 1-4 which are appended). However, despite repeated requests summary tables were not provided for many studies in the original IND submissions. Therefore, some studies were reviewed again when additional data was provided with the NDA.

Toxicology studies were performed according to GLP by Roussel UCLAF, Romaineville, France.

Acute Toxicity - signs of toxicity via both intraperitoneal and oral routes included apathy, lethargy, hypomotility, locomotor and respiratory difficulties.

Nilutamide (RU 23908)

		<u>LD 50 mg/kg</u>	
		Males	Females
Mice, CD-1 (n=10/sex)	ip	180	150
	oral	215	200
Rats, SD (n=10/sex)	ip	135	125
	oral	195	210

Data regarding the acute toxicity of the metabolites of RU 23,908 are summarized in the table below. The metabolites RU 45,018 and RU 43,866 (rat, dog, man), and RU 48,275 (dog) are all less toxic than the parent drug. The acute toxicity of metabolite VI (dog) and RU 48,276 (man) were not tested.

RU 43,866 (amino metabolite)

		<u>LD 50 mg/kg</u>	
		Males	Females
Mice, CD-1 (5/sex)	ip	695	595
	po	730	835
Rats, SD (5/sex)	ip	415	415
	po	560	435

RU 45,018

		<u>LD 50 mg/kg</u>	
		Males	Females
Mice, CD-1 (5/sex)	ip	630	720
	po	1215	1315
Rats, SD (5/sex)	ip	790	790
	po	730	705

RU 48,275

		<u>LD 50 mg/kg</u>	
		Males	Females
Mice, CD-1 (5/sex)	ip	> 2000	> 2000
	po	> 2000	> 2000
Rats, SD (5/sex)	ip	> 2000	> 2000
	po	> 2000	> 2000

30-Day Oral Toxicity in the Dog (#89251/89252)

Beagle dogs (3/sex/dose) were administered 0, 3(LD), 10(LMD), 30(HMD), and 60(HD) mg/day nilutamide as capsules for 30 days.

Mortality- all dogs receiving 60 mkd died or were sacrificed in extremis prior to study completion.

Deaths occurred in 1 F on day 19 and 1 M on day 30, both animals displayed marked cachexia.

Four HD animals were killed moribund on day 24 (2 F) and day 30 (2 M)

Signs - there were no clinical signs of toxicity in dogs receiving the two lowest dose levels (3 and 10 mkd)

Dogs treated with 30 mkd (AUC exposure in dogs 1/4 to 1 times human therapeutic AUC exposure) demonstrated hypotonicity and locomotor difficulties from week 2. Vomiting and soft stools were noted infrequently. Mucous membranes were pale.

Dogs treated with 60 mkd (1-2 times human exposure) displayed hypotonicity and locomotor difficulties from the first week of dosing becoming increasingly severe over the course of treatment. Episodic vomiting and soft stools/diarrhea were noted infrequently in some animals. Pallor of mucous membranes and salivation with dosing were also noted. Dogs treated with the HD were dehydrated beginning in week 3 and had progressive cachexia.

Body weight - weight loss in all HD dogs (2.5-4.2 kg) and 1/3 HMD (30 mkd) male over the course of the study.

Food consumption - decreased in 2/3 HMD males, normal in HMD females. Reduced by the end of week 1 in both sexes of HD animals (2/3 M, 3/3 F) progressing to no food consumption by week 3 in females and week 4 in males.

ECG/blood pressure - unaffected

Ophthalmology - discoloration of the conjunctiva in 3/3 HD males
no other drug-related abnormalities

Hematology-

RBC, Hgb, Hct - decreased in all groups including controls
reticulocytes - markedly elevated in 30 and 60 mkd groups of both
sexes (no data for 3 and 10 mkd gps)
(increased reticulocyte counts are indicative of
continued or recurrent blood loss)
platelets - increased in HD animals
fibrinogen - increased in HD animals
WBC - decreased in HD dogs

Blood chemistry-

Electrolytes were abnormal in HD animals at the time of sacrifice (day 24 F,
day 30 M) as follows-

Increased potassium, magnesium, phosphorus
Decreased sodium, calcium, chloride
urea - increased in HD both sexes
creatinine - increased in HD both sexes
total bilirubin- mildly increased in HMD and HD dogs
ALT- mildly increased in HD dogs

Organ weights -

Spleen - markedly decreased absolute and relative wts in HD
animals
Thymus - decreased abs/rel wts in all treated males, markedly
decreased wts in HD both sexes
Liver - increased abs/rel wts in HMD, HD dogs
Testes - marked decrease in abs/rel wts in HD males
Prostate- marked decrease in abs/rel wts all treated males

Histopathology - As has been a consistent problem with this IND/NDA, no
histopathology summary tables were provided with the study report. I requested
data from the sponsor and they provided a table which included data for
prostate, testes, epididymes, spleen and thymus only (see submission of
1/27/95). Data below were generated from individual histopathology reports.

Heart -calcification/fibrosis of valves 1/6 HMD, 2/6 HD dogs

Thymus - marked cortical involution 1/6 HMD, 6/6 HD dogs

Spleen - congestion 1/6 LD, 2/6 LMD, 4/6 HMD,
hypoplastic white pulp -1/6 HMD, 5/6 HD dogs

Prostate - marked involution 2/3 LD, 1/3 LMD, 3/3 HMD, 3/3 HD M
interstitial fibrosis - 1/3 LD, 2/3 LMD

Testes- absence of sperm -1/3 LD, 1/3 LMD, 2/3 HMD, 3/3 HD
degenerated seminiferous tubules- 1/3 LD, 1/3 LMD, 1/3 HMD

Epididymes- atrophy 0 C, 0 LD, 0 LMD, 1/3 HMD, 3/3 HD
myofibroblastic thickening 0 C, 0 LD, 0 LMD, 1/3 HMD, 3/3 HD

Stomach- hemaorrhagic foci 0 C, 0 LD, 0 LMD, 0 HMD, 2/6 HD

Intestines -

glandular dilatation 0 C, 1/6 LD, 0 LMD, 1/6 HMD, 1/6 HD

Liver- hepatocyte rarefaction -2/6 HD

Drug Toxicokinetics- concentrations of nilutamide in drug treated dogs were measured by HPLC with UV detection. Plasma half-life in males was 8 hours, half-life in females was 10 hours.

Dose (mg/kg)	AUC 0-24 (ug.hr/ml)		Multiple of Human AUC
	Day 1	Day 30	
3	19.5	21.8	0.1 - 0.25
10	46	47.7	0.25 - 0.5
30	101	90	0.5 -1
60	223	###	1-2 X
MAN			
150mg (2.5 mkd) 21 days	90		
300mg (5 mkd)	180		

###- 60 mkd (exposure = human AUC) was lethal in all HD dogs.

Summary and Conclusions-

Administration of nilutamide to dogs for one month at a dose of 60 mkd (1-2 times human therapeutic AUC exposure) was lethal. No mortality was observed with doses $\leq$ 30 mkd. Signs of drug intolerance including hypoactivity and locomotor difficulties were noted in dogs receiving 30 and 60 mkd. High dose dogs also displayed decreased food consumption leading to dehydration and cachexia.

Decreased red blood cell parameters were observed in all dogs including controls and were attributed to the repeated blood samplings on day 1 (for toxicokinetics). Markedly elevated reticulocytes were observed in MD, HD dogs. Other changes in hematology and blood chemistry including increased platelets, fibrinogen, decreased WBC, disturbed electrolyte balance, increased urea, creatinine, total bilirubin and ALT were observed in HD dogs at the end of the study. Animals were dehydrated and cachexic at death/sacrifice and, therefore, it is impossible to interpret the observed changes.

Histopathologic changes observed in HMD and HD treated dogs included marked atrophy of the testes, epididymes and prostate. These are expected pharmacologic effects. Marked thymic involution and splenic hypoplasia were observed in HD dogs. Again it is difficult to conclude whether these effects were drug-induced or secondary to dehydration and/or starvation.

It is important to note that moribund animals in the 1 and 6 month study displayed dehydration and cachexia. However, development of these signs was secondary to poor condition. In both studies animals were observed to be curled up in a ball unresponsive. Animals were in such poor condition that they did not get up to eat for many days and developed dehydration and cachexia prior to death.

In the one year study, animals were killed as soon as they became moribund. Animals did not display decreases or absence of food consumption and consequent dehydration and cachexia. All animals killed moribund in the 1 year study displayed marked to massive liver pathology and moderate renal tubular damage (which clearly was not secondary to dehydration or starvation).

Mild GI lesions were observed infrequently in the dog studies and did not display an incidence or severity which would suggest association with drug-induced lethality.

Eight Week Oral Toxicity Study in Dogs to Investigate Hematologic Changes (Study 86/23651/TX)

Male beagle dogs (n = 5/gp) were dosed for 8 weeks with 0 or 20 mg/kg, po nilutamide (RU 23908).

Mortality- none

Signs - decreased motor activity 2/5 treated dogs (# 77, 79).

Body weight- food consumption and body wt was decreased in the 2 dogs with signs (77 & 79).

Hematology -

RBC, Hgb, Hct - moderate decrease in 5/5 treated dogs.
decreased RBC life span and decreased corpuscular volume in 4/4 treated dogs
platelets- marked increase in 5/5 treated dogs

Organ weight/Histopathology-

Prostate - decreased prostate weights and prostatic epithelial atrophy were observed in 5/5 treated dogs.

Liver - increased weights in 3/5 treated dogs. Hemosiderin deposits were also observed in the livers of dogs with increased liver wts.

Spleen - discoloration and numerous hemosiderin deposits were observed the spleens of all nilutamide treated dogs.

Conclusion - Nilutamide produces moderate anemia secondary to peripheral destruction of erythrocytes.

Twenty Six Week Oral Toxicity Study in Dogs (# 299-TCR)

Beagle dogs (n = 5/sex/dose) were administered 0, 3, 10, 20 and 30 mg/kg/day nilutamide in gelatin capsules for 2 weeks.

Mortality- 1/5 control males of enteritis

No deaths in 3 or 10 mkd groups.

20 mkd - 2/5 males died during month 5

30 mkd - 3/5 M, 4/5 F - found dead or sacrificed

cachexic. 1M, 1 F died month 1, 2 F died month 2

Signs- Premature decedents displayed body weight loss, decreased food consumption, dehydration, and cachexia. Hypertrophy of mandibular glands, excess salivation, pallor of mucous membranes were observed in HD dogs.

Body weight - sporadic weight loss in 3/5 males and 4/5 females dosed with 30 mkd resulting in mean body weight loss of 1 kg in males and 3 kg in females. Body weight loss was observed in HD (30 mkd) dogs from the beginning of the study. A reduction in body weight gain was observed in LD, LMD, and HMD dogs. Dogs that died or were killed moribund consistently displayed absence of food consumption for many days prior to death. (Affected dogs were observed to be hypoactive and unresponsive).

Water consumption - reduced in surviving HD males.

ECG - sinus bradycardia in HMD male # 48 during weeks 5, 13 and 27.

Blood pressure - decreased systolic and diastolic BP in HD animals 24 hours postdose (wks 13, 27).

Ophthalmology - no drug-related changes

Hematology (weeks 5, 13, 27) -

RBC, Hgb - dose-related decrease in all drug treated groups, all timepoints

WBC - decreased HD week 5

lymphocytes - decreased (20%) at all dose levels, week 5

Blood chemistry (weeks 5, 13, 27)

No changes in blood chemistry were observed in LD (3 mkd) dogs.

BUN, creatinine - increased in HD dogs

Urea - increased at ≥ 10 mkd (LM, HM, HD)

alkaline phosphatase, ALT - increased at ≥ 20 mkd (HM, HD)

glucose - increased in 2/5 HD dogs

creatinine phosphokinase, AST - decreased in HD dogs

lactate dehydrogenase - decreased at ≥ 10 mkd

Albumin - increased at ≥ 10 mkd

α 1, α 2, and β -globulin - decreased at ≥ 10 mkd

Urinalysis

Epithelial cells were observed in the urine of HMD and HD dogs. Marked glycosuria was observed in the 2 HD male dogs with increased glucose levels.

Feces - occult blood was not found in the feces of any treated animals

Organ weights -

Kidney - dose-related decrease in absolute wts

Heart - increased wt in HD dogs

Prostate - marked dose-related decrease in abs/rel wts

Uterus - decreased abs/rel wts in LD, HMD and HD females

Liver - increased abs/rel wts in treated dogs

Spleen - increased rel wts in HMD, HD dogs

Histopathology -Despite requests to sponsor, histopathology summary tables and lesion severity data have not been provided for this study. The submission of 1-27-95 provides a summary table for the incidence of findings in liver lungs, prostate, testes, kidneys, and uterus only. These tables are not in complete agreement with data on incidence tabulated from the individual histopathology reports.

Brain - distended lateral ventricles-

0 C, 1 LD, 2 LMD, 1 HMD, 1 HD

Kidney - pyelonephritis -

0 C, 3/10 LD, 9/10 LMD, 3/10 HD

Liver - congestion -1/10 C, 1/10 LD, 3/10 LMD, 4/10 HMD, 6/10 HD

Lungs- fibrosis 1/10 C, 3/ 10 LD, 4/10 LMD, 2/10 HD

Pancreas - acinar cell vacuolization 2/10 HD

Testes- reduced/arrested spermatogenesis

0 C, 0 LD, 3/5 LMD, 5/5 HMD, 4/5 HD

Prostate - atrophy - 0 C, 3/5 LD, 5/5 LM, 5/5 HM, 5/5 HD males

Spleen - hyperemia 0 C, 1 LD, 1 LM, 2 HD

Thymus- involution - 1/10 C, 1/10 LD, 1/10 LMD, 5/10 HMD, 7/10 HD

SUMMARY AND CONCLUSIONS

Drug-related deaths were observed in 20% of dogs dosed with 20 mkd and 70% of dogs dosed with 30 mkd (¼ -1 times human therapeutic exposures). The maximum tolerated dose in the dog was 10 mkd which produces drug AUC exposures in the dog ¼ - ¼ human therapeutic AUC exposures (see table in one month dog study).

Signs were similar to those observed in the one month study namely, decreased food consumption, body wt loss, dehydration and pallor of mucous membranes. Drug-induced anemia was observed in all drug-treated dogs. Increases in creatinine, alkaline phosphatase, and alanine aminotransferase were seen only in the two highest dose groups.

Histopathologic reports were incomplete and, therefore, it is impossible to determine the cause of death in premature decedents. Drug-related lesions were observed in the kidneys, liver, lungs, pancreas and thymus of nilutamide treated dogs. (The histopathologic changes were observed in low and low middle dose dogs which did not display signs of toxicity suggesting the lesions are drug-related and not secondary to the dehydration and cachexia observed in the HD dogs).

Prostatic atrophy and arrest of spermatogenesis (expected pharmacologic effects) were also observed. There were no lesions in the GI tract, no drug-related increase in vomiting or diarrhea, and no occult blood in the feces. Therefore, the loss of appetite and cachexia were not secondary to GI intolerance. As previously stated, dogs displayed decreased motor activity, were moribund and unresponsive, and severely affected dogs did not eat for several days prior to death/sacrifice.

One Year Oral Toxicity Study with Nilutamide in Dogs (Study 1042 TCC)

Beagle dogs (n = 6/sex/dose) were administered 0, 3, 6, and 12 mg/kg/day nilutamide in gelatin capsules for 1 year.

Mortality- 1/6 males @ 3 mkd, month 11
2/6 M, 2/6 F @ 6 mkd (1 M, 1 F month 9; 1 M, 1 F month 11)
3/6 M, 3/6 F @ 12 mkd

Signs- dehydration, pallor of mucous membranes, decreased body wt/food consumption, polyuria in premature decedents.

Body weight - Dogs in all treated groups were displaying slight weight gain until week 21 of the study. After week 21 treated groups displayed body weight loss (not dose-related).

Food consumption- sporadically decreased in animals that died prematurely, but no marked anorexia prior to death as was noted with the toxic doses (20 and 30 mkd) in the 6 month study.

Water consumption- variable, no clear drug effects.

ECG- unremarkable

Blood pressure- systolic and diastolic BP increased 24 hours after dosing in all treated males and MD, HD females (no effects at 2 hours post dose),

Ophthalmology- unremarkable

Hematology - (wks 12, 26, 52)

RBC, Hgb, PCV- decreased in all drug treated males at all timepoints

Platelets- increased 25-50% in treated males (wk 5 in HD; wk 26 in MD, HD; Week 52 at all dose levels).

Blood chemistry-

Alkaline phosphatase - increased (2-fold) in treated males wks 5, 12, 26 (by week 52 affected animals were dead)

LDH- dose-related increase in treated males from wk 12; in females, from week 26.

Creatinine phosphokinase - increased in treated males wks 26, 52; HD females wk 52

Potassium decreased, **Chloride** increased-treated males weeks 26, 52.

Marked alterations in electrolytes and enzymes in dogs killed in extremis.

Urinalysis - increased urine volume in MD, HD females. Polyuria (> 1 L/day) in 1 MD and 2 HD dogs.

Feces- no occult blood in feces.

Organ weights -

Spleen - increased abs/rel wt HD M, md, HD F

Adrenal- decreased abs/rel wt HD M

Liver -increased abs/rel wt MD, HD both sexes

Testes- increased abs/rel wt all treated males

Prostate - decreased abs/rel wt all treated males

Epididymes - decreased abs wts MD, HD males

Gross pathology- livers of animals that died were pale, enlarged, discolored (yellowish), some had white foci. These observations were seen in the 4 MD and 6 HD animals that died prematurely or were killed moribund.

Histopathology-

Prostate - tubulo-alveolar atrophy in all drug-treated dogs

Testes - inhibition of spermatogenesis 0 C, 2 LD, 1 MD, 3 HD

Liver - swelling and vacuolization of hepatocytes in 0 C, 2/12 LD, 1/12 MD and 6/12 HD.

The 6 HD animals with liver lesions were the premature decedents. Liver pathology was graded marked to massive (grade 4 or 5). This was the only lesion of this severity which strongly suggests deaths were due to liver toxicity. Animals in this study were killed prior to loss of appetite and development of cachexia.

Lungs - chronic interstitial pneumonia was observed in dogs of all groups 8/12 C, 6/12 LD, 8/12 MD, 9/12 HD. This is not a common spontaneous lesion in one year dog studies. The sponsor was requested to grade the severity of the lesions in dogs. The follow-up report submitted 1-20-95 suggests no difference in severity of the lesion in nilutamide treated dogs. The reason for the observation of chronic interstitial pneumonia (equivalent to interstitial pneumonitis in man and chronic alveolitis in rats) in this study is unclear.

Kidney - moderate tubuloepithelial vacuolization observed with slight increase in frequency in males (high control incidence in females)

Males - 0/6 C, 2/6 LD, 2/6 MD, 2/6 HD

Females - 4/6 C, 3/6 LD, 3/6 MD, 3/6 HD

Summary and Conclusions-

Drug-related deaths were observed at all dose levels in dogs treated with Nilandron for one year (8% LD, 33% MD, 50% HD). These dose levels (3, 6, 12 mkg) produce drug exposures (AUC) in dogs that are 1/10 to 1/5th therapeutic AUC exposures in man.

The observed toxicities are the same as those observed in the one and six month studies, namely body weight loss, anemia, prostate/ testicular atrophy, liver and kidney toxicity. Nilandron toxicity is cumulative since lethality was observed with dose levels administered for one year which did not produce deaths when given for $\leq$ 6 months.

Histopathology data available from this study (which includes lesion severity) demonstrate that the drug-related deaths were due to liver toxicity. Absence of GI intolerance, GI pathology or cachexia/dehydration in animals in this study also confirm that the observed toxicities are drug-induced and not secondary to poor condition.

Chronic interstitial pneumonia (interstitial pneumonitis) was observed in dogs in this study at a frequency much higher than seen historically. However, the incidence and severity in treated dogs was not higher than in controls. The pathologist's report stated that the lesions in drug-treated dogs had a more chronic nature than those in control dogs. These observations coupled with the increased incidence of lung fibrosis in dogs in the 6 month study and similar lung lesions in rats and men suggest an association with drug.

SUMMARY AND EVALUATION

Nilutamide (Nilandron) is a non-steroidal antiandrogen indicated for use in combination with surgical or medical castration in patients with Stage D₂ prostate cancer. Preclinical pharmacology studies have demonstrated that nilutamide binds weakly and transiently with androgen receptors. In a general pharmacology screen, Nilutamide had no significant effects on CNS, ANS, cardiovascular, renal or GI function at oral doses $\leq$ 100 mg/kg. Studies examining the receptor binding and activity of nilutamide and several metabolites have demonstrated that parent drug is the active moiety. Nilutamide (at doses which produce therapeutic plasma or tissue drug concentrations) significantly inhibits hepatic cytochrome P 450 activity in treated rats and mice, or human liver microsomes.

Nilutamide is metabolized to nitro-anion free radicals capable of generating reactive oxygen species (demonstrated in rat lung, rat liver and human liver microsomes). This metabolism is similar to that observed with another nitroaromatic compound, nitrofurantoin. The interstitial lung disease and liver toxicity observed in animals and men treated with Nilutamide are similar to the lung and liver toxicity observed in men treated with nitrofurantoin.

Nilutamide is completely absorbed (97 - 100%) in all species. In rats, the drug and/or metabolites accumulate in the target organ of toxicity, namely the lungs, liver, kidneys and adrenal glands. The metabolism of nilutamide is very different in rats, dogs and men (see page 6). Slow metabolism in men results in relatively high plasma nilutamide concentrations with therapeutic dosing. A 5 mg/kg dose (300 mg/day) produces AUC exposures in men 4 times higher than those measured in dogs and 8 times higher than those attained in rats given the same dose. The pharmacokinetics of Nilutamide are linear for the therapeutic doses and the doses utilized in the preclinical studies. Drug plasma half-lives are 5 hours in the rat, 9 hours in the dog and 45-56 hours in men. The plasma half-life of metabolites of nilutamide (radioactivity) are twice as long as the T_{1/2} of parent drug. Nilutamide and its metabolites are eliminated primarily in the urine in all species.

Acute toxicity of Nilutamide and several of its metabolites have been evaluated. Parent drug is more toxic than any of the metabolites studied. Nilutamide is also more toxic than flutamide in acute toxicity tests.

Atrophy of the prostate, epididymes and seminal vesicles (desired effects) are observed at doses $\geq$ 5 mkg in rats and $\geq$ 3 mkg in dogs. Inhibition of spermatogenesis is observed in nilutamide-treated dogs. Leydig cell hyperplasia/adenomas are observed in rats doses with 45 mkg for 78 months. The Leydig cell hyperplasia is secondary to loss of feedback inhibition by testosterone (DHT ?) at the pituitary and elevated LH concentrations.

The target organs of toxicity for Nilutamide are the red blood cells, kidneys and lungs of rats and dogs. Nilutamide is also a potent liver toxin in dogs producing drug-related deaths in treated dogs at dose levels $\geq$ 6 mg/kg/day. The doses of nilutamide which are lethal in dogs produce drug AUC exposures which are only a fraction (1/10 - 1/2) of human therapeutic drug exposures. No liver pathology was evident in nilutamide-treated rats. Drug-related increases in the incidence of LFT elevations, nausea and vomiting, and flu-like syndrome have been observed in Nilutamide-treated men in the controlled trials (see Appendix 2).

Anemia and increased reticulocyte counts were observed in nilutamide-treated rats and dogs. Anemia has not been a reported adverse reaction in men treated with Nilutamide. Anemia is a common adverse event in men treated with the

antiandrogen Flutamide.

Nilutamide produces interstitial lung disease in rats and men. Nilutamide-treated rats (males in particular) had an increased frequency of inflammatory cell infiltration (granulomatous inflammation), alveolar hemorrhage and alveolitis. Alveolitis in rats is a comparable lesion to chronic interstitial pneumonia in dogs and interstitial pneumonitis in humans. Numerous drug-related cases of interstitial lung disease have been reported in Nilandron-treated men (see Appendix 2). Lung lesions including fibrosis and chronic interstitial pneumonia were also observed in Nilutamide-treated dogs, however, the incidence pattern does not show a clear association with drug as was observed in other species.

The preclinical toxicity profiles of Nilutamide and the approved antiandrogen, Flutamide are compared in Appendix 2. Information regarding the frequency of related adverse events in men is also provided.

LABELLING

The Medical, Pharmacology and Statistical Reviewers are recommending Non-approval of the NDA. Therefore, labelling revisions are not proposed at this time.

The sections of the labelling dealing with pharmacology and toxicology issues are currently deficient or absent. In the event that the NDA is approvable, major labelling revisions will be required.

NDA 20-169
Nilutamide/Anandron

APPENDIX 1

PHARMACOLOGY REVIEWS # 1 - # 4

IND

Review #1

G.H. Besselaar Associates
Princeton, NJ 08540

July 2, 1985

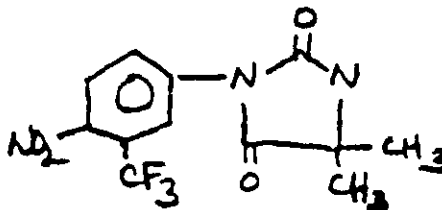
Submission: June 7, 1985

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Drug: RU 23908

Review #1

Structure:



Category: anti-androgen

Clinical studies: RU 23908 is used orally in treatment of prostatic cancer in doses ranging from 70 to 900 mg/day (equivalent to 1.4 to 18 mg/kg/day for a 50 kg patient). These values are in the low and mid-dose ranges of both the rat and dog studies. Four Phase I studies and interim reports on 2 Phase II studies were submitted. One Phase II study used 300 mg/day plus either an LHRH agonist or surgical castration on sixty stage C and D patients. The other Phase II study compared 150 and 300 mg/day of RU 23908 plus orchiectomy vs orchiectomy alone in 81 stage D patients.

The Phase III study would include two double blind multicenter trials with 200 patients each in stages C or D of prostate cancer. They would last for 18 months and would compare a) RU 23908 (100 mg t.i.d.) and orchiectomy vs orchiectomy alone and b) RU 23908 (100 mg t.i.d.) and DES vs DES alone.

Pharmacology:

Ten mg/kg of ¹⁴C-RU 23908 were given orally to a male Beagle dog. The concentration plateaued after 4 to 8 hours at 6 ug/ml in the plasma. Absorption was 98% of the ingested dose. Bioavailability was estimated at 70%.

The major excretory route was in the urine (about 70%) with a peak on the second day. Total excretion was about 90% of the administered dose. The kinetics of elimination were complex with an estimated t_{1/2} of 8 hours.

Mode of action: RU 23908 is an anti-androgen and does not bind to other steroidal hormone receptors. The binding affinity for the testosterone receptor is relatively weak and decreases with time of incubation in vitro. The drug antagonizes 95% of the activity of exogenous testosterone. However, its action is complete only in the castrated rat. In the intact male, it blocks the testosterone inhibition of LH release causing testosterone levels to rise, and for this reason, clinical studies use RU 23908 plus either castration or an LHRH agonist.

JUL 24 1985

Toxicology:

GLP and Quality Assurance statements were provided for each study.

Acute studies: LD50

Centre de Recherches Roussel Uclaf, Romainville, France. June 27, 1984.
The LD50 of RU 23908 administered in 0.5% methylcellulose to male rats orally by gavage was 195 mg/kg.

The LD50 administered in 0.5% methylcellulose to male mice orally, by gavage, was 215 mg/kg. August 21, 1984.

13-week oral toxicity in the rat
Study #943-TCR,

Treatment: Four groups (15/s/g) were given 0, 10, 50, or 250 mg/kg/day of RU 23908 in 1% aqueous carboxymethyl cellulose. Treatment was by gavage. At the end of the 13th week, 10/s/g were killed. There was a 4 week withdrawal period for 5/s/g to investigate the reversibility of the pathology and hematology findings. This study was done before the LD50 studies.

Results

Mortality: 23/30 HD died by day 29 and the rest of the group were killed on day 37.

Physical signs: None reported other than a 16% weight loss in the HD group vs a weight gain in the rest of the animals, but the fact that the remaining HD were killed early implies that there were other symptoms.

Hematology:

HD: RBC, Hb, and HCT decreased; WBC increased

MD: RBC and Hb down

LD: anemia in females only

These parameters were back to normal after a 4 week recovery period

Serum biochemistry: Creatinine up in both sexes MD and HD; HD data only available at week 5.

Urinalysis: The sponsor says no findings related to drug treatment, but no data are given even though the protocol states that they are to measure 11 parameters.

Postmortem:

Gross pathology:

HD: GI tract autolysis, enlarged spleen, mesenteric lymph nodes, and adrenals; atrophy of thymus, testes, epididymis and prostate.

MD: Spleen dark and enlarged (males and females); atrophy of prostate, epididymis, and seminal vesicles.

LD: 1/15 atrophied prostate

Sacrifice following 4 week recovery period: LD and MD males no abnormalities; 3/5 LD females, hydronephrosis

Organ weights of males at end of treatment: Increases in spleen, pituitary, and liver (MD and HD), and increases in adrenal, heart, thyroid, and testes (MD).

Organ weights of males after 4 week recovery: all in normal ranges.

Histology

Spleen: macrophages/hemosiderin (all doses; autolysis at HD)

GI tract: erosion and desquamation ileal villi (all doses; autolysis HD)

Kidneys: scattered pycnosis of interstitial tubules (LD and MD; autolysis HD)

Lungs: large atelectatic patches (LD and MD)

Testes: hyperplasia of interstitial tissue (MD)

Prostate: hypertrophy of glandular epithelium (MD)

Similar findings in animals killed 4 weeks after the end of treatment.

The picture is cloudy here in that the controls had mild erosion of duodenal villi and macrophages in the spleen, symptoms which were much intensified by drug treatment. It seems possible that some of this could be due to the vehicle (carboxymethylcellulose) and some to general poor health of rats.

26-Week Oral Toxicity in Rats

Study #300-TCR. Roussel-Uclaf, Paris, France. C. Delhoste, study director.

Treatment: Four groups (20/s/g) received 0, 8, 20 or 50 mg/kg/day, by gavage, for 26 weeks. Drug was administered initially in 0.5% methylcellulose. From day 20, RU 23908 was ground in 1% aqueous Tween 80 and 0.5% aqueous methylcellulose. The final concentrations were not at all clear; this information has been requested from the sponsor.

Results

Mortality: 7, stated by sponsor to be due to intubation errors.

Body weight: decreased in males from week 3 onwards at all doses; no effect on females.

Ophthalmology: discoloration of iris and conjunctiva, likely related to decrease in RBC; cataracts at HD. Data given only for 0 and HD groups.

Hematology: RBC, Hb, and HCT decreased in all treated groups except LD males. MCV and reticulocyte counts up in MD and HD. WBC and prothrombin times up in HD.

Clinical chemistry: changes scattered and not consistent with either time or dose. Glucose up at 5 weeks in HD, something seen in clinical patients, too, without any explanation for either observation.

Urinalysis: "no dose-related changes" but the pH was down and protein was present in HD animals.

Postmortem

Gross pathology: dose-related decreases in prostate and seminal vesicles and dose-related increases in testes. The males were more severely affected with increases in heart, liver, adrenal, and pituitary weights (MD and HD); kidney, brain, and thyroid weights (HD). The females had kidney weights up (MD and HD) and adrenal, liver, and heart up (HD). Spleen weights were increased in all groups in both sexes.

Histopathology

Pigment deposits in spleen and liver (hemosiderin) and kidney (unknown).

Tubular dilatation of kidney tubules (HD), hyperplasia of testes (HD).

hypoplasia of prostate (all doses) and vacuolated cells in the pituitary (HD).

26-Week Toxicity in Beagle Dogs
Study #299-TCC.

Treatment: 5/s/g were given 0, 3, 10, or 30 mg/kg/day (study group 1) or 0 and 20 mg/kg/day (study group 2), orally, by gelatin capsule once daily. The animals in group 1 were supplied by an English breeder; those in group 2 by a French breeder after early deaths of HD animals in group 1.

Results

In this study male and female data, except for mortality data, were averaged together.

Mortality: 2/5 males (20 mg/kg/day); 3/5 males and 4/5 females (30 mg/kg/day)

Clinical findings: None (3 and 10 mg/kg/day); hypertrophy of mandibular glands, excessive salivation, dehydration, diarrhea, and pallor of mucus membranes (20 and 30 mg/kg/day).

EKG: no drug-related findings

Blood pressure: diastolic down at 30, systolic down at 10 and 30 mg/kg/day.

Ophthalmology: no drug-related findings

Hematology: anemia all groups at 13 weeks; by 27 weeks, only HD group. Platelet counts were up at 10 mg/kg/day and higher; AP up 20 and 30; BUN up at 30 mg/kg/day. The picture is complex with many changes being of a transient nature; this was seen in the clinical patients also.

Urinalysis: "no drug-related findings" but 2/10 had glycosuria at 20 mg/kg/day and the pH was down at 30 mg/kg/day (drug week 5).

Postmortem

Gross pathology: prostate weight down markedly at all doses; testes weight up at all doses; liver up at 10 mg/kg/day or greater; kidney and spleen up at 20 mg/kg/day, and thyroid up at 30 mg/kg/day (all based on relative weights).

Mutagenicity

1. Micronucleus test in the mouse

Centre de Recherche Roussel Uclaf, Romainville, France. B. Vannier, study director. November 1983.

A single dose of 200 mg/kg gave results similar to the negative control in terms of the per cent micronucleated erythrocytes. The ratio of polychromatic/normochromatic erythrocytes was significantly different from the negative control.

2. Mutagenicity studies by bacteriological methods

Centre de Recherche, Roussel Uclaf, Romainville, France. M. Peyre and J. F. Chantot, directors. October 1979.

There was no evidence of mutagenic activity in either the diffusion or Ames tests.

Summary and Evaluation: RU 23908 is a non-steroidal anti-androgen to be used in the treatment of prostatic cancer. It binds to the cytoplasmic androgen receptor of the rat prostate with a relatively weak binding affinity and is usually used clinically in conjunction with either orchiectomy or an LHRH agonist (chemical sterilization).

A major finding from the rat and Beagle studies is the expected atrophy of the prostate, although there are clear species differences. The Beagle is much more sensitive to RU 23908 with an almost 70% decrease in prostate weight at 3 mg/kg/day, whereas the rat, after the same length of treatment and dose, had only a 15% decrease in weight. The dog was also more sensitive to the toxicity of the drug with 40% dying at 20 mg/kg/day; no rats died until the dose reached 250 mg/kg/day (although there was a gap between 50 and 250 mg/kg/day in the testing protocol).

All animals of both species developed anemia, perhaps as an effect on production of RBC (bone marrow) but unfortunately this was not checked. Although no Hb was reported in the urine, red cells apparently were breaking down with the excess iron being stored as hemosiderin in the spleen and liver. The anemia is a common clinical finding also. The sponsors tended to blame other factors for this in spite of the fact that 95% of 60 patients in one study had anemia at least for some part, if not all, of their treatment. Androgens stimulate the production of erythropoietin and this lack could lead to lower RBC production, but since the anemia occurs in females also, some other factors may be involved.

Other areas of toxicity included the liver, spleen, and kidney. In the rat, in addition, there appeared to be an effect on the lining of the GI tract: at 250 mg/kg/day, the entire GI tract autolysed. Although RU 23908 was very toxic to Beagles, no cause of death was given; liver dysfunction was mentioned but the pathology report did not reveal a cause.

Clearly with patients severely ill with prostate cancer, more risks are acceptable, but the doses needed might require trial and error (do people respond at low doses like the Beagle or at higher doses like the rat?). In summary, RU 23908 looks like a very promising therapy when combined with an LHRH agonist as done in the clinical trials.

All the data in this submission were from foreign sources.

6.
Recommendations: Pharmacology has no objection to the initiation of clinical studies. However, the sponsor should submit the complete ophthalmology and histopathology data from the 26-week toxicity study in rats as well as the complete histopathology data in the form of a summary table from the 26-week toxicity study in dogs. This table should allow for comparison of the incidence of individual organ pathology between controls and the three treatment groups. The sponsor has already been asked to provide information on the drug formulation given to rats in the 26 week study.

Elizabeth K. Barbehenn
E. K. Barbehenn, Ph.D.

A Jordan

7/17/85

cc:

Orig. IND

HFN-810

HFN-340

HFN-810/EK Barbehenn

HFN-801/W Galbraith

Wang 2044D

IND

April 4, 1986

G.H. Besselaar Associates (representatives for Roussel-Uclaf)
Princeton, NJ 08540

Submission: February 11, 1986

Pharmacology Review of Amendments

Review # 2

Drug: Anandron (RU 23908)

Related: Flutamide (IND NDA 18554)

Category: anti-androgen

Clinical: Phase III is planned with orchiectomy alone vs orchiectomy plus either 150 or 300 mg/day of Anandron for the treatment of stage D prostatic cancer.

The IND was on clinical hold as a result of a July 23, 1985 meeting with the sponsor. The present submission contains information requested at that meeting (26-week oral toxicity studies in dogs and rats) plus some additional studies on drug and hormone levels and mutagenicity.

Foreign data (all submitted data)

26-week oral toxicity study in rats

#300-TCR. Doses were 0, 8, 20, and 50 mg/kg/day by gavage.

Ophthalmology: Data had been requested for the LD and MD rats. The sponsor replied that they did not examine these animals.

Histopathology: Complete data was requested. The sponsor submitted individual data but no summary tables. The sponsor stated that dose-response relationships consisted of brown-pigmented epithelial cells in the renal tubules, hemosiderosis of the spleen, and interstitial cell hyperplasia (Leydig cells). In addition, there was also a dose-dependent increase in hemosiderin in the liver and kidney and hyperplasia of the testes.

An analysis of drug indicated that for the first 17 days (10% of the study), the ID was 22-33% too low (34-39 mg/kg/day vs 50 mg/kg/day). They state that after this time, satisfactory levels were obtained although data are only supplied for weeks 1, 13, and 26. The excipient was changed from 0.5% methylcellulose to 1% Tween 80 + 0.5% methylcellulose after 3 weeks.

Femoral and sternal bone marrow: The sponsor gives individual data but states that there was a dose-related increase in activity of bone marrow plus fatty metamorphosis coinciding with increased hemosiderosis of the spleen.

Hormone levels:

Males (doses across were 0, 8, 20, and 50 mg/kg/day; levels are ng/ml)

Testosterone	1.1	6.2	16.5	19
LH	1.1	2.8	3.3	3.3
Prolactin	11.3	15.9	31.7	38.4
Corticosterone	240	182	353	291

APR - 4 1986

Females: 26-week rat toxicity (ng/ml)				
LH	2.3	2.8	2.4	2.4
Prolactin	117	65	49	62
Corticosterone	493	356	532	496

26-week oral toxicity in dogs

#299-TOC. Doses were 0, 3, 10, and 30 (group 1) and 0 and 20 (group 2).

Histopathology: Data was requested as a summary table. This was provided but data indicated only the presence or absence of a finding without any information on the severity.

Group 1:

liver: congestion-dose-related
 prostate: atrophy in 0/5, 3/5, 5/5, 5/5
 prostatitis in 0, 2, 0, and 2/5
 fibrosis in 1, 3, 5, and 4/5
 thymus: involution in 3/5 males at 30 mg/kg/day vs 1/5 in control
 pancreas: islelet cell atrophy in 1/5 males at 30 mg/kg/day
 acinar cell vacuolation in 1/5 M and F at 30 mg/kg/day
 spleen: hyperemia in 0, 1, 1, and 1/5 males; no hemosiderosis, M or F
 testes: spermatogenic arrest in 3/5 at 30 mg/kg/day; no sperm in 2/5 at 10 mg/kg/day
 bone marrow: no drug effect

Group 2:

liver: congestion in 3/5 males
 kidney: edema in 2/5 F
 prostate: fibrosis in 5/5 males
 testes: spermatogenic arrest in 3/5 and atrophy in 1/5
 thymus: involution in 4/5 males

Hormone (ng/ml) and drug levels (ug/ml)

	Dose	Male		Female	
		Day 0	Day 184	Day 0	Day 184
Cortisol	0	37	19	28	36
	3	28	33	30	40
	10	26	33	35	24
	30	29	21	32	41
	0	25	14	20	21
	20	25	25	20	33

Testosterone

0	4.6	5.1 (24 hours after dose)
3	4.3	11.2
10	7.7	21.4
30	2.4	14.2 (only one dog)
0	3.8	4.3 (time after dose not given)
20	5.4	3.8

RU 23908 (Day 184)

	Males	Females
0	0.01	0.01
3	0.62	0.78
10	2.96	2.17
30	12.6	8.64

Mutagenicity Studies

Mutagenic activity in vitro with Schizosaccharomyces pombe

MB95.

There were no increases in mutation frequency due to drug at levels of 250 to 2000 ug/ml. This must be a mistake since 120 ug/ml is stated in another study to be the limit of solubility.

Mutagenic activity with Saccharomyces cerevisiae

MB96. Place and time same as above.

There was no effect at doses of up to 2000 ug/ml +/- metabolic activation.

Mutagenic activity with HeLa cells: unscheduled DNA synthesis

MB97. Place and time same as above.

There was no effect up to 100 ug/ml +/- metabolic activation; 1000 ug/ml was a toxic level

Metaphase chromosome analysis of human cultured lymphocytes

RSL 680/85745.

Maximum solubility of drug was stated to be 120 ug/ml, 0.38 mM.

There was no drug effect with metabolic activation (S-9 present) but without activation chromosomal aberrations were 9/200 cells for 0.4 mM Anandron and 27/200 cells for 4 mM ethylmethanolsulfonate, the positive control.

Mutagenic activity in CHO cell in vitro

RSL 681/85768.

The drug was cytotoxic at dose levels above 100 ug/ml without S-9 and cytotoxic above 250 ug/ml with S-9, but it was not mutagenic under either condition.

Drug binding to serum proteins

The per cent of drug binding to serum proteins of both rat and dog remained constant at about 80% of added drug from 10 to 10,000 ng/ml. However, the total amount bound increased proportionately from 8 to 8000 ng.

Peak plasma drug concentration

Peak plasma concentration (3.4 ug/ml) occurred at 8 hours after oral dose at 10 mg/kg; by 24 hours it was 1 ug/ml.

Summary and evaluation: Anandron is a nonsteroidal anti-androgen very similar in structure to Flutamide. Both are substituted anilides and thus potentially able to cause methemoglobin formation. This was observed in dogs with Flutamide and it is stated in that IND that it would be expected to occur in man. This was apparently never tested in animal studies with Anandron, although the preclinical data that is available indicates much similarity between the two in both toxicity as well as in anti-androgenic effects.

The toxicity in dogs is much greater than in rats with 2/5 dying at 20 mg/kg/day and 3/5 males and 4/5 females dying at 30 mg/kg/day. These doses are 3.3- and 5-times higher than the higher of the two doses to be tested in man. The cause of death was not determined. In rats, on the other hand, there were no deaths due to drug up to 50 mg/kg/day.

Histopathology data indicated a breakdown of hemoglobin in rats with hemosiderin in kidney, liver, and spleen. There was also an increase in bone marrow activity, but no quantitation was provided. Dogs were also anemic, but no hemosiderin was reported nor was there any effect on bone marrow. There was dose-related congestion in the liver, hyperemia in the spleen (1/5 of all doses), involution of the thymus (at 20 mg/kg/day and above), as well as fibrosis and atrophy of the prostate and spermatogenic arrest in the testes.

Testosterone, LH, and prolactin all increased as a function of dose in male rats while there were no effects on female rats. In dogs, testosterone levels rose about 3-fold. Cortisol levels remained unchanged in dogs and corticosterone levels were not affected in rats.

Five mutagenicity studies were submitted. One of these, a metaphase analysis of cultured human lymphocytes, indicated a mutagenicity comparable to the positive control when tested in the absence of S-9 from rat liver: 9/200 cells showed aberrations with 0.4 mM Anadron vs 27/200 cells showing aberrations with 4 mM ethylmethanesulphonate. Rat liver may be able to transform the drug to a less toxic form.

Recommendations: In reference to the dog toxicity study #299-TOC, ask the sponsor 1) for the cause of death in male and female dogs; 2) if they have checked for methemoglobin formation in this study; and 3) why male and female data were pooled.

Ask for an explanation for the inconsistencies in the degree of solubility of Anadron in the different mutagenicity studies: solubility was stated to be 120 ug/ml in one study but was stated to be tested up to 2000 mg/ml in another. In addition, ask the sponsor to explain why positive results were not noted for study #RSL 680/85745 on metaphase chromosome analysis in human cultured lymphocytes. The data showed that, without activation, Anadron at 120 ug/ml (0.38 mM) gave positive results of 9/200 aberrations while ethylmethane sulphonate at 500 ug/ml (4.0 mM) gave 27/200 aberrations.

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cc
Orig IND
IFN-345
IFN-810
IFN-810/Pharmacology
IFN-810/EBarbehenn
IFN-801/WGalbraith
#3213D

Jordan
4/4/86

IND

October 11, 1989

Sponsor: G.H. Besselaar Associates for Roussel-UCLAF
Princeton, N.J. 08543

Submission Dates: 8-10-88 (16 volumes); 7-20-89 (1 volume); Received 9-12-89

PHARMACOLOGY REVIEW OF IND ANNUAL REPORTS
(Review # 3)

PHARMACOLOGY STUDIES

1. Antiandrogenic Activity of RU 23,908 in the Castrated Dog/Study AT 39.

Castrated beagle dogs (n = 3/g) were treated for 13 days with 0.5 mkd of testosterone propionate. RU 23,908 was orally administered at doses of 0, 0.3, 1, 3 and 10 mkd. RU 23,908 at a dose between 1 and 3 mkd inhibited 50% of the trophic effect of testosterone on the prostate. This compares with an ED₅₀ of 10 mkd for atrophic effects in the rat.

2. Comparison of RU 23,908 and Four of its Metabolites/ Study AU 07.

Activities of RU 23,908 and its metabolites, RU 43,866, RU 45,108, RU 48,166 and RU 48,275 were compared. Metabolite RU 48,275 was the only one which interacted with the androgen receptor and displayed dose-dependent antiandrogenic activity comparable to RU 23,908 in rat accessory sex organs (prostate and seminal vesicles). In addition, like RU 23,908, the metabolites do not interact with mouse or rat estrogen, mineralocorticoid, glucocorticoid, and progestin receptors. RU 23,908 or its metabolites at doses of 2, 10 or 50 mkd for 8 days had no androgenic effects on the prostate and seminal vesicles of castrated male rats.

3. Interaction of RU 23,908 with "Retinol-Binding Proteins" of the Adenomatous Prostate/Study AU 19.

The interaction of RU 23,908 with cellular and plasma retinoid-binding proteins was measured in the human prostate and serum and in purified human plasma proteins. The effects of RU 23,908 were compared to the anti-androgen, flutamide, and the androgen RU 1881. None of the compounds displaced retinol and retinoic acid from their respective binding proteins in prostate or plasma.

4. Metabolism of RU 23,908 in the Rat and Dog/Study 86-028-CN.

Following a 10 mg/kg, iv dose of radioactive RU 23,908 drug and metabolite were quantified in urine and plasma. Eight metabolites were identified; 7 were common to rats and dogs.

NDA 28-169

4 OF 6

<u>Urinary Radioactivity as % of Dose</u>									
	<u>RU 23,908</u>	<u>II</u>	<u>III</u>	<u>IV</u>	<u>V</u>	<u>VI</u>	<u>VII</u>	<u>VIII</u>	<u>IX</u>
RAT	3.9	1.2	11.1	12.7	6.2	3.9	3.1	3.9	---
DOG	1	5.6	8	8.2	2.5	6.1	2.7	4.5	5.8

<u>Plasma Profiles 24 Hrs Post-Treatment (UG/ML Plasma)</u>							
	<u>RU 23,908</u>	<u>III</u>	<u>IV</u>	<u>V</u>	<u>VII</u>	<u>VIII</u>	<u>IX</u>
RAT	0.22	0.34	0.08	-	--	0.04	--
DOG	0.82	0.21	0.13	0.03	0.42	0.38	0.03

5. Variations in Plasma Concentrations of RU 23,908 in Rats During Chronic Oral Treatment/ Study 87-461-CN.

Sprague Dawley rats were administered RU 23,908 in 0.5% methylcellulose/0.2% polysorbate 80 orally by gavage at a dose of 10 mkg for 15 days. Plasma kinetics were examined after the first and 15th dose. Plasma drug concentrations were examined at 4 and 24 hrs after some intermediate doses.

<u>DAY</u>	<u>C_{max}(ug/ml)</u>	<u>T_{max}(hrs)</u>	<u>T 1/2 (hrs)</u>
1	2.95	2.0	8.4
15	3.75	1.5	9.3

Mean Plasma Concentration (ug/ml) - 4 hours postdose 2.58
24 hours postdose 0.16

6. Biliary Excretion and Enterohepatic Cycle of RU 23,908 in the Rat/ Study 87-451-CN.

Biliary excretion accounted for 25% of iv administered drug. Enterohepatic cycling of RU 23,908 was of little importance.

7. One Year Oral Toxicity Study in Dogs/ Study 1042 TCC (Volume 3).

Beagle dogs were orally administered RU 23,908 in gelatin capsules at doses of 0, 3, 6 and 12 mg/kg/day for 1 year (HTD = 6mkd).

Clinical signs- Dehydration and pallor of the mucous membranes was observed in all drug-treated animals. Polyuria was noted for a few days prior to death in animals that died during the study. Animals that died showed decreased food consumption and body weight prior to death.

Mortality- A dose-related increase in mortality was observed in drug-treated dogs of both sexes - 1/12 (M) controls, 1/12 (M) LD, 4/12 (2 M, 2 F) MD, and 6/12 (3 M, 3 F) HD. Death in the control animal was due to accidental aspiration/respiratory failure. Cause of death in the drug-treated dogs was not specified.

Food consumption/Body weight - were not influenced by treatment in surviving animals. All treated animals that died or were killed in extremis showed decreased food consumption and weight loss.

EKG/ Blood Pressure/ Ophthalmology - No drug-related changes.

Hematology- decreased RBC, Hgb, PCV in all drug-treated males; marked decreases were observed in the animals that died. Time and dose-related increase in platelet count (Wk 5 -HD; Wk 26- MD, HD; Wk 52- LD, MD, HD).

Moderate treatment related anemia was observed. In dogs that died anemia was marked and accompanied by increased reticulocyte counts and fibrinogen levels. Quantitative analysis of bone marrow (Appendix I, Annual Report submitted 7/20/89) did not reveal any abnormalities in cellular elements.

Biochemistry- decreased potassium MD: Wk 52; HD: Wk 12, 26, 52.
HD males, Wk 52 increased Cl, glucose, cholesterol, total protein, alkaline phosphatase, decreased calcium.

Animals that died or were killed had significant alterations in all biochemical parameters indicating impairment of vital functions.

Histopathology-

Prostate - tubulo-alveolar atrophy in all drug-treated males.

Testes - mild to moderate inhibition of spermatogenesis in treated males.

Liver - vacuolization and hypertrophy of hepatocytes in 0/13 controls, 2/12 LD, 1/12 MD, 6/12 HD.

Lungs- chronic interstitial pneumonia was observed in dogs of all groups, 9/13 controls, 6/12 LD, 8/12 MD, 9/12 HD (severity not graded).

Urinalysis - increased urinary volume wk 39 in MD, HD females.

Organ weights -

Liver - increased absolute and relative wts MD, HD of both sexes.
Prostate - dose-related decrease in absolute and relative wts.
Testes - increased absolute and relative wts
Ovary - increased wt in HD females.
Spleen - increased relative wts in MD, HD females (trend in males).

Summary - Treatment of beagle dogs with RU 23,908 for one year produced a dose-related increase in mortality at doses comparable to the human therapeutic dose. Plasma drug levels were not provided so it is impossible to compare levels in dog vs. man. Decreased prostate wts and prostatic atrophy, the desired pharmacologic effects, were observed. Drug treatment resulted in inhibition of spermatogenesis. Chronic interstitial pneumonia was observed in dogs of all treatment groups, including controls. Since cause of death and severity of lung lesions were not specified it is impossible to determine if the high incidence of pneumonia was due to drug treatment or poor husbandry. Dyspnea and interstitial pneumonia have been the most prevalent adverse reactions in patients treated with anandron in the U.S. clinical trials and in France where the drug is approved.

8. Eighteen Month Oral Toxicity Study in Rats/ Study 20.(Volume 8)

Sprague Dawley rats (n = 40/s/g) were orally administered RU 23,908 admixed with the diet at doses of 0, 5, 15 and 45 mkg (1, 2.5, 7.5 x HTD) for 18 months.

Clinical signs - pallor of eyes and piloerection observed in all treated animals for several weeks. Hypotonicity present in all HD males wks 32-50. Swollen testes 0/40 controls, 2/40 LD, 5/50 MD, 23/40 HD males.

Mortality- no drug-related effects

80, 77, 80, 95% survival for control, LD, MD, HD males, respectively.
77, 87, 90, 90% " " " " " " females, "

Food consumption - dose-related decrease in MD, HD rats (7% in MD; 23% in HD M, 17% in HD F). Food conversion ratios (the efficiency of food utilization) were decreased in all drug treated rats

Body weight- dose-related decrease 4, 11, 26% in LD, MD, HD M, respectively.
5, 18% in MD, HD F, respectively.

Water consumption - decreased in HD rats of both sexes.

Ophthalmology - increased incidence of lens opacities in treated animals, wk 78
0/10 control, 0/10 LD, 3/10 MD, 5/9 HD males.
0/10 control, 0/10 LD, 1/10 MD, 2/9 HD females.

Hematology - Dose-related increased incidence of anemia, significant in MD, HD animals of both sexes. Decreased Hgb MD, HD F; HD M. Slightly decreased RBC, PCV. Increased mean corpuscular volume and reticulocyte counts MD, HD M and F. Prothrombin time prolonged in MD, HD males wks 15, 26, 39, 52.

Blood biochemistry - Increased urea MD, HD M; HD F.
Increased creatinine, 5' nucleosidase activity HD males.
Dose-related decrease in triglycerides in males.
Increased albumin, decreased γ globulin all treated M.
Increased total bilirubin MD, HD females.

Urinalysis - increased urinary volume, decreased specific gravity HD males.

Gross pathology - dose-related decrease in prostatic and seminal vesicle wts.
Increased incidence of hydrometra in HD females; 2.5% C, 10% LD, 12.5% MD, 35% HD.
Increased absolute and relative splenic wts.
Decreased absolute and relative thymic wts.

Histopathology -

Neoplastic lesions - Leydig cell tumors (benign) in 0% control, 7.5% LD, 2.5% MD, and 35% HD male rats. (Historical control incidence = 7.5%).

Non-neoplastic lesions-

Adrenal - degeneration in 12.5% control, 58% LD, 68% MD, 21% HD females.

Prostate - dose-rel. tubuloalveolar atrophy 0/39 C, 5/40 LD, 11/40 MD, 35/40 HD
" " epithelial cell atrophy 2/39 C, 15/40 LD, 19/40 MD, 36/40 HD

Seminal vesicles- dose-related glandular atrophy and decreased secretory activity.

Testes - seminiferous tubule atrophy 7/40 C, 11/40 LD, 14/40 MD, 31/40 HD
inhibition of spermatogenesis 7/40 C, 11/40 LD, 14/40 MD, 30/40 HD
Leydig cell hyperplasia 0/40 C, 13/40 LD, 25/40 MD, 35/40 HD

Epididymides - decreased sperm count 17% C, 22% LD, 17% MD, 73% HD.
epithelial cell atrophy 2.5% C, 10% LD, 12% MD, 75% HD.

Kidney - decreased incidence of glomerular nephropathy in HD males; 35% C, 39% LD, 33% MD, 8% HD.

Uterus - myometrial hypertrophy 10% C, 20% LD, 20% MD, 25% HD.
endometrial epithelial hypertrophy 2.5% C, 28% LD, 25% MD, 28% HD.

Vagina - basal cell hyperplasia 12% C, 2% LD, 0% MD, 72% HD.

Rectum - squamous metaplasia 1/80 C, 0/14 LD, 0/12 MD, 9/80 HD.

Lungs - Alveolar hemorrhage 5% C, 10% LD, 30% MD, 18% HD.
Foamy alveolar macrophages 1% C, 7% LD, 3% MD, 18% HD.

Thymus - capillary hemorrhage 4% C, 25% LD, 18% MD, and 14% HD.

Summary - Dose-related decreases in food consumption and body weight were observed in drug treated rats. Treatment with RU 23,908 increased lens opacities in rats at doses equivalent to 2.5 times the HTD. A dose-related anemia was observed in MD and HD rats. The desired pharmacologic effects of decreased prostatic and seminal vesicle weights were observed. Seminiferous tubule atrophy and inhibition of spermatogenesis were observed. Drug treatment resulted in leydig cell hyperplasia which progressed to leydig cell tumors (benign) in HD male rats.

Pathological Examination of the Lungs from Animals in the 12 Month Dog and 18 Month Rat Chronic Toxicity Studies, Study 88/882/TX, Appendix I in Annual Report submitted 9/20/89.

Lungs from control and high dose groups from the studies reviewed above were examined.

Dog study - Dogs from both groups had diseased lungs with marked congestion, foci of alveolitis and lesions associated with chronic interstitial pneumonia. The pathologist concluded " The lesions observed in animals in the top dose group (12 mkd = 2 x HTD) may have a more chronic aspect than those in the control group." Since the severity of the lung lesions was not quantitated it is impossible to assess if the pneumonia was drug-related.

Rat study - Moderate lesions of alveolitis and granulomatous infiltration (foamy macrophages) were observed in lungs of control and HD (45 mkd) rats. The report states no significant differences between control and treated rats. Again, severity of the lesions was not graded but incidence of both histopathological findings was increased in the drug treated rats.

ALVEOLITIS

	<u>Control</u>	<u>45 mkd</u>
Original slides		
Males	10/40 (25%)	18/40 (45%)
Females	10/40 (25%)	22/39 (55%)
Resectioned slides		
Males	10/40 (25%)	22/40 (55%)
Females	7/21 (33%)	23/39 (58%)

GRANULOMATOUS INFLAMMATION

	<u>Control</u>	<u>45 mkd</u>
Original Slides		
Males	0/40	27/40 (77%)
Females	3/40 (7.5%)	9/39 (22%)
Resectioned slides		
Males	3/40 (7.5%)	21/40 (52%)
Females	1/21 (5%)	7/39 (18%)

Conclusions - The terms chronic interstitial pneumonia (dog), chronic alveolitis (rat), and interstitial pneumonitis (man) all describe the same lung histopathology and are interchangeable (see Principles of Toxicological Pathology, John Glaister, p. 69, 1986). Since the most common adverse reactions in man are dyspnea and interstitial pneumonitis it is likely the pneumonia observed in the chronic animal studies is also drug-related.

Test for Pulmonary Sensitization in the Rat: Study 89/1130/TX.

Male Brown-Norway rats received daily subcutaneous injections of RU 23,908 (1 mg/ml) for 8 day followed 7 and 14 days later by intraperitoneal booster injections (0.1 mg/ml). The 3 treatment groups included controls (adjuvant/vehicle only), sensitized controls and treated animals (sensitized and challenged with intratracheal administration of 0.1% RU 23,908). Controls received intratracheal challenge with saline only. Control animals were killed 24, 48, 72 and 168 hrs post-challenge, while treated animals were killed 24, 48, 72, 96 and 168 hrs post-challenge. No lesions indicative of pulmonary sensitization were observed. In addition, RU 23,908 antibodies were not detected in the plasma of sensitized control or treated animals.

Effect of RU 23,908 on Alcohol Dehydrogenase and Aldehyde Dehydrogenase Activity In vitro: Study 88/929/TX.

Some prostatic cancer patients treated with anandron have displayed a side effect resembling "antabuse-like" intolerance of alcohol. The effects of RU 23,908 and its hydroxylated metabolite, RU 48,275, on alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) activity in vitro were studied. Effects of the compounds on ADH and ALDH activity were measured using an Ethanol kit supplied by Boehringer. RU 23,908 and RU 48,275 were diluted in human plasma and tested at concentrations of 10^{-6} to 10^{-3} M. The effects of human plasma from RU 23,908 treated patients was also tested to assure no other metabolites affected ADH or ALDH activities. RU 23,908 and its metabolite(s) had no effect on the activity of these enzymes in this in vitro test system. Androgens have been reported to increase renal ADH synthesis and it is possible that anandron mediates its effects on alcohol metabolism by antagonizing the effects of androgens on enzyme synthesis.

Bioavailability Study in Healthy Volunteers: Study 88/763/CN.

Bioequivalence of tablets containing 50 or 150 mg of RU 23,908 was established. C_{max} , T_{max} , and $T_{1/2}$ were comparable for the 2 dosage forms (i.e., 1 x 150 mg or 3 x 50 mg). The AUC for the 3 x 50 mg dosage form was slightly (11%) higher than for the single 150 mg tablet. It was concluded that the slight difference in absorption would not significantly effect clinical use.

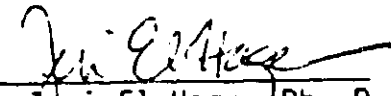
Conclusions - RU 23,908 inhibits the effects of testosterone in rats and dogs. Dogs appear to be more sensitive to drug inhibition and toxicity. Dose-related mortality was observed in the 1 year chronic toxicity studies at doses equivalent to the human therapeutic dose (i.e., 6 mkd). The cause of death was not specified but was characterized by decreased food consumption and body weight, marked anemia, significant alterations in all biochemical parameters and chronic interstitial pneumonia.

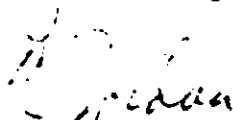
No drug-related mortality was observed in rats. Dose-related decreases in food consumption and body weight were observed. Dose-related increases in the incidence of lens opacities and anemia were observed. Treatment of dogs and rats produced the desired pharmacologic effects on male reproductive organs (decreased prostatic weight with tubuloalveolar atrophy, atrophy of seminal vesicles, inhibition of spermatogenesis). In rats these effects were accompanied by a dose-related increase in the incidence of leydig cell hyperplasia and a significant increase in benign leydig cell tumors in HD (45 mkd) rats. The drug-induced leydig cell hyperplasia was observed in other rat toxicity studies but has not been observed in dogs. Interstitial pneumonia was observed in animals from both chronic toxicity studies. An increased incidence of alveolitis and inflammation was observed in treated rats but pneumonia could not be definitively attributed to drug-treatment in dogs due to the high incidence in control animals.

Recommendation - Dyspnea and interstitial pneumonia have been the most common adverse reaction in men receiving anandron. The increased incidence of pneumonia in the chronic animal studies supports the previous conclusion that the pneumonia in man is drug-related. A letter should be drafted to the sponsor requesting the following information:

1. Cause of death (or poor condition resulting in killing) should be provided for dogs in the 1 year oral toxicity study.
2. Slides of the lungs from all groups in the 1 year dog and 18 month rat chronic toxicity study should be reexamined and the severity of the lung lesions should be graded.
3. Since the drug produced significant mortality in dogs at doses equivalent to the HTD, the sponsor should provide information regarding metabolism of the drug in different species (rats, dogs and man) including bioavailability, AUC, C_{max}, C_{SS}, T 1/2, and metabolite profiles.

cc: IND, HFD-510 IND, HFD-345
HFD-502/ Weissinger
HFD-510/ A Jordan/ J El-Hage
0610p


Jeri El-Hage, Ph. D.


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November 28, 1990

Drug: Anandron/ Nilutamide, RU-23,908

Sponsor: G.H. Besselaar Associates, Princeton, N.J. 08543
(for Roussel-UCLAF)

Submission Dates: 8-15-90, Annual Report; 9-24-90, Toxicology
Reports; 10-15-90 Background for Meeting.

Pharmacology Review of IND Amendments
Review #4

Annual Report, 1989

An overview of the pharmacokinetic data available for nilutamide was submitted. Raw data were not provided. The metabolic pathways for Nilutamide in rats, dogs and man are summarized in Figure 1. The pharmacokinetic data for Nilutamide in rat, dog and man are summarized in Table 1. It is noteworthy that the half-life of RU 23,908 is significantly longer in man than in other species (Man: $T_{1/2}$ = 59 hrs; Dog: $T_{1/2}$ = 9 hrs; Rat: $T_{1/2}$ = 4-8 hrs). In addition, the steady state plasma concentration achieved after 2 weeks dosing with 3 mg/kg/day nilutamide in man is greater than the C_{max} attained in rats or dogs dosed with 10 mkg. Data on C_{max} , AUC, $T_{1/2}$ values after multiple dosing were not provided. RU 23,908 is approximately 80% protein bound in all 3 species. Excretion of RU 23,908 is primarily renal with 66% urinary and 1-7% fecal excretion of total radioactivity within 5 days of dosing. RU 23,908 is extensively metabolized with only 2% of urinary radioactivity being parent compound.

Effects of RU 23,908 on Drug Metabolizing Enzymes in the Rat.

Doses of RU 23,908 $\geq$ 5 mg/kg/d produced 30% decreases in liver cytochrome P-450 activity (benzopyrene hydroxylase and benzphetamine N-demethylase). Changes observed are qualitatively similar to those produced by castration and, therefore, are probably related to the antiandrogenic activity of the compound. Neither RU 23,908 or castration had effects on adrenal cytochrome P-450, benzopyrene hydroxylase or progesterone-21-hydroxylase activity.

RU-23,908 (110 μ M) inhibited the activities of hexobarbital hydroxylase, benzphetamine N-demethylase, benzo(a) pyrene hydroxylase and 7-ethoxy-coumarin-O-deethylase by 85, 40, 35 and 25%, respectively, in human liver microsomal preparations.

Administration of RU 23,908 (15 or 30 μ M/kg, ip) increased hexobarbital-induced sleeping time by 40 and 60%, respectively (doses are comparable to the HTD).

RU 23,908 produces dark adaptation disorders (25% of orchiectomy + anandron patients; 50% of leuprolide + anandron treated subjects) comparable to those observed in hypovitaminosis A. RU-23,908 (10 or 20 μ M) had no effect on retinol/retinoic acid binding to cellular or plasma retinol-binding proteins. At high concentrations (120 μ M) Ru 23,908 displaced retinol from retinol binding protein in the human prostate.

Nilutamide produces alcohol intolerance in some patients. RU 23,908 (10^{-4} to 10^{-3} M) or its metabolite RU 48,275 had no effect on the in vitro activity of alcohol or aldehyde dehydrogenase.

The activities of 4 metabolites of RU 23,908, namely, RU 43,866, RU 45,018, RU 48,166, and RU 48,275 were compared. Only RU 48,275 interacted with androgen receptors and exerted dose-related anti-androgenic effects comparable to RU 23,908. The NO₂ group seems to be important in the antiandrogenic activity.

Pulmonary Sensitization in the Rat - Male Brown-Norway rats were administered 0.05 mg RU 23,908, intratracheally and then received a challenge injection of drug. Rats displayed no pulmonary sensitization to Anandron.

In vitro Study in Rat Hepatocytes - RU 23,908 was added to the nutrient medium of primary rat hepatocyte cultures and concentrations of intracellular enzymes in the medium and cellular cytochrome P-450 activities were measured. RU 23,908 was tested at concentrations of 0, 20, 40, 60, 80 and 100 μ g/ml (0, 0.63, 1.26, 1.89, 2.52 and 3.15 times 10^{-4} M). After 24 hours of incubation doses $\geq$ 60 μ g/ml increased LDH and doses $\geq$ 80 μ g/ml increased SGPT/SGOT. No effects on intracellular cytochrome P-450 activity were observed.

A similar study was conducted examining the effects of Flutamide on rat hepatocytes in vitro. Doses utilized were 0, 20, 40, 60, 80 and 100 μ g/ml (0, 0.72, 1.45, 2.17, 2.9, and 3.62×10^{-4} M). Significant release of all liver enzymes (i.e., LDH, SGOT, SGPT) was observed at concentrations $\geq$ 60 μ g/ml after both 8 and 24 hours of incubation. The 100 μ g/ml concentration of flutamide also produced a significant reduction of intracellular cytochrome P-450 concentration.

Human Pharmacokinetics and Bioavailability

Nilutamide concentrations in plasma of treated subjects were measured by RIA and HPLC in order to determine the comparability of the two assays. The RU 43,866 and 45,018 metabolites displayed 58 and 34% cross-reactivity, respectively, with the RU 23,908 antiserum. It was determined that the radioimmunoassay overestimated the nilutamide concentration by 24% compared to the

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RU 23,908/Nilutamide

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HPLC values.

Subjects were administered a single 100 mg dose of ^{14}C -nilutamide. 62% of the total radioactivity was excreted in the urine and 1-7% excreted in the feces within 120 hours. The $T_{1/2}$ of anandron in man was calculated to be 60-90 hours. The $T_{1/2}$ of some RU 23,908 metabolites were longer than the parent compound. Only 2% of parent compound was excreted suggesting anandron is extensively metabolized. A small percent of radioactivity was excreted in the feces suggesting the drug is almost completely absorbed.

PHARMACOLOGY

All pharmacology and toxicology studies were performed by Roussel-UCLAF unless stated otherwise.

Effect of RU 23,908 on Carrageenin Pleurisy in the Rat. Study 349

Male CFHB rats were administered 0, 10, or 50 mg/kg/d RU 23,908, po for 10 days. Carrageenin (1 mg) was injected into the left pleural cavity on day 10 and exudate volume and total cell numbers were measured 24 hours later. RU 23,908 had no effect on carrageenin-induced pleurisy in the rat.

Effect of Ru 23,908 on N-methyl-N-nitrosourea (NMU) Induced Rat Mammary Carcinomas. Study 86/271/PH

Female Wistar rats were administered 50 mg/kg NMU, sc on days 0, 14, and 28. This regimen is known to produce multiple mammary tumors within 3-4 months in 95% of treated rats. Animals (n = 12/gp) with established tumors were fed RU 23,908 at doses of 0, 10 or 20 mg/kg/day for 4 weeks. No significant differences in the number of animals showing tumor regression or progression were noted between treatment groups.

TOXICOLOGY

Acute Oral Toxicity of RU 46,275 in the Mouse. Study 88/987/TX (88-308).

Swiss OF1 mice (5/s/gp) were orally administered 0 or 2000 mg/kg RU 46,275 in 0.5% methylcellulose. No mortality, changes in body wt or gross histopathological changes were observed. All drug-treated males displayed unprovoked squeals 30 minutes after dosing. Ptosis was observed in 2/5 M and 2/5 F drug-treated animals on the day following drug administration. The lethal dose in mice is greater than 2,000 mg/kg, po.

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RU 23,908/Nilutamide

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Acute Oral Toxicity of RU 48,275 in the Rat. Study 88/989/TX (88-306)

Sprague-Dawley rats (5/s/gp) were orally administered 0 or 2000 mg/kg RU 48,275 in 0.5% methylcellulose. No mortality or changes in body weight gain were observed. Signs observed in drug-treated animals included:

Arched back observed from 30 minutes through day 2 in 5/5 M and 5/5 F.
Locomotor difficulties for 2 hours after dosing in 5/5 M, 3/5 F
Distension of abdomen on day 2 in 5/5 M.

Gross histopathologic examination on day 14 revealed congestion of gastric fundus in 1/5 M. No abnormalities were noted in females.

The lethal dose of RU 48,275 in the rat is greater than 2,000 mg/kg, po.

Acute Intraperitoneal Toxicity of RU 48,275 in the Mouse. Study 88/986/TX (88-309).

Swiss Of mice (5/s/gp) were administered 0 or 200 mg/kg RU 48,275, ip. No mortality or changes in body weight gain were observed. Drug-treated males displayed slight hypotonia and piloerection; 1/5 M had diarrhea on day 2. Drug-treated females displayed ptosis and hypomotility; 1/5 F had diarrhea on day 2. White precipitate in the abdominal cavity and adhesions between viscera were observed on day 15 in 4/5 M and 4/5 F.

The lethal dose of RU 48,275 in the mouse is greater than 2,000 mg/kg, ip.

Acute Intraperitoneal Toxicity of RU 48,275 in the Rat. Study 88/988/TX (88-307)

Sprague-Dawley rats (5/s/gp) were administered a single dose of 0 or 2000 mg/kg RU 48,275, i. No mortality or effects on body wt gain were observed. Signs observed in drug-treated rats included:

Hypotonia - 5/5 M, 5/5 F through day 4
Arched back - 5/5 M, 5/5 F through day 3
Locomotor difficulties - 5/5 M, 5/5 F through day 3
Hollow flanks - 5/5 M, 5/5 F through day 7

Histopathology - White deposits on liver - 5/5 M, 3/5 F.
Adhesions between viscera - 4/5 M, 5/5 F.

The lethal dose of RU 48,275 in the rat is greater than 2,000 mg/kg, ip.

Acute Oral Toxicity of RU 23,908 in Beagle Dogs. Study # 5029.

Beagle dogs were orally administered a single dose of 1,000 (n=2 M) or 2,000 mg/kg (n=2/s) RU 23,908 in gelatin capsules.

Mortality - none.

Signs - Hypotonia after dosing in 1/2 LD M, 2/2 HD M and F.
Vomiting (LD, HD) and diarrhea (HD) observed on day 1.

Body wt and Food consumption were decreased on days 1-4.

No drug-related effects on organ wts or gross histopathology were observed.

Histopathology-

Lungs- chronic interstitial pneumonitis 1/2 HD M, 1/2 HD F.

Administration of a single 1,000 or 2,000 mg/kg, po dose of RU 23,908 to dogs produced hypotonia, diarrhea and vomiting and reduced food consumption and body weight. No mortality was observed.

One Year Oral Toxicity Study in Beagle Dogs. Study 1042 TCC.
Supplemental Report of Lung Histopathology.

Lung tissue from all treatment groups (0, 3, 6, and 12 mkd) in the one year oral toxicity study in dogs was examined histopathologically. Morphologic changes in the lungs were observed in comparable incidence and severity in control and drug-treated dogs.

78 Week Oral Toxicity Study of RU 23,908 in the Rat.
Supplemental Report of Lung Histopathology.

Lung tissue from all treatment groups (0, 5, 15 and 45 mkd) of the 78 week oral toxicity study in rats were examined histopathologically. Morphologic changes in the lungs were comparable in incidence and severity in control and drug-treated rats suggesting the chronic interstitial pneumonitis observed was not drug-related.

Segment I - Male Fertility Study

The effects of RU 23,908 administered orally prior to and during early pregnancy in the rat were assessed. The study was conducted at

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RU 23,908/Nilutamide

Male Sprague-Dawley rats were treated with 0, 5, 15 or 45 mg/kg/day RU 23,908 for 63 days prior to and during the mating period (1-5 days). Females were treated for 14 days prior to and during mating (1-5 days) and for the first 7 days of pregnancy with 45 mg/kg/day RU 23,908. Animals were mated as follows- Control M + Control F, LD M + untreated F, MD M + untreated F, HD M + untreated F, HD M + HD F.

Results - No mortality or signs were observed. No effects on food consumption or body weight were observed in treated females. Dose-related decreases in body weight gain and food consumption in drug-treated males. Drug treatment increased testicular wts and decreased prostate, epididymal, and seminal vesicle wts in MD and HD males. No drug-related effects on male fertility rate were observed.

Untreated females mated with HD males had decreased numbers of corpora lutea and decreased implantation sites, however, these parameters were normal in HD females mated with HD males. An increased incidence of dead/resorbed fetuses were observed in untreated F mated with LD or HD males. Again no drug effects were observed in HD F mated with HD males.

Drug treatment had no effects on sex ratio, pup weights, or the frequency of external or skeletal anomalies in the pups.

Summary - RU 23,908 had sex specific effects producing decreases in food consumption and body wt gain, splenic enlargement, and decreases in the weights of reproductive organs in males but had no systemic effects on female rats. The effects of RU 23,908 on reproductive parameters are questionable. Mating of HD males to untreated females produced impairments while females treated with high doses of drug and mated with HD males showed no reproductive abnormalities. No lethal, teratogenic or growth suppressive effects on fetuses were observed.

Conclusion: Doses of RU 23,908 up to 45 mg/kg/day (9 x HD) had no effects on the reproductive capacity of male rats.

Thirty Day Subchronic Oral Toxicity Study in the Dog
(#89/1376/TX)

Beagle dogs (3/s/gp) were administered 0, 3, 10, 30 and 60 mg/kg/day RU 23,908 in gelatin capsules for 30 days.

Mortality - All HD animals died or were killed in extremis.

Signs - no signs were observed in control, LD or LM dose dogs.

Dogs receiving 30 mkd(HM) displayed hypotonicity and locomotor difficulties from week 2. Female dogs also displayed episodic vomiting and soft stools.

Dogs receiving 60 mg/kg/day displayed hypotonicity and locomotor difficulties from week 1 becoming increasingly severe over the course of treatment (animals became totally nonresponsive). HD animals displayed episodic vomiting, generally within hours of dosing. HD animals had soft stools, diarrhea, and pallor of mucous membranes and refused to eat or drink beginning in week 2 leading to dehydration and cachexia.

Body weight - All HD animals had decreased food consumption and lost weight (3 kg).

ECG - No drug-related effects on ECG, HR, or BP were observed.

Ophthalmology - conjunctival discoloration was observed in 3/3 HD M dogs. No other ophthalmic changes were observed.

Hematology -

Decreased RBC, Hgb and Hct were observed in all dose groups including controls. Sponsor suggests anemia was due to repeated blood sampling performed during the first week of study (for determination of pharmacokinetic parameters).

Increased platelet counts in HD dogs.

Biochemistry -

Day 15 - decreased Na 1/3 HD F ; decreased P 1/3 HD M, F; decreased Cl 1/3 HD F; increased Mg 1/3 HD M, 3/3 HD F.

Increased urea 1/3 HD M, 1/3 HD F

Day 30- decreased Cl 1/3 HD M, 1/3 HD F; increase Mg 2/3 HD M, 2/2 HD F. Increased cholesterol 2/3 HD M, 1/3 HD F.

Increased blood glucose 1/3 HD M, 1/3 HD F.

Increased bilirubin 1/3 HD M, 1/3 HD F.

Increased urea 3/3 HD M, 2/2 HD F, increased urea was not associated with a change in creatinine.

Urinalysis - normal except in HD M which displayed diuresis on day 30.

Gross histopathology -

Hemorrhagic lesions of vesicle mucous membranes in 30 and 60 mkd males and all drug-treated females.

Hemorrhagic and/or ulcerative lesions of GI mucosa in HD dogs which died.

Atrophy of testes and prostate in 2/3 HD male dogs.

Atrophy of thymus in 2 HD M and 1 HD F.

Organ weights-

Prostate- dose-dependent decrease in prostate weights

Thymus- decreased wts in 1 LD, 1 LM, 1 HM, 3 HD males, all HD F.
Liver - increased wts in 1 HM M, 1 HM F; 3 HD M, 1 HD F.

Histopathology-

Prostate - marked fibrous involution in all drug-treated males.
Testes- absent or incomplete spermatogenesis 2/3 LD, 3/3 LM, HM, HD males.
Epididymes - atrophy and peritubular myofibroblastic thickening 2/3 HM, 3/3 HD males.
Thymus - pronounced involution in 3/3 HD M and 2/3 HD F.

Plasma Drug Levels (Study # 90/1904/CN)

Plasma drug concentrations were measured in dogs from the 30 day toxicity study reviewed above. Blood samples were obtained at 0, 1, 2, 4, 7, 12 and 24 hours after dosing on day 1 and 24 hours after dosing on days 2, 5, 6, 9 and 15.

Plasma drug concentrations increased with increasing dose but not proportionally (see Table below taken from Vol. 20.1, Attachment 4, p. 5). No sex differences were observed in Cmax or AUC and no plasma drug accumulation was noted after multiple dosing. Sex differences were noted in plasma half-life of RU 23,908; $T_{1/2}$ = 7.75 hrs in M and 10.3 hrs in F.

Dose (mg.kg ⁻¹)	3	10	30	60
Cmax (mg.l ⁻¹)				
D1 and D30	1.65 ± 0.11	3.50 ± 0.24	5.95 ± 0.73	-
D1	1.51 ± 0.21	3.46 ± 0.47	6.47 ± 0.84	13.7 ± 2.4
AUC (mg.l ⁻¹ .h)				
D1 and D30	21.8 ± 1.4	47.7 ± 3.7	90 ± 12	-
D1	19.5 ± 2.2	46.2 ± 6.0	101 ± 14	223 ± 44
Cmax/dose				
D1 and D30	0.549 ± 0.037	0.350 ± 0.024	0.198 ± 0.025	-
D1	0.503 ± 0.069	0.346 ± 0.047	0.215 ± 0.028	0.229 ± 0.040
AUC/dose				
D1 and D30	7.27 ± 0.47	4.77 ± 0.37	2.99 ± 0.41	-
D1	6.48 ± 0.73	4.63 ± 0.60	3.36 ± 0.47	3.71 ± 0.74
C24 (mg.l ⁻¹)				
D1 to D30	0.204 ± 0.020	0.935 ± 0.085	3.14 ± 0.30	-

SUMMARY AND CONCLUSIONS

- The pharmacokinetics of nilutamide in man are quite different from rat and dog. ($T_{1/2}$ = 59 hrs in man, 9 hrs in dog and 4-8 hrs in rat). Steady state plasma concentrations in patients receiving 150 mg/day (3mkd) are higher than the C_{max} concentrations in rats and dogs dosed with 10 mkd. The 6 and 12 mkd doses of RU 23,908 produced 33 and 75% mortality, respectively, in the 1 yr dog study. It is disconcerting that therapeutic doses of nilutamide produce steady state plasma drug concentrations in man higher than those which are lethal in dogs; especially since the cause of toxicity and death in dogs is unknown. The dog is more sensitive to the antiandrogenic and toxic effects of anandron. Nilutamide has a higher affinity for dog prostatic androgen receptor than for rat or human androgen receptors (25 times affinity for the rat receptor and 2.5 times the affinity for the human receptor). High doses of nilutamide were toxic in dogs of both sexes, suggesting the toxicity may not be due to an exaggerated pharmacologic effect.

A supplemental 30 day oral toxicity study in dogs was submitted. The 60 mkd dose was lethal to dogs of both sexes (females more sensitive). Dogs were non-responsive (curled up in corner of cage) refusing to eat or drink and died of dehydration and malnutrition (lost 3 kg). Signs including hypoactivity, vomiting, diarrhea were also observed in dogs receiving 30 mkd. The cause of death in the dogs was most probably dehydration and malnutrition but the reason the animals refused to eat or drink is not clear.

Interstitial pneumonitis has been observed in 1.5-3% of the subjects treated with nilutamide in the clinical trials. A high incidence of interstitial lung disease was also observed in the chronic oral toxicity studies (1 yr dog and 18 mos rat). Re-examination of lung tissue from these studies failed to demonstrate a drug-related increase in the incidence or severity of lung disease.

Dose-related anemia (decreased RBC, Hgb, Hct) has been observed in rats and dogs receiving nilutamide. The anemia was especially severe in HD animals of both species which died as a result of drug treatment. Drug treatment has not significantly increased the incidence of anemia in man.

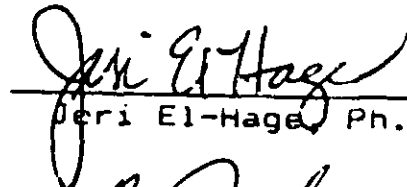
Besselaar (Roussel-UCLAF) has continuously submitted Toxicology studies without summary tables. Several written requests have been sent and a verbal request for summary tables was made again at the 11-28-90 meeting with the firms. Mr. Burns assured me that the problem would be corrected for all studies submitted in the NDA.

IND
RU 23,908/Nilutamide

10

Recommendation - No action indicated.

cc: IND, HFD-510 IND, HFD-345
HFD-510/ A Jordan/ J El-Hage
26525.amd
11-29-90


Jeri El-Hage Ph.D.

11/30/90

Table 1: Pharmacokinetic Parameters of Nilutamide (RU23 908)

Oral Dosing	C _{max} (μg/ml)	T _{max} (hr)	AUC _{0-24h} (μg/ml x hr)	Elimination T _{1/2} (hr)	Serum Binding to protein (%)
Rat (Sprague-Dawley male) 10mg/kg 15 days n = 5	Day 1	2.95	2.0	2 Exp. 4.0 1 Exp. 8.4	-80
	Day 15	3.75	1.5	4.8 9.3	(concentrations .01 - 10 μg/ml)
	Steady state achieved after 2nd dose				
Dog (Beagle-male) 10mg/kg 15 days n = 4	Day 1	3.39±0.75	8	50.8±8.3	-80
	Day 15	5.20±0.73	4	80.2±17.4 9.11±1.4	(concentrations .01 - 10 μg/ml)
	Steady state achieved after 2nd dose				
Human (male) 150mg (.3mg/kg) 21 days n = 10	Single Dose	.90±0.22	2.8±1.1	38.6±8.4 59.1±17.3	-80
	Repeated Dose	Steady state achieved after approximately 2 weeks (4.4 - 8.5 μg/ml)			
	(concentrations .32 - 32 μg/ml)				

$\frac{150\text{mg}}{70\text{kg}} = 2.14\text{ mg/kg}$
 $T_{1/2}$ in man $\frac{59\text{hrs}}{2.14\text{ mg/kg}} \geq C_{\text{max}}$ in dog 1 day on 10 mg/kg/day
 $C_{\text{ss}} = 4.4 - 8.5 \mu\text{g/ml}$

APPENDIX 2

COMPARATIVE TOXICITY NILUTAMIDE VS FLUTAMIDE

Drug: Nilutamide (Anandron, Nilandron)

Sponsor: Roussel UCLAF, Romaineville, France

COMPARATIVE TOXICITY OF NILUTAMIDE AND FLUTAMIDE

A comparison of the preclinical toxicity profiles of the previously approved anti-androgen Flutamide and Nilutamide has been conducted and is presented below. The preclinical toxicity studies with nilutamide demonstrate fatal liver toxicity in dogs and interstitial lung disease in rats administered dose levels which produce plasma drug exposures (AUC) comparable to exposures obtained with the therapeutic doses of 150 or 300 mg/day. Therefore, the preclinical data do not support the safety of the proposed therapeutic doses. Preclinical toxicology studies with flutamide demonstrate that doses of flutamide which produce AUC exposures in the therapeutic range are well tolerated. Toxicity is observed in rats and dogs treated with flutamide when AUC exposures are ≥ 8 times therapeutic AUC exposures.

There is biochemical evidence to suggest the mechanism involved in Nilutamide-induced liver and lung toxicity. Several published papers have demonstrated that Nilutamide is reduced to a nitro anion free-radical capable of generating toxic reactive species under both aerobic and anaerobic conditions. (Berson et al, JPET 257, 1991; Berger et al, Biochem. Pharm. 43, 1992). Metabolism of nilutamide to superoxide anions and increased production of hydrogen peroxide have been demonstrated in rat lung, rat liver and human liver microsomes. The hepatic and pulmonary toxic effects observed with nilutamide are similar to the adverse effects observed with other nitroaromatic compounds, such as nitrofurantoin. Like Nilutamide, nitrofurantoin has been demonstrated to form nitroanion free radicals in the rat lung and produce interstitial fibrosis/pneumonitis in humans. Flutamide does not form nitro anion free radicals in similar experiments or produce interstitial lung disease in animals or man.

Metabolism

Flutamide

The metabolism of Flutamide is qualitatively and quantitatively similar in all species. Flutamide is rapidly and extensively metabolized to hydroxy-flutamide, the active drug. The half-life of OH-flutamide is 6-8 hours in all species and drug is extensively protein bound (92-94%).

Nilutamide

The metabolism of Nilutamide is very different between species resulting in large differences in plasma half-lives and drug exposures (AUC) for comparable doses (see Table 1). The plasma half-life of nilutamide is 5 hrs in rats, 9 hours in dogs and 45-60 hours in man. The long plasma half-life of nilutamide in man is of concern since data suggests toxicity is associated with the parent compound. Nilutamide displays less extensive protein binding than flutamide with 80% of drug bound to plasma proteins in all species.

Acute Toxicity

Acute toxicity testing also suggests Nilutamide is more toxic than flutamide. Oral LD 50 for nilutamide in rats or mice = 200 mg/kg; oral LD 50 for flutamide > 2000 mg/kg (LD 50 for flutamide in male rats = 3258 mg/kg).

The acute toxicity of the primary metabolites of Nilutamide in the rat and dog has been tested. RU 45,018, RU 43,866, and 48,275 are all less toxic than the parent compound, Nilutamide. The acute toxicity of RU 48,276, a metabolite found only in man has not been tested.

Drug-Related Toxicity

The target organs of toxicity for flutamide and nilutamide are depicted in the Table 2. The target organs are similar for the two compounds except for lung toxicity, which is observed only with Nilutamide.

TABLE 2 DRUG-RELATED TOXICITIES OBSERVED

	<u>Anemia</u>	<u>Liver</u>	<u>Kidney</u>	<u>Lung</u>
RAT				
Nilutamide	+	+	+	+
Flutamide	+	+	+	-
DOG				
Nilutamide	+	+	+	+
Flutamide	+	+		-
MAN				
Nilutamide	-	+	?	+
Flutamide	+	+		-

COMPARATIVE TOXICITY OF NILUTAMIDE AND FLUTAMIDE IN THE DOG

NILUTAMIDE

<u>Species</u>	<u>Dose (duration)</u>	<u>Nilutamide AUC (ug.hr/ml) *</u>	<u>% Mortality</u>	<u>Multiple of Human AUC</u>
DOG	60 mkd (1 month)	223	100%	1-2 X
	30 mkd (6 month)	90-100	70%	1/2-1 X
	20		20%	
	10	48	0%	1/4-1/2 X
	12 mkd (12 month)	50	50%	1/4-1/2 X
	6		33%	
	3	22	0%	0.1 X
MAN	150 mg/d (2.5 mkd)	90		
	300 mg/d (5 mkd)	180		

FLUTAMIDE

		<u>AUC OH-Flu amide</u>		
DOG	75 mkd (6 wks)			
	+ 50 mkd (9 wks)	100-150	65%	12-18 X
	35 mkd (15 wks)	70	15%	8.5 X
	11 mkd (6 mos)	23	0%	3 X
	40 mkd (13 mos)	80	20%	10 X
	25	50	0%	6 X
	15	30	0%	4 X
MAN	750 mg/d	8		

* Mean plasma drug AUC (0-24) at steady state in both dogs and man.

DOGS

Deaths in Nilutamide treated dogs were associated with liver toxicity. Marked to massive hepatocyte swelling and vacuolization were observed histologically in affected dogs. The liver toxicity observed with Nilutamide is cumulative, appearing at lower dose levels as the duration of treatment increases. Liver toxicity with Flutamide does not appear to be cumulative with the lowest toxic dose being 35-40 mg/kg/day (8 to 10 times human exposure) regardless of duration of dosing. The only liver enzyme with consistent elevations in all dogs displaying nilutamide or flutamide liver toxicity was alkaline phosphatase (2-fold). ALT, LDH and CPK were sporadically increased in nilutamide treated dogs displaying liver toxicity. Flutamide increases additional enzymes (ALT, 5 NT) in rats and man.

CONCLUSION

In dogs, the best animal model for nilutamide and flutamide metabolism, lethality occurred at AUC's ≥ 8 times the maximum human exposure with flutamide but at only 0.1 to 1 times the human exposure with nilutamide.

TABLE 3. COMPARATIVE TOXICITY OF NILUTAMIDE AND FLUTAMIDE IN RATS

NILUTAMIDE

<u>Dose</u>	<u>% mortality</u>	<u>AUC*</u>	<u>Liver</u>	<u>Lung</u>	<u>Kidney</u>
RAT					
250mkd, 13 wks	70%	-	+	+	+
50	0%	220	+	+	+
10	0%	44	-	+	+
50mkd, 26wks	0%	220	+		+
20		90	+		
10		44	-		-
45mkd, 78wks	0%	200	+	+	+
15		60	-	+	+
5			-	-	-
MAN					
150 mg/d (2.5 mkd)		90	+	+	
300 mg/d (5 mkd)		180	+	+	

FLUTAMIDE

		<u>AUC</u>	<u>Liver</u>	<u>Lung</u>	<u>Kidney</u>
RAT					
150mkd, 13wks	0%		+		+
75			+		-
25			-		-
180mkd, 52wks	0%		+		+
90			+		-
30		75-90	-		-
MAN					
250 mg, tid		8	+		

AUC = area under the concentration time curve from 0-24 hours after dosing in ug.hr/ml. Values presented are AUC's at steady state for all species.

* In rats, the steady state AUC for the 10 mkd dose of nilutamide is 44 ug.hr/ml. The AUC for doses above 10 mkd have not been determined. Assuming linear pharmacokinetics, the AUC for the 45-50 mkd dose = 200-220 ug.hr/ml, roughly equivalent to the AUC with the 300 mg/day therapeutic dose.

RATS

Nilutamide at doses ≥ 15 mkd (AUC exposures less than human exposure on 150 mg/day) produces anemia, lung and kidney toxicity in treated rats. Lung changes observed in the rat included increases in the frequency of granulomatous inflammation, alveolitis (defined as alveolar septal thickening and interstitial fibrosis) and alveolar hemorrhage. Liver toxicity in the rat was observed with the 45 and 50 mkd doses which produce AUC exposures 1-2 times human therapeutic exposure. Liver toxicity again was not clearly associated with increases in liver enzymes. (liver weights increased and increased frequency of chronic hepatocyte necrosis).

No drug-related toxicities were observed in rats dosed with 20 to 30 mkd of **flutamide** which produces an AUC exposure 10 times that achieved with therapeutic doses. Mild liver toxicity consisting of sporadic changes in liver enzymes was observed with high doses (≥ 75 mkd) of flutamide. Lung toxicity was not observed with flutamide.

INTERSTITIAL PNEUMONITIS IN MAN

The sponsor evaluated the relationship between plasma drug concentrations in subjects with and without pneumonitis. The validity of this evaluation is questionable since blood samples were obtained at variable intervals from dosing and may represent maximum plasma concentrations in some subjects and trough concentrations in others. If mean steady state plasma concentrations for each study are compared to the incidence of interstitial pneumonitis observed in each study there is a clear dose-response relationship.

	<u>Mean plasma Nilandron (ug/ml)</u>		<u>Incidence of Pneumonitis</u>
	DOSE		
Study	300mg/d	150mg/d	
86/908/01	3.8	2.1	1/225 (0.4%)
GHBA 606	5.7	2.6	7/209 (1.8%)
89/1108/CN (Japanese)	8.9	4.9	8/47 (17%)

Note: In controlled trials, 86/908/01 and GHBA 606, 7/8 cases of pneumonitis were diagnosed within the first 60 days of dosing. This also suggests a causal relationship with the higher 300 mg/day dose.

Data regarding the onset of pneumonitis and liver toxicity in Japanese subjects treated with Nilutamide (Study J87/908/02) is summarized below. The higher blood levels of Nilutamide in the Japanese may be a function of lower body weight (and therefore higher mg/kg dosing) in these subjects.

Incidence of Adverse Reactions in Japanese Men

Wks on Study	<u>Interstitial Pneumonitis</u>	<u>Increased LFT</u>
< 12 wks	3/47	9/47
> 12 wks	5/29	1/29
Total Incidence	8/47 (17%)*	10/47 (21%)**

* Four additional cases of possible interstitial pneumonitis were reported but judged retrospectively not to be pneumonitis.

** As has been previously reported for Flutamide, the majority of liver enzyme elevations are reported within the first 3 months of treatment.

The most frequently reported adverse events in subjects treated with Nilutamide in the controlled trials are summarized in the attached tables (see next page). The most commonly reported adverse reactions in men were visual disturbances, nausea and vomiting, dyspnea, and alcohol intolerance. An increased number of subjects with liver enzyme elevations was seen only in study 86/908/01 (4% of placebo, 8% of nilutamide treated men).

The table below demonstrates that the incidence of adverse events was greater in study 606, in which patients had higher plasma nilutamide concentrations at steady state. In addition, more than 75% of adverse events were reported by day 38 of treatment (i.e., 19/25 and 45/64 cases of nausea/vomiting; 47/64 and 121/138 cases of visual disturbances).

Overall incidence of nausea/vomiting - visual disturbances
Number and percent of patients with early * occurrence

	FF/86/908/01 N = 225 No of patients (%)	GHBA 606 N = 209 No of patients (%)
<u>Nausea/vomiting</u>		
At any time	25 (11 %)	64 (31 %)
≤ day 38	19 (8.4 %)	45 (22 %)
<u>Visual disturbances</u>		
At any time	64 (28 %)	138 (66 %)
≤ day 38	47 (21 %)	121 (58 %)

NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY REPORTED
ADVERSE EXPERIENCES IN STUDY NO. FF/86/908/01

Adverse Experience	Number (%) of Patients	
	Nilutamide (N=225)	Placebo (N=232)
Hot Flushes	63 (28)	51 (22)
Death	34 (15)	28 (12)
Impaired Adaptation to Darkness	29 (13)	3 (1)
Nausea	20 (9)	13 (6)
SGOT increased	17 (8)	9 (4)
SGPT increased	17 (8)	10 (4)
Dizziness	16 (7)	9 (4)
UTI	16 (7)	18 (8)
Constipation	14 (6)	8 (3)
Abnormal vision	13 (6)	4 (2)
Dyspnea	13 (6)	14 (6)
Hypertension	11 (5)	5 (2)
Alcohol Intolerance	11 (5)	1 (<1)

NUMBER (%) OF PATIENTS WITH THE MOST FREQUENTLY REPORTED
ADVERSE EXPERIENCES IN STUDY NO. GNBA-606

Adverse Experience	Number (%) of Patients	
	Nilutamide (N=209)	Placebo (N=202)
Hot Flushes	137 (66)	118 (58)
Dark Adaptation Impairment	118 (56)	11 (5)
Nausea	49 (23)	15 (7)
Pain	48 (23)	48 (24)
Constipation	40 (19)	30 (15)
Asthenia	38 (18)	38 (19)
Insomnia	31 (15)	32 (16)
Testicular Atrophy	31 (15)	21 (10)
Headache	27 (13)	19 (9)
SGOT Increased	26 (12)	28 (14)
Libido Decreased	23 (11)	9 (4)
Peripheral Edema	23 (11)	32 (16)
Dyspnea	22 (11)	12 (6)
Impotence	22 (11)	24 (12)
Infection	22 (11)	26 (13)
Anorexia	20 (10)	12 (6)
Back Pain	20 (10)	30 (15)
Death	20 (10)	16 (8)
Dizziness	19 (9)	20 (10)
SGPT Increased	19 (9)	18 (9)
Abdominal Pain	18 (9)	11 (5)
Chromatopsia	18 (9)	0 (0)
Depression	18 (9)	14 (7)
Gynecomastia	18 (9)	20 (10)
Hypertension	16 (8)	18 (9)
Urinary Tract Infection	16 (8)	42 (21)
Anemia	15 (7)	12 (6)
Hematuria	15 (7)	14 (7)
Light Adaptation Impairment	15 (7)	2 (1)
Bone Pain	13 (6)	10 (5)
Dyspepsia	13 (6)	8 (4)
Flu Syndrome	12 (6)	4 (2)
Sweating	12 (6)	6 (3)
Urinary Tract Disorder	12 (6)	14 (7)
Vomiting	12 (6)	8 (4)
Alopecia	11 (5)	1 (<1)
Chest Pain	11 (5)	8 (4)
Dry Skin	11 (5)	5 (2)
Fever	11 (5)	13 (6)
Rash	11 (5)	8 (4)
Hypesthesia	10 (5)	4 (2)
Nocturia	10 (5)	10 (5)

NDA 20-¹⁶⁹~~469~~

January 2, 1996

Drug: Nilutamide, Casodex

Sponsor: Corning Besselaar, Princeton N.J. for
Roussel UCLAF, Romaineville, France

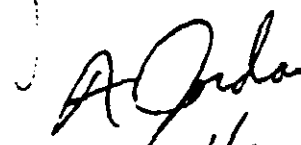
Submission Date: December 15, 1995

Pharmacology Review of Revised Labelling

The original labelling had omitted the Animal Pharmacology and Toxicology section specifically requested by the division. The data on the liver toxicity of nilutamide in dogs and free radical generation in the lungs and livers of nilutamide-treated rats and humans have been included in the revised labelling (see page 7 of the revised label dated 12-7-95).

The Pharmacology section of the revised labelling dated 12-7-95 is acceptable.


Jeri El-Hage, Ph.D.


1/2

cc: NDA 20-469, HFD-510 NDA
HFD-510/ A Jordan/ J El-Hage
20469.lab

425,000

FEB 6 1995

NDA 20-169

NILANDRON (ANANDRON, NILUTAMIDE)

SPONSORS: ROUSSEL UCLAF
Paris, France

G.H. BESSELAAR ASSOCIATES
Princeton, New Jersey

RECOMMENDATION -

Nilandron produces fatal liver toxicity in dogs and interstitial lung disease in rats at dose levels which produce plasma drug exposures (AUC) less than or equal to AUC exposures obtained in men on therapeutic doses. The preclinical toxicity studies do not support the safety of the therapeutic dose levels and, therefore, the NDA is non-approvable for Pharmacology/Toxicology.

Jeri El-Hage 2/5/95
Jeri El-Hage, Ph.D.

A Jordan
2/6

CC: NDA 20-169, HFD-510 NDA, HFD-502
HFD-510/ A Jordan/ J El-Hage
NDA 20-169

NDA 20-169

April 11, 1996

Drug: Nilandron; Nilutamide

Sponsor: Besselaar Associates for Roussel UCLAF-

Submission Date: March 15, 1996

This submission contains information regarding the environmental assessment for Nilandron and the revisions to the patient package insert recommended by the division. The pharmacology/toxicology sections of the label have been revised as requested and are acceptable.

Jeri El-Hage
Jeri El-Hage, Ph.D.

stat

FEB 3 1995

Statistical Review and Evaluation

NDA#: 20-169/1-S

Applicant: Roussel-UCLAF

Name of Drug: Anandron (nilutamide)

Indication: Stage D2 prostate cancer

Documents Reviewed: Vols 2.52, 2.53, 2.59, 2.62

Medical Officer: Jean Fourcroy, M.D., HFD-510

Background

The sponsor has submitted two randomized, multicenter, double blind trials evaluating the safety and efficacy of nilutamide in the treatment of Stage D2 prostatic cancer. In study FF/86/908/01 (GHBA-608 & GHBA-610), all patients had received orchiectomy before being randomized to either nilutamide or placebo. In study 606, all patients received leuprolide as chemical castration before being randomized to nilutamide or placebo.

The sample sizes for both trials (approximately 200 patients/arm) were based upon detecting a 20-30 week difference in time to objective progression assuming that the median time to progression would be 65 weeks in the placebo arm (one-sided test at the .05 level). Both protocols state: "Treatment comparisons will be based on time to objective and subjective progression (NPCP), survival, clinical response (signs, symptoms and global responses), pain, and performance (Karnofsky)."

Study FF/86/908/01

According to the study report, the primary clinical outcomes were objective response, best response to treatment, time to objective progression, time to objective or subjective progression, time to death from prostate cancer, and time to death from any cause. Secondary outcomes included metastatic pain, Karnofsky performance status, urinary obstruction, and patients' and investigators' global evaluations.

Two hundred twenty-five (225) patients were randomized to nilutamide and 232 to placebo between June 1986 and August 1989. Two hundred seven (207) nilutamide patients and 216 placebo patients were deemed 'evaluatable' defined as 'adherence to protocol entry criteria'. The data cutoff for the study report is 31 August, 1989. There were a total of 66 investigators among 15 countries, 11 European, U.S.A., Uruguay, Argentina and South Africa. Stratified analyses used countries as strata. Countries with less than 10 patients were pooled with the nearest country: Sweden with the

Two hundred twenty-five (225) patients were randomized to nilutamide and 232 to placebo between June 1986 and August 1989. Two hundred seven (207) nilutamide patients and 216 placebo patients were deemed 'evaluable' defined as 'adherence to protocol entry criteria'. The data cutoff for the study report is 31 August, 1989. There were a total of 66 investigators among 15 countries, 11 European, U.S.A., Uruguay, Argentina and South Africa. Stratified analyses used countries as strata. Countries with less than 10 patients were pooled with the nearest country: Sweden with the Netherlands and Uruguay with Argentina.

The study report states that patients were to continue in the study for 18 months unless they had objective disease progression. If **objective progression occurred**, the code was broken and patients who were receiving nilutamide could continue receiving nilutamide on an open label basis and also receive additional therapy. **Patients who were stable or who had regression of disease** and who did not have significant adverse experiences or toxicity during the first 18 months were permitted to continue the double-blind medication for an extended period with efficacy evaluations every six months. Patients who progressed while receiving placebo were withdrawn from the study.

Table 1 displays demographic and pretreatment characteristics of all randomized patients. There was no evidence of imbalances between treatment groups with respect to these or efficacy variables at baseline. **Table 2** displays numbers and reasons for discontinuation. **Table 3** displays the reasons for exclusion from analyses. **Table 4** displays the results for Best Response to Treatment (best objective response at any time during the study), **Figure 1** displays results for time to objective progression, **Figure 2** displays results for time to death due to prostate cancer, and **Figure 3** displays results for time to death due to any cause. Results were similar for 'evaluable' patients, i.e. excluding patients with missing bone scans or scans not performed in the right time interval. The report contains tables which report somewhat different p-values than those reported on these figures: for progression, .009 instead of .0079 (median 19.6 months on nilutamide and median=14.9 months on placebo); for death due to prostate cancer, .049 instead of .093; and for death due to any cause, .14 instead of .18 (median= 27.2 months on nilutamide and median= 23.6 months on placebo). The slight differences in p-values

are probably due to the 'life table' versus 'continuous time' approaches to computing a logrank statistic.

In general, the p-values suggest a benefit in the nilutamide group for time to objective progression and a suggestion of benefit for time to death due to prostate cancer. However, there was no statistically significant difference between the groups with respect to all cause death for either all patients randomized or the evaluable subset.

Among different countries, the direction of effect was in favor of nilutamide with two notable exceptions. Among 'evaluable' patients (423/457), the odds ratio for objective progression was 1.1 in favor of placebo in the USA (40 patients total) and 1.1 in favor of placebo in the Netherlands (111 patients total). The range of other countries' contributions was from 4 to approximately 50 patients.

Dr. Fourcroy identified **metastatic related pain** and **Karnofsky Status** as supplementary medical outcomes. There was no evidence that Karnofsky scores improved from baseline throughout the 30 months of follow up compared to placebo. Nor was there statistical evidence of improvement on the investigator global scale. Patient attrition was particularly severe beginning at 6 months. With respect to pain, the data was divided between those who entered the trial with and without pain. Among those with pain at baseline, approximately 70% of the placebo patients improved in LOCF (last observation carried forward) analyses at both 3 and 6 months. At 3 months, 85% of the nilutamide patients had improved and at 6 months, 80% of the nilutamide patients had improved, yielding respective p-values of .001 and .06 against placebo. These analyses stratified on baseline pain and deleted patients with the worse baseline pain (17 patients) since the numbers were small and all 17 patients in both groups improved by either 3 or 6 months.

Among patients with no pain at baseline, there was no evidence of a treatment effect.

Study 606

This study randomized 209 patients to nilutamide and 202 patients to placebo after all patients had been treated with leuprolide. The number of 'evaluable' patients were 197 and 193, respectively. Table 5 displays the demographic and prognostic profiles of all randomized patients.

The resulting progression-free survival and survival profiles are essentially superimposable without evidence of any trend in either treatment group's favor (approximately 25 months on either treatment. See Figures 4 and 5. The estimated difference between groups with respect to median time to all-cause mortality difference (four months more on nilutamide 40 months vs 36 months) is due to a short time window just after which the survival curves cross.

The results for Best Response to Treatment according to NPCP criteria were mixed. After excluding 33 patients with no NPCP data, the p-value was .037 for regression (57% on drug, 46% on placebo). However with regression grouped with stable disease, the p-value was .254.

With respect to change in metastatic pain, there were no statistical differences with approximately 65-70% of the patients improving from baseline up to 3 months after randomization. Although there was no statistically significant difference with respect to change in metastatic pain at month 1, 60% of the patients on nilutamide who had pain at baseline improved while 49% of the placebo patients did. The sponsor states "These trends may indicate nilutamide's effect on the 'flare' phenomenon which has been reported to occur in a small percentage (approximately 10%) of leuprolide-treated patients during the first two weeks of treatment."

With respect to improvement in Karnofsky status, there was no statistically significant difference at 3 months or at endpoint for those with impaired performance at entry. The only statistical difference in favor of nilutamide occurred at month 6 among

patients who had no impairment at entry but who deteriorated during the trial: 13/147=9% on nilutamide vs 30/145=21% on placebo.

The Role of PSA in Projecting Treatment Effect

Approximately 65% of the patients in each study received PSA blood level determinations.

In the face of the null results of study 606, the sponsor investigated the general relationship between laboratory values and survival/progression without regard to treatment group identification. This exercise found a relationship between the concentration of PSA at 3 months & Alkaline Phosphatase at baseline and the time to event endpoints. Then, by defining a 'responder' as one who exhibited a PSA level less than the upper limit of normal at 3 months combined with an ALK level less than 2 times the upper limit of normal at baseline, the sponsor found that, in both studies, the nilutamide group had statistically significantly more responders than in the placebo group. See Table 6. By joining the association between PSA and clinical endpoint, together with a greater proportion of responders in the nilutamide group, the sponsor implies that a treatment difference 'should' have been seen in both studies.

Discussion

The problem with this exercise is that the only thing it can imply is something that was vitiated by the very data that went into the analysis, itself, namely that study 606 did not provide any evidence of a treatment benefit with regard to progression or survival. A partial explanation comes from examining the 35%-40% of patients who did not have PSA determinations in the study. Table 7 displays the fact that in study 606, there was a treatment difference of 12% for progression (67%-55%) in patients with PSA. However, among patients without PSA measurements, patients in the nilutamide group 'out progressed' placebo patients by 62% to 57%,

a reverse treatment difference. If, as the sponsor claims, patients who did and did not get PSA measurements are similar, then the reversal of treatment differences in these two post hoc strata is an impediment to their argument.

A further problem arises in study 908/01 with regard to mortality. Contrary to expectation, the mortality in the nilutamide group among PSA patients is essentially the same as that in placebo PSA patients. It is the non-PSA patients (76% placebo mortality vs 61% nilutamide mortality) who produce the treatment difference of 59% vs 65% in the entire sample. See Table 7. How can the sponsor argue with an indirect argument that there should be a treatment difference when there is in fact none in the data which they used to make the argument in the first place? The explanation of this seeming paradox is that the sponsor's argument does not take into account an important component of the problem, viz the actual death rates in the responder and non-responder subgroups in each treatment group. The explanation lies in the fact that the death rates in both responders and non-responders were greater in the nilutamide group (50% vs 41% and 85% vs 73%), respectively. Regardless of any putative underlying association between PSA and survival and a greater proportion of responders in the nilutamide group, the actual death rates in the two groups can be the same if the following equation is satisfied:

$$\begin{aligned} &\Pr(\text{Death}|P, \text{PSA}<4) * P_p + \Pr(\text{Death}|P, \text{PSA}>4) * (1-P_p) = \\ &\Pr(\text{Death}|N, \text{PSA}<4) * P_n + \Pr(\text{Death}|N, \text{PSA}>4) * (1-P_n), \end{aligned}$$

where P=Placebo group, N=nilutamide group, P_p is the proportion of responders in P, and P_n is the proportion of responders in N. The top line is the probability of death in the placebo group and the bottom line is the probability of death in the nilutamide group.

In this case, $.41*.50 + .73*.50 = .56$ and
 $.50*.76 + .85*.24 = .57$.

However, there is little question that nilutamide patients tended to have lower levels of PSA than placebo patients:

Table 8 displays the median PSA from baseline to 3 months. Note that the median PSA in the placebo group in study 908/01 is barely

below 4.0 ng/ml.

Table 9 displays the two groups' PSA percentiles among patients with PSA's below 4.0, i.e., those which can be classified as responders according to Dr. Fourcroy. Even though the minima and maxima are the same in the two groups, the other percentiles in the placebo group are exactly twice those in the nilutamide group.

Table 10 displays the relationship between Gleason grade at baseline and PSA at baseline and PSA at 3 months. The top table suggests little overall relationship between the two variables at baseline. However, at 3 months, the placebo patients who have the most poorly differentiated cells in study 908/01 have a markedly higher median PSA than patients in the respective nilutamide subgroup (5.7 vs 0.6). It may be of interest that a Cox regression analysis of the relation between progression and Gleason grade is not statistically significant in study 606, whereas in study 908/01, the association is very significant with the 'poor' stratum showing the only contribution to the statistical relationship.

Effect Among Responders (PSA less than 4.0 ng/ml at 3 months)

As a supplementary investigation, Dr. Fourcroy suggested looking for a treatment advantage among those whose PSA had decreased to below 4.0 ng/ml by 3 months.

In Study 606, 104 of the 118 (88%) of the evaluable patients with PSA measurements responded in the nilutamide group and 88/124 (71%) responded in the placebo group. Both differences were statistically significant. Among responders, approximately 60% of the patients died on either treatment arm, while progression rates were 60% and 55% in the placebo and nilutamide arms, respectively.

In Study 908/01, the respective numbers were 112/145 (76%) in the nilutamide group and 70/141 (50%) in the placebo group. Among responders, approximately 40% of the placebo patients died while 50% of the nilutamide patients died. Sixty percent (60%) of the placebo patients had objective progression and 55% of the nilutamide patients progressed.

Analysis of survival and time to objective progression restricted to this subgroup fails to show any advantage in the nilutamide-treated group ($p > .50$ compared to placebo) in either study.

In fact, in study 908/01 the relationship between mortality and PSA level is complicated. In the subset which had PSA levels taken (272/457) a greater percentage of nilutamide than placebo patients died in both non-responder and responder strata (85% vs 72% and 53% vs 40%, respectively). However, among those who did not have PSA measurements, 75% of the placebo patients died and 58% of the nilutamide patients died. However, results were consistent with respect to progression: a greater proportion of placebo patients progressed in both strata.

As for the overall relationship between 'response' and outcome, i.e. without regard to treatment assignment, the table below displays percentages of patients with medical outcomes by response status:

Study 908/01

	<u>Pain Improved</u>	<u>Obj. Progression</u>	<u>Death</u>
Non-resp.	71%	79%	76%
Resp.	86%	57%	48%
	$p = .02$	$p < .001$	$p < .001$

Study 606

	<u>Pain Improved</u>	<u>Obj. Progression</u>	<u>Death</u>
Non-resp.	62%	76%	82%
Resp.	71%	57%	61%
	$p = .29$	$p = .02$	$p = .007$

Conclusions

Several observations may be useful:

- 1) The proportion of responders in the 'placebo' group in study 606 was substantially larger than that in Study 908/01.
- 2) The survival profile of placebo patients in study 606 was better than that of the nilutamide patients in study 908/01.
- 3) The general condition of evaluable patients in study 606 was better than those in study 908/01. Patients in the latter were older, had more urinary obstruction and lower average Karnofsky status.
- 4) A larger percentage of patients 'normalized' their PSA (less than 4 ng/mL at 3 months) in study 606 than in study 908/01.
- 5) The median baseline PSA was substantially lower in study 606 than in study 908/01.
- 6) The sponsor's assumption used in the sample size calculation, viz that the placebo groups' median progression-free survival would be 65 weeks, was accurate in study 908/01 but was badly off the mark in study 606, underestimating by approximately 40 weeks.

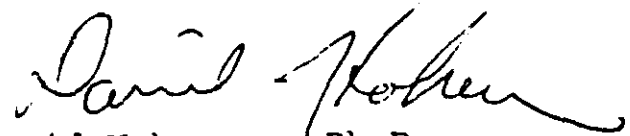
Study 606 does not provide statistical evidence that nilutamide increases overall survival or time to progression in either the overall patient population or a subgroup defined as patients whose PSA level at 3 months falls below 4.0 ng/mL. The sponsor has argued that since 1) survival is associated with PSA level and 2) there are more 'responders' in the nilutamide group than placebo group, then the conclusion is that nilutamide should increase survival. When restricted to patients with PSA measurements, this argument does not find support when the actual survival is analyzed. Perhaps using androgen blockers after surgical or chemical castration is more effective in patients with more severe disease. A brief review of the literature reveals that the median survival

in study 606 (approximately 40 months) is far greater in some cases than the majority of those in other trials, viz 16, 28, 28, 29, 35 and 36 months on active treatment after either surgical or chemical castration.

Study 908/01 provides statistical evidence of a lengthening of approximately 4 months of median time to objective progression. There is a suggestion of lower mortality due to prostate cancer (p-value less $<.10$).

The sponsor's predictive marker analysis is flawed because

- 1) For progression in study 606, the treatment difference found in PSA patients is reversed in non-PSA patients,
- 2) For survival in study 908/01, there is no treatment difference in PSA patients.



David Hoberman, Ph.D.
Mathematical Statistician

This review consists of 10 pages of text, 10 tables and 5 figures.
Concur: Dr. Nevius *SEN 2-2-95*

Dr. Dubey *6-2-2-95*

cc: Orig NDA 20-169
HFD-510
HFD-510/Dr. Fourcroy
HFD-510/Dr. Fleming
HFD-510/Dr. Sobel
HFD-510/Ms. Pauls
HFD-713/Dr. Nevius
HFD-713/Dr. Hoberman
HFD-713/Dr. Dubey [File 1.3.2 NDA]
HFD-344/Dr. Lisook
Chron

TABLE 1

SUMMARY OF DEMOGRAPHIC AND PRETREATMENT CHARACTERISTICS
 (All Patients)

	Orchiectomy + <u>Nilutamide</u>	Orchiectomy + <u>Placebo</u>	<u>p-value*</u>
Age (years)			
N	225	232	
< 50	0 (0 %)	1 (0 %)	
50-59	18 (8 %)	7 (3 %)	
60-69	73 (32 %)	67 (29 %)	
70-79	100 (44 %)	120 (52 %)	
≥ 80	34 (15 %)	37 (16 %)	
Mean	71.2	72.1	0.215
Range	50 - 85	46 - 92	
Race			
N	225	232	
Caucasian	205 (91 %)	213 (92 %)	
Black	8 (4 %)	7 (3 %)	0.708
Hispanic	8 (4 %)	10 (4 %)	
Oriental	2 (1 %)	2 (1 %)	
Other	2 (1 %)	0 (0 %)	
Weight loss before entry**			
N	225	231	
Yes	42 (19 %)	38 (16 %)	0.521
No	183 (81 %)	193 (84 %)	
Duration of Stage D2 Diagnosis (months)			
N	222	231	
Mean	1.8	1.8	0.933
Range	0 - 90	0 - 59	

* Based on the Cochran-Mantel-Haenszel test or the F-test

** > 10 % during the six months prior to entry into the study

000177

TABLE 1 (cont)

SUMMARY OF DEMOGRAPHIC AND PRETREATMENT CHARACTERISTICS
 (All Patients)

	Orchiectomy + <u>Nilutamide</u>	Orchiectomy + <u>Placebo</u>	<u>p-value*</u>
Histologic Finding			
N	225	231	
Well differentiated	30 (13 %)	27 (12 %)	0.936
Moderately differentiated	100 (44 %)	100 (43 %)	
Poorly differentiated	72 (32 %)	76 (33 %)	
Anaplastic	4 (2 %)	7 (3 %)	
Unknown	8 (4 %)	7 (3 %)	
Other	11 (5 %)	14 (6 %)	
Gleason Grade (Central Lab)			
N	156	155	
2-4	10 (6 %)	4 (3 %)	0.174
5-7	83 (53 %)	85 (55 %)	
8-10	63 (40 %)	66 (43 %)	
Gleason Grade (Local Lab)			
N	65	61	
2-4	16 (25 %)	17 (28 %)	0.651
5-7	33 (51 %)	28 (46 %)	
8-10	16 (25 %)	16 (26 %)	
Hemoglobin			
N	225	230	
< 12 g/dl	57 (25 %)	69 (30 %)	0.257
≥ 12 g/dl	168 (75 %)	161 (70 %)	
Testosterone (ng/dl) (Central Lab)			
N	113	112	
Mean	374.4	377.6	0.605
Range	16 - 1051	17 - 1084	

* Based on the Cochran-Mantel-Haenszel test or the F-test

000178

TABLE 1 (cont)

SUMMARY OF DEMOGRAPHIC AND PRETREATMENT CHARACTERISTICS
(All Patients)

	Orchiectomy + <u>Nilutamide</u>	Orchiectomy + <u>Placebo</u>	<u>p-value*</u>
Hydronephrosis			
N	215	227	
Yes	51 (24 %)	43 (19 %)	0.202
No	164 (76 %)	184 (81 %)	
Previous Radiotherapy			
N	225	232	
Yes	23 (10 %)	30 (13 %)	0.302
No	202 (90 %)	202 (87 %)	
Previous Prostatectomy			
N	225	232	
Yes	103 (46 %)	100 (43 %)	0.486
No	122 (54 %)	132 (57 %)	

* Based on the Cochran-Mantel-Haenszel test or the F-test

TABLE 2

NUMBER OF PATIENTS DISCONTINUED FROM THE DOUBLE-BLIND PHASE OF STUDY

<u>Primary Reason for Discontinuation</u>	<u>Orchiectomy + Nilutamide</u>	<u>Orchiectomy + Placebo</u>
N	225	232
Adverse Experiences (Including Intercurrent Events)	35	20
Objective Progression	85	114
Protocol Violation	19	14
Subjective Progression	13	15
Withdrew consent	5	4
End Part A	6	7
Lost to follow-up	4	5
Bad compliance	1	3
Total	168	182

000183

TABLE 3

EXCLUSIONS FROM THE EFFICACY ANALYSIS*

<u>Reason for Exclusion</u>	<u>Orchiectomy + Nilutamide</u>	<u>Orchiectomy + Placebo</u>
Age > 85 years	0	1
Stage C or D1	4	0
Previous hormonal therapy	0	1
Previous radiotherapy	0	1
Use of antiandrogenic drugs	5	5
History or presence of another cancer	3	3
Severe hepatic or renal dysfunction	2	3
Concomitant Paget's disease	4	0
Drug started more than 12 days after orchiectomy	0	2

Subtotal	18	16
Pretreatment bone scan more than 3 months before inclusion or more than 15 days after inclusion **	5	8
TOTAL	23	24

* When a patient had several reasons for exclusion, only the main reason was indicated in this table.

** Patients were excluded only from the analyses of objective response, best response to treatment, progression of prostate cancer and bone scan isotope uptake.

000184

TABLE 4

BEST RESPONSE TO TREATMENT
 MODIFIED NATIONAL PROSTATIC CANCER PROJECT CRITERIA
 (All Patients)

	Orchiectomy + <u>Nilutamide</u>	Orchiectomy + <u>Placebo</u>	<u>p-value*</u>
N	200	213	
Complete Objective Regression	16 (8 %)	10 (5 %)	
Partial Regression	61 (30 %)	37 (17 %)	
Objectively Stable Disease	68 (34 %)	83 (39 %)	
Subjective Progression**	13 (6 %)	15 (7 %)	
Objective Progression	31 (15 %)	56 (26 %)	
None of the above	11 (5 %)	12 (6 %)	
Regression	77 (41 %)	47 (23 %)	< 0.001
Stable + Progression	112 (59 %)	154 (77 %)	
Regression + Stable	145 (77 %)	130 (65 %)	0.004
Progression	44 (23 %)	71 (35 %)	

- * Based on the Cochran-Mantel-Haenszel test
 ** Without evidence of objective progression

NOTE : This table presents the best objective response at any time during the study.
Excluded 44 patients (25 nilutamide and 19 placebo) with no NECP data.

000211

TABLE 5

Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
 GHBA Protocol 606
 Investigator: Combined

19SEP90

SUMMARY OF DEMOGRAPHIC AND PRETREATMENT CHARACTERISTICS
 (ALL PATIENTS)

	Leuprolide + <u>Nilutamide</u>	Leuprolide + <u>Placebo</u>	<u>p-value*</u>
Age (years)			
N	209	202	
< 50	4 (2 %)	0 (0 %)	
50-59	30 (14 %)	23 (11 %)	
60-69	90 (43 %)	98 (49 %)	
70-79	72 (34 %)	74 (37 %)	
>= 80	13 (6 %)	7 (3 %)	
Mean	67.2	67.8	0.343
Range	40.0- 86.0	54.0- 86.0	
Race			
N	209	202	
Caucasian	165 (79 %)	154 (76 %)	0.610
Black	37 (18 %)	43 (21 %)	
Hispanic	6 (3 %)	5 (2 %)	
Oriental	1 (0 %)	0 (0 %)	
Weight Loss Before Entry**			
N	208	202	
Yes	25 (12 %)	26 (13 %)	0.890
No	183 (88 %)	176 (87 %)	
Duration of Stage D ₂ Diagnosis (months)			
N	208	202	
Mean	2.2	1.2	0.002
Range	0.0- 37.2	0.0- 12.2	

* Based on the Cochran-Mantel-Haenszel test or the F-test.

**>10% during the six months prior to entry into the study.

TABLE 5 (cont)

Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
 GHBA Protocol 606
 Investigator: Combined

19SEP90

SUMMARY OF DEMOGRAPHIC AND PRETREATMENT CHARACTERISTICS
 (ALL PATIENTS)

	Leuprolide + Nilutamide	Leuprolide + Placebo	p-value*
Histologic Finding			
N	208	202	
Well Differentiated	22 (11 %)	18 (9 %)	0.640
Moderately Differentiated	70 (34 %)	68 (34 %)	
Poorly Differentiated	76 (37 %)	70 (35 %)	
Anaplastic	0 (0 %)	2 (1 %)	
Unknown	35 (17 %)	41 (20 %)	
Other	5 (2 %)	3 (1 %)	
Gleason Grade (Central Lab)			
N	86	88	
2-4	2 (2 %)	6 (7 %)	0.586
5-7	38 (44 %)	37 (42 %)	
8-10	46 (53 %)	45 (51 %)	
Gleason Grade (Local Lab)			
N	131	136	
2-4	23 (18 %)	20 (15 %)	0.358
5-7	69 (53 %)	65 (48 %)	
8-10	39 (30 %)	51 (38 %)	
Hemoglobin			
N	207	199	
< 12 g/dl	27 (13 %)	37 (19 %)	0.189
>= 12 g/dl	180 (87 %)	162 (81 %)	
Testosterone (ng/dl) (Central Lab)			
N	166	161	
Mean	394.9	392.4	0.854
Range	1.7-951.0	26.0-997.0	

* Based on the Cochran-Mantel-Haenszel test or the F-test.

TABLE 5 (cont)

Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
 GHBA Protocol 606
 Investigator: Combined

19SEP90

SUMMARY OF DEMOGRAPHIC AND PRETREATMENT CHARACTERISTICS
 (ALL PATIENTS)

	Leuprolide + <u>Nilutamide</u>	Leuprolide + <u>Placebo</u>	<u>p-value*</u>
Hydronephrosis			
N	208	200	
Yes	34 (16 %)	27 (14 %)	0.563
No	174 (84 %)	173 (87 %)	
Previous Radiotherapy			
N	209	202	
Yes	64 (31 %)	56 (28 %)	0.718
No	145 (69 %)	146 (72 %)	
Previous Prostatectomy			
N	209	202	
Yes	95 (45 %)	92 (46 %)	0.952
No	114 (55 %)	110 (54 %)	

* Based on the Cochran-Mantel-Haenszel test or the F-test.

ROUSSEL-UCLAF
 Nilutamide versus Placebo
 Investigator: Combined

TABLE 6
 COMBINED PROGNOSTIC FACTORS
 DISTRIBUTION OF PATIENT IN EACH PROGNOSTIC GROUP
 EFFICACY OF NILUTAMIDE

FF/86/908/01

Month-3 PSA	BASELINE ALP $\leq$ 2 N		p-value
	Orchiectomy + Nilutamide n = 84	Orchiectomy + Placebo n = 72	
$\leq$ N	55/84 (66%)	25/72 (35%)	<0.0001
> N	29/84 (34%)	47/72 (65%)	

Study GHBA-606

Month-3 PSA	BASELINE ALP $\leq$ 2 N		p-value
	Leuprolide + Nilutamide n = 88	Leuprolide + Placebo n = 94	
$\leq$ N	70/88 (80%)	54/94 (56%)	<0.0001
> N	18/88 (20%)	40/94 (44%)	

000155

Table 7

Progression and Survival (All Patients)

	<u>908 / 01</u>	
	<u>Nilutamide</u>	<u>Placebo</u>
Progression	56% (20)*	69% (15) p = .008
Mortality	59% (27)	65% (24) p = .18

	<u>606</u>	
	<u>Nilutamide</u>	<u>Placebo</u>
Progression	58% (25)	63% (25) p = .35
Mortality	64% (40)	68% (36) p = .47

PSA Patients Only

	<u>908 / 01</u>	
	<u>Nilutamide</u>	<u>Placebo</u>
Progression	57%	70% p = .03
Mortality	58%	57% p = .84

	<u>606</u>	
	<u>Nilutamide</u>	<u>Placebo</u>
Progression	55%	67% p = .05
Mortality	63%	69% p = .35

Non-PSA Progression in 606

<u>Nilutamide</u>	<u>Placebo</u>
62%	57%

* Number in parentheses is in median months

Table 8

Median PSA (ng/ml) Over Time

	<u>908 / 01</u>		<u>606</u>	
	<u>Nilutamide</u>	<u>Placebo</u>	<u>Nilutamide</u>	<u>Placebo</u>
Baseline	142	134	47	41
1-Month	5.2	8.9	1.8	7.5
3-Months	0.7	3.4	0.3	0.9
p = .13 Bsl - 3 months		p = .84 Bsl - 3 months		

Table 9

Distribution of PSA < 4.0 in 606 at 3 Months

	<u>Nilutamide</u>	<u>Placebo</u>
Maximum	3.5	3.25
75%	.49	.98
Median	.24	.49
25%	.13	.28
Minimum	.075	.075

Table 10

Median PSA by Gleason Category at Baseline

	<u>908 / 01</u> <u>Differentiation</u>		
	<u>Well</u>	<u>Mod</u>	<u>Poor</u>
PBO	140	160	130
Nilutamide	110	153	126

606

	<u>Well</u>	<u>Mod</u>	<u>Poor</u>
PBO	52	27	50
Nilutamide	55	54	27

Median PSA at 3 months by Gleason Category at baseline

	<u>908 / 01</u>		
	<u>Well</u>	<u>Mod</u>	<u>Poor</u>
PBO	2.4	4.0	5.7
Nilutamide	0.6	0.6	0.6

606

	<u>Well</u>	<u>Mod</u>	<u>Poor</u>
PBO	1.3	0.8	0.7
Nilutamide	0.3	0.3	0.2

PROBABILITY OF PROGRESSION - FREE SURVIVAL
OBJECTIVE PROGRESSION
All patients

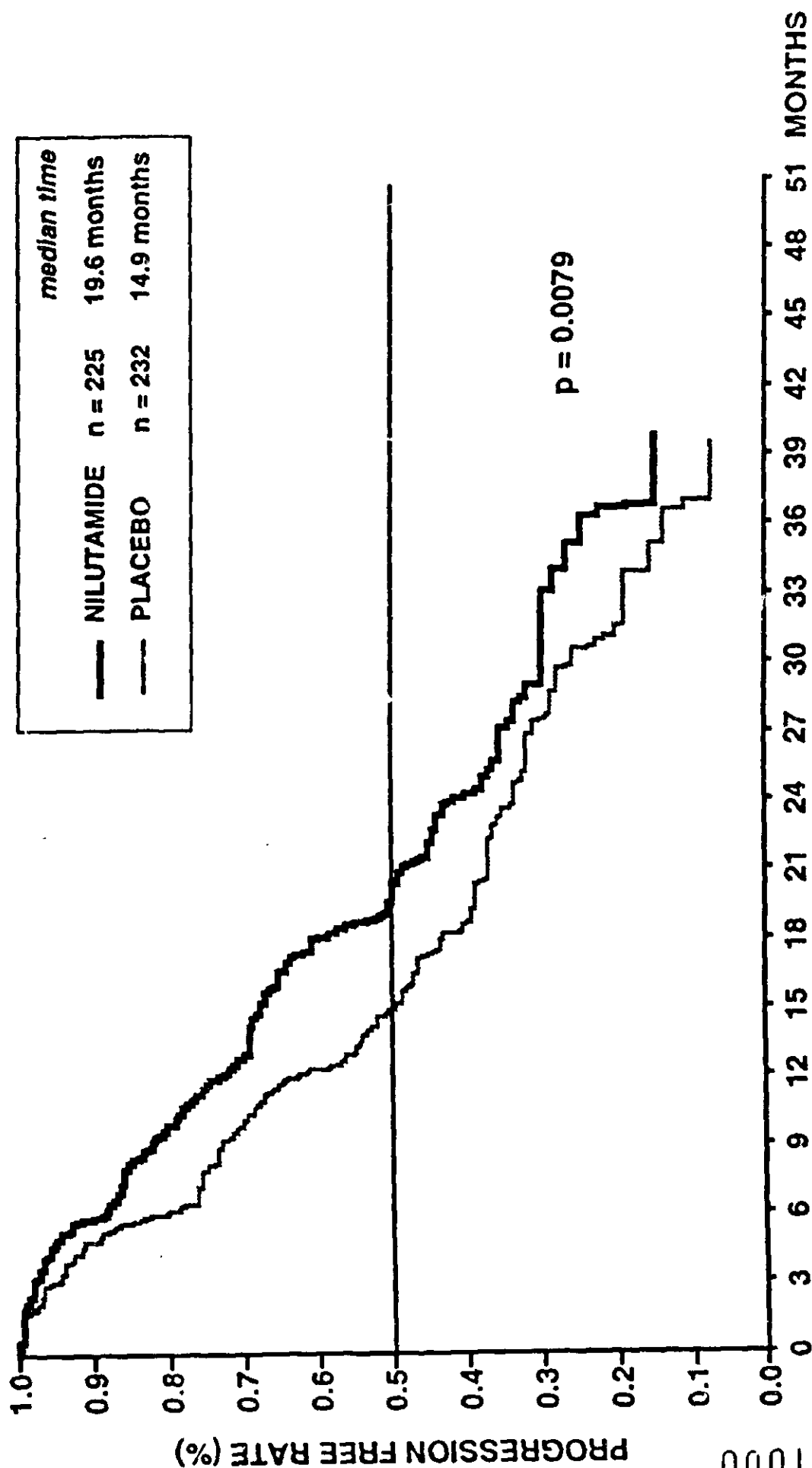
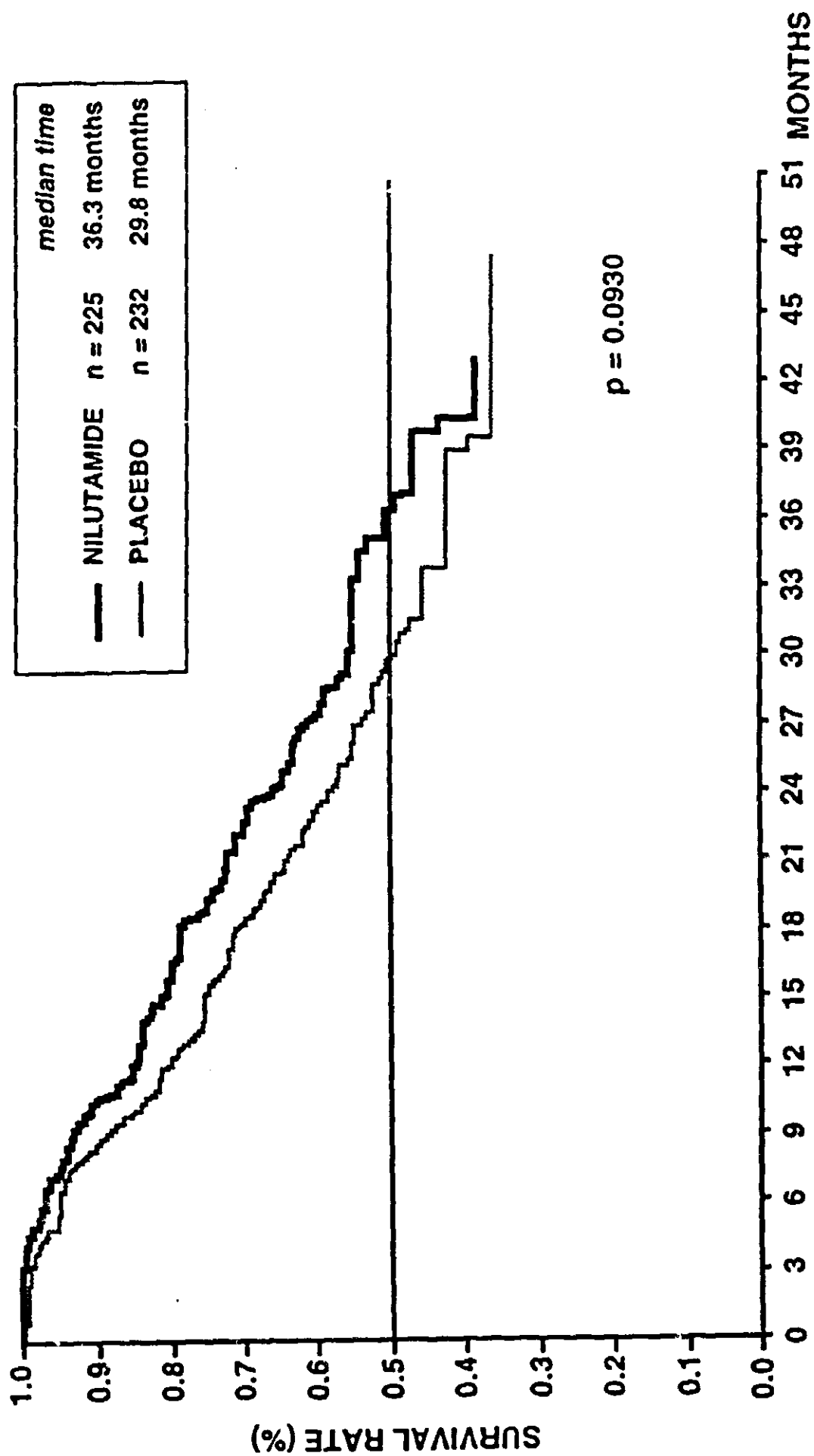


FIGURE 1

PROBABILITY OF PROSTATE CANCER SURVIVAL
All patients



000140

FIGURE 2

PROBABILITY OF OVERALL SURVIVAL
All patients

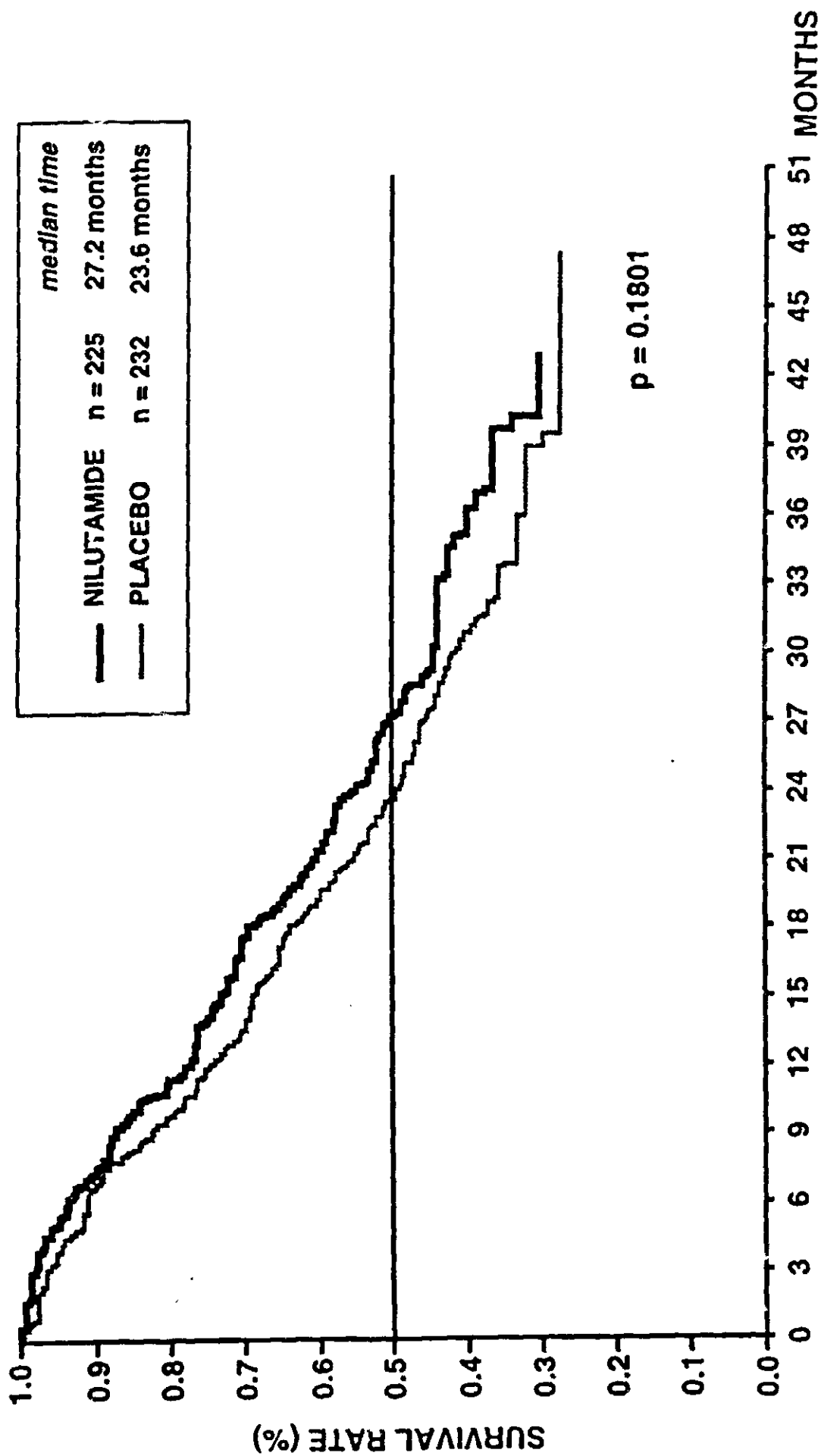
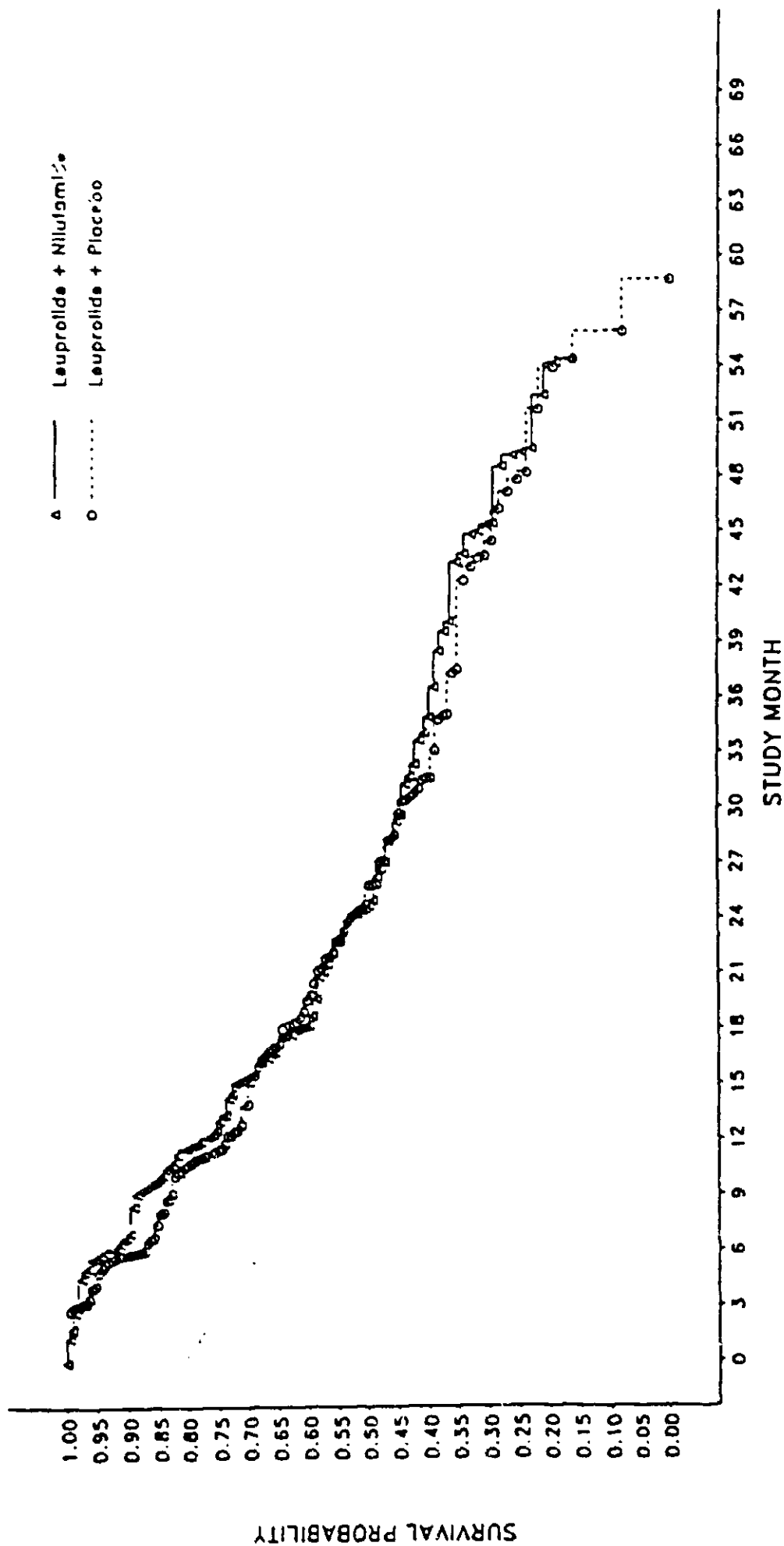


FIGURE 3

Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
 GHBA Protocol 606
 Investigator: Combined

12SEP93

PROBABILITY OF PROGRESSION-FREE SURVIVAL (ALL PATIENTS)



080000

FIGURE 4

Roussel UCLAF
 Nilutamide versus Placebo in
 Leuprolide-Treated Patients
 GHBA Protocol 606
 Investigator: Combined

12SEP93

PROBABILITY OF OVERALL SURVIVAL (ALL PATIENTS)

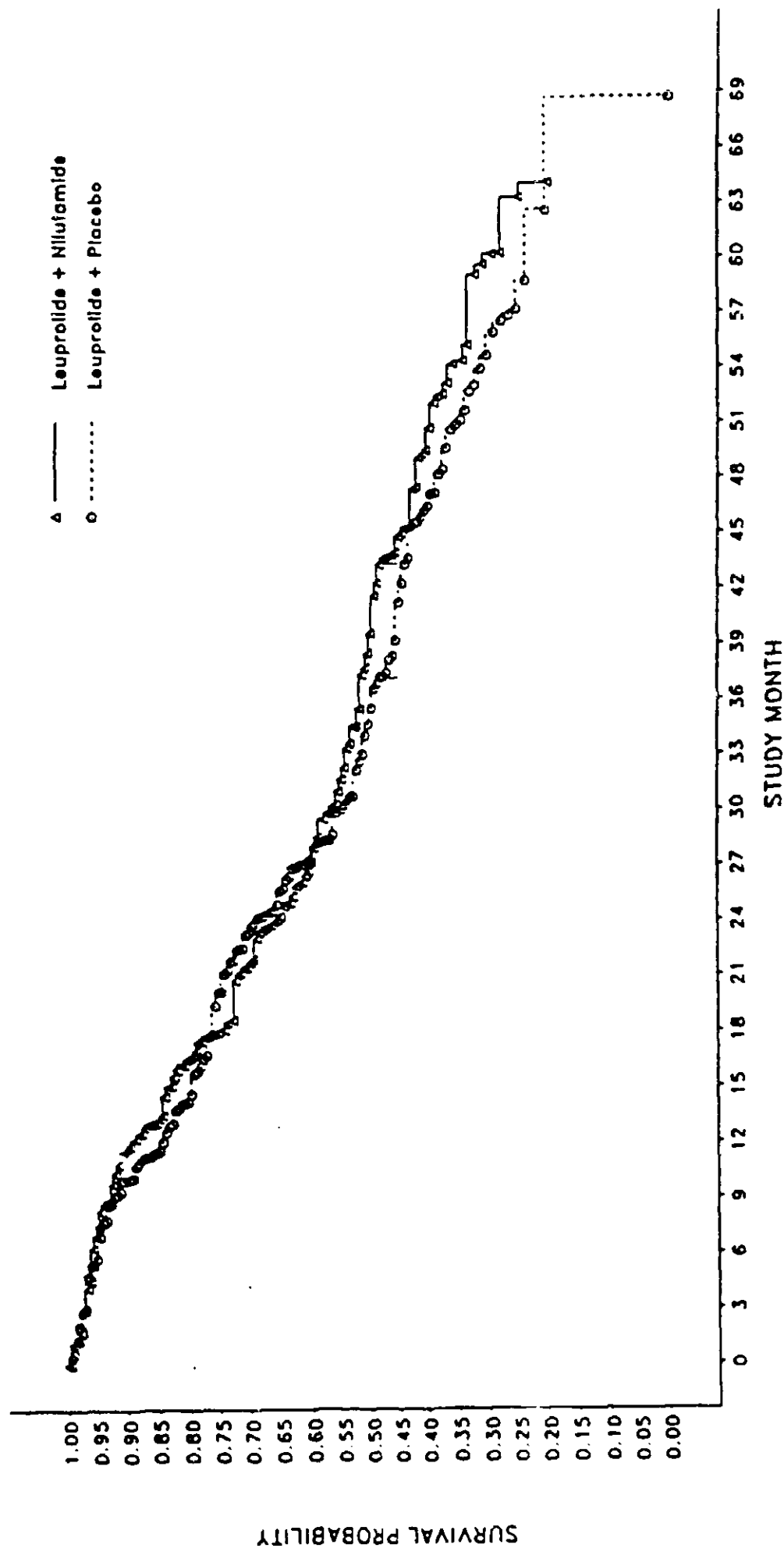


FIGURE 5

480000

Chem

JUN 14 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA: 20-169 CHEMISTRY REVIEW #: 4 DATE REVIEWED: 12-JUN-1996

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>
Original	14-JUN-1991	
Resubmission	07-MAR-1994	

NAME & ADDRESS OF APPLICANT:

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DRUG PRODUCT NAME	Proprietary:	Nilandron Tablets
	Nonproprietary/Established/INN:	Nilutamide
	Code Name #:	RU 23908
	Chem. Type / Ther. Class:	1 S

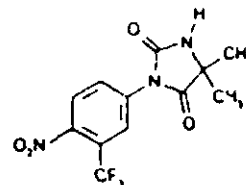
User fee I.D. number: 2510

PHARMACOLOGICAL CATEGORY/INDICATION: Antiandrogenic (blocks by competition the binding of androgens with their receptors). Treatment of metastatic prostate cancer in combination with surgical or medical castration.

DOSAGE FORM:	Tablet
STRENGTHS:	50 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA:

C₁₇H₁₀F₃N₂O₄
M.F. = 317.25
5,5-Dimethyl-3-((4-nitro-3-(trifluoromethyl)phenyl)-2,4-imidazolidinedione



COMMENTS: The two pending issues, a satisfactory Environmental Assessment (EA) from the applicant and approval of the established name by USAN Council have satisfactorily addressed.

CONCLUSIONS & RECOMMENDATIONS: From the chemistry viewpoint this NDA is recommended as approvable.

Orig. NDA 20-169
cc HFD-510/Division File
HFD-510/JEI-Hage/JFourcroy/SMoore/LPauls/XYsern

Xavier Ysern, PhD

R/D Init by:

6/14/96

filename: 20169_4.nda

FEB - 7 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA: 20-169

CHEMISTRY REVIEW #: 3

DATE REVIEWED: 5-FEB-1996

SUBMISSION TYPE

Amendment

DOCUMENT DATE

15-AUG-1995

CDER DATE

22-AUG-1995

NAME & ADDRESS OF APPLICANT:

Roussel-UCLAF
102 and 111 Route de Noisy
93230 Romainville
France 011-33-14991-4991

G. H. Besselaar Associates (Agents for Roussel-UCLAF)
Princeton Forrestal Center
103 College Road East
Princeton, NJ 08540-6681 (609) 452 8550

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/Established/TNN:
Code Name #:
Chem. Type / Ther. Class:

Nilandron Tablets
Nilutamide
RU 23908
I S

User fee I.D. number: 2510

PHARMACOLOGICAL CATEGORY/INDICATION: Antiandrogenic (blocks by competition the binding of androgens with their receptors). Treatment of metastatic prostate cancer in combination with surgical or medical castration.

DOSAGE FORM:

Tablet

STRENGTHS:

50 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

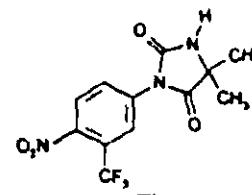
☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA:

C₁₂H₁₀F₃N₃O₄

M.F. = 317.25

5,5-Dimethyl-3-((4-nitro-3-(trifluoromethyl)phenyl)-2,4-imidazolidinedione



COMMENTS: The response to the Biopharmaceutics suggestion (March 7th., 1995) regarding a change in the dissolution specification is provided in the document STE-125-A-40-1. A more stringent dissolution specification, using the original dissolution media, is recommended as part of the CMC drug product specifications.

CONCLUSIONS & RECOMMENDATIONS: From the chemistry viewpoint this NDA is recommended as approvable. Receipt of a satisfactory EIA from the applicant and approval of the established name by USAN Council are pending. The recommendation stated in the Biopharm review dated 31-JAN-1996, on the dissolution method and specification should be communicated to the applicant.

Orig. NDA 20-169

cc: HFD-510/Division File

HFD-510/JEI-Hage/JFourcroy/SMoore/LPauls/XYsem

Xavier Ysem
Xavier Ysem, PhD

R/D Init by:

Stephen Moore
2/7/96

filename: 20169_3.nda

Pauls
FEB 14 1995

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA: 20-169

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 13-FEB-1995

SUBMISSION TYPE

Original

Resubmission

Amendment

DOCUMENT DATE

14-JUN-1991

7-MAR-1994

27-JAN-1995

CDER DATE

7-MAR-1994

30-JAN-1995

NAME & ADDRESS OF APPLICANT:

Roussel-UCLAF
102 and 111 Route de Noisy
93230 Romainville
France 011-33-14991-4991

G. H. Besselaar Associates (Agents for Roussel-UCLAF)
Princeton Forrestal Center
103 College Road East
Princeton, NJ 08540-6681 (609) 452 8550

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/Established/TNN:
Code Name #:
Chem. Type / Ther. Class:

Nilandron Tablets
Nilutamide
RU 23908
1 S

User fee I.D. number: 2510

PHARMACOLOGICAL CATEGORY/INDICATION: Antiandrogenic (blocks by competition the binding of androgens with their receptors). Treatment of metastatic prostate cancer in combination with surgical or medical castration.

DOSAGE FORM:

Tablet

STRENGTHS:

50 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

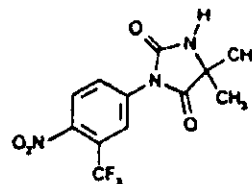
☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA:

C₁₂H₁₀F₃N₃O₄

M.F. = 317.25

5,5-Dimethyl-3-((4-nitro-3-(trifluoromethyl)phenyl)-2,4-imidazolidinedione



COMMENTS: The January 26 1995 amendment provides the response to the Agency facsimile communication (chemistry draft deficiency letter) dated December 22 1994.

CONCLUSIONS & RECOMMENDATIONS: The amendment satisfactory answers the Agency December 12 1994 CMC requests (attached). cGMP evaluation of the drug substance and drug product manufacturing facilities are acceptable. Environmental Impact Assessment consult has not been received. From the chemistry viewpoint, this NDA will become approvable when a satisfactory EIA is received and the established name approved by USAN Council. NDA 20-169 13-FEB-1995 CMC Summary attached (20169smb.nda).

Orig. NDA 20-169

cc: HFD-510/Division File

HFD-510/JEI-Hage/JFourcroy/LPauls/XYsem

R/D Init by: Y-YChiu

Xavier Ysem, PhD

filename: 20169_2.nda

Y-Chiu
2/14/95

DEC 20 1994

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA: 20-169

CHEMISTRY REVIEW #: 1

DATE REVIEWED: 14-DEC-1994

SUBMISSION TYPE

DOCUMENT DATE

CDER DATE

Original

14-JUN-1991

Resubmission

7-MAR-1994

7-MAR-1994

Amendment

22-AUG-1994

24-AUG-1994

DRAFT

Amendment

27-SEP-1994

28-SEP-1994

NAME & ADDRESS OF APPLICANT:

Roussel-UCLAF
102 and 111 Route de Noisy
93230 Romainville
France 011-33-14991-4991

G. H. Besselaar Associates (Agents for Roussel-UCLAF)
Princeton Forrestal Center
103 College Road East
Princeton, NJ 08540-6681 (609) 452 8550

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/Established/INN:
Code Name #:
Chem. Type/Ther. Class:

Nilandron Tablets
Nilutamide
RU 23908
1 S

User fee L.D. number: 2510

PHARMACOLOGICAL CATEGORY/INDICATION: Antiandrogenic (blocks by competition the binding of androgens with their receptors). Treatment of metastatic prostate cancer in combination with surgical or medical castration.

DOSAGE FORM:

Tablet

STRENGTHS:

50 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

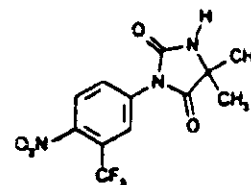
☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA:

C₁₂H₁₀F₃N₃

M.F. = 317.25

5,5-Dimethyl-3-[(4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione



CONCLUSIONS & RECOMMENDATIONS: The Chemistry section of this NDA contains minor deficiencies as delineated in the draft letter. Also, cGMP evaluation of the drug substance and drug product manufacturing facilities as well as EA have not been received. From the chemistry viewpoint, this NDA will become approvable when all these issues are resolved. Summary attached.

Orig. NDA 20-169

cc: HFD-510/Division File
HFD-510/JEI-Hage/JFourcroy/LPauls/XYsem
HFD-102/CKumkumian
R/D Init-by: Y-YChiu

Xavier Ysem, PhD
Review Chemist

filename: 20169_1.nda

RELATED DOCUMENTS (if applicable):

IND

IND

DMF

Roussel UCLAF Plant 2 (Compiègne, France)

DMF

Roussel UCLAF Plant 3 (Neuville-sur-saone, France)

DMF

DMF

DMF

Roussel UCLAF USIPHAR Plant at Compiègne (France)

DMF

PATENTS: USP 4,097,578 expiring 27 June 1995 (Nilutamide alone)
 USP 4,472,382 expiring 18 September 2001 (Nilutamide with LHRH agonist)

CONSULTS: EIA Originated 22-MAR-1994 *Pending*

REMARKS/COMMENTS:

 This NDA is a resubmission. It was originally submitted on June 14, 1991, and refused-to-file by the Agency (letter dated August

 Amendment dated 22-AUG-1994 provides additional stability data to support an extension of the shelf-life from 2 years to 3 years.

 Amendment submitted on 27-SEP-1994 provides additional information to supplement the biopharmaceutics section and to answer an Agency request dated on 27 April 1994. In addition, the firm proposes the use of the name NILANDRON as the trade name of the dosage form since the original proposed trade name ANADRON was not accepted by the Agency.

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Yana Mille, Chair, HFD-600 MPN II

From: Division of Metabolism and Endocrine D. P./HFD-510
Attention: Xavier Ysem Phone: (301) 443-3510

Date: 31-OCT-1994

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: NILANDRON

NDA #: 20-169

Established name, including dosage form:

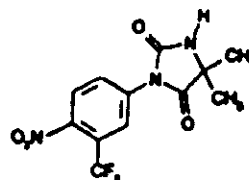
Nilutamide tablets 50 mg

 $C_{17}H_{19}F_3N_3O_2$

M.F. = 317.25

CAS 63612-50-0

Chemical name: 5,5-dimethyl-3-[(4-nitro-3-(trifluoromethyl) phenyl)-2,4-imidazolidinedione]



Other trademarks by the same firm for companion products: - N.A. -

Indications for Use (may be a summary if proposed statement is lengthy):

Treatment of metastatic prostate cancer in combination with chemical castration with an LHRH agonist or following surgical castration. Nilutamide is nonsteroid antiandrogen that blocks by competition, the binding of androgens with their receptors.

Initial comments from the submitter (concerns, observations, etc.):

The firm previously proposed their trademark name ANANDRON as tradename for nilutamide. Although the firm commercializes this drug under this name in Europe and some countries in Latinamerica, the CDER Nomenclature and Labeling Committee found the previously proposed name unacceptable (consult # 300, 31-MAY-1994). The firm on September 27, 1994, proposed the name NILANDRON as tradename for Nilutamide 50 mg Tablets (NDA 20-169).

filename: 20169b.tm

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 1993

COMPLETED

Consult #373 (HFD-510)

NILANDRON

Nilutamide Tablets
50 mg

A review did not reveal names which look or sound like the proposed name.

The Committee discussed whether or not the use of "nil" (which implies "no" androgen) should be viewed as misleading due to its fanciful nature [21 CFR 201.10(c)(3)]. Some members were of the opinion that the name may imply an effectiveness greater than the product exhibits. However, the majority of the Committee did not believe this was a concern since "nil" is also found in the established name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Yana Mille, Chair

11/27/74

COMPLETED

NDA 20-169
Nilandron® (nilutamide) Tablets
Roussel-UCLAF (Besselaar Associates)

Microbiology Review

No microbiology review is required for a tablet formulation.

E A And
Fonsi

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

NDA 20-169

NILANDRON®

(nilutamide)

Tablets

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-169

NILANDRON® (nilutamide) Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for NILANDRON®, Roussel Uclaf has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Nilutamide is a synthetic drug which will be administered orally in the treatment of patients with advanced prostate cancer with metastases (Stage D2). Drug substance and drug product will be manufactured at ROUSSEL UCLAF, France. One synthetic step in the drug substance manufacture will be performed at Société Nationale des Poudres et Explosifs, France. The finished drug product will be used in hospitals, clinics and homes.

Nilutamide may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The infrequent use of this product will limit introduction into the environment from patient use.

Disposal may result from production waste such as out of specification lots or returned goods and user disposal of empty or partly used product and packaging. In the U.S. returned or expired goods will be disposed of at a licensed incineration facility. At U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to standard procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

6/2/96
DATE

Nancy B. Sager
PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

6/3/96
DATE

Charles P. Hoiberg
CONCURRED
Charles P. Hoiberg, Ph.D.
Division Director, Office of New Drug Chemistry-1
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

c.c. original NDA 20-169/LPauls copy to NDA/HFD-510
HFD-357/EA File NDA #20-169
HFD-357/Docket File
HFD-205/FOI COPY

ROUSSEL UCLAF



*Direction des Enregistrements Santé
Service des Techniques et Enregistrements*

NILUTAMIDE 50 mg Tablets

(NILANDRON®)

New Drug Application

Freedom of Information (FOI) Summary
of
Environmental Assessment Report (EAR)

(According to US 21 CFR 25.31.)

STE-125-A-42-1

August 1995

11/09/95

102, Route de Noisy 93235 Roissy Cedex
Tél. + 33 (1) 49 91 49 91 Fax + 33 (1) 49 91 48 19
SIRET 542 008 081 00052 00045

Roussel Uclaf, Société Anonyme à Directoire et Conseil de Surveillance
au capital de 544 749 300 F.
Siège social : 35, Boulevard de

NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

Environmental Assessment FOI Summary

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STE-125-A-42-1

NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

Environmental Assessment FOI Summary

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The whole file consists of 28 pages.

NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

Environmental Assessment FOI Summary

1. DATE

August 1995

2. NAME OF APPLICANT

Roussel Uclaf.

3. ADDRESS

35, Boulevard des Invalides
75007 PARIS
FRANCE

102, Route de Noisy
93235 ROMAINVILLE cedex
FRANCE (*)

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Brief description of the requested approval

The purpose of this NDA application is to seek approval from FDA to market NILANDRON® NILUTAMIDE 50 mg Tablets, a new drug used for treatment of advanced prostate cancer.

4.2. Need for the action

Nilutamide is a new non-steroidian anti-androgen agent (N-phenyl-imidazolidine-dione) used for treatment of advanced prostate cancer in association with surgical castration.

Until now, only one non-steroidian anti-androgen was available in the USA, this is why NILANDRON® provides a good alternative to this one. The various trials carried out in the United States and in Europe have demonstrated that a total androgenic blockage (suppression of testicular and adrenal androgens activity), using a combination of castration and NILANDRON®, provides a significant improvement in

(*) New address, as from march 1995

NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

Environmental Assessment FOI Summary

patient comfort. Pain related to bone metastasis is reduced, as are secondary symptoms linked to urinary obstruction. In addition, NILANDRON® provides further benefit in terms of cancer stabilization and survival rate, as compared to castration alone.

However, NILANDRON® is to be prescribed for a relatively rare disease i.e., advanced prostate cancer with metastases (Stage D2). This type of cancer is affecting only a limited number of patients.

This is the reason why, in accordance with 21CFR § 25.31. a (b) (3) (ii), Format items 7 through 11 are not required to be documented.

4.3. Expected locations of use of the drug product

The use of NILANDRON® is limited to patients treated for advanced prostate cancer with metastases (relatively rare disease). The drug will be administered to patients located throughout the United States. The drug will be available only on doctor's prescription.

4.4. Locations where the products will be manufactured

Note : All manufacturing and packaging stages are performed in FRANCE (outside of the USA).

- Drug substance : bulk nilutamide

Steps 1,2,3 of the synthesis	ROUSSEL UCLAF Plant 3 31, Quai Armand Barbès 69250 Neuville-sur-Saône FRANCE
Step 4 of the synthesis	Société Nationale des Poudres et Explosifs (SNPE) Chemin de la loge 31078 TOULOUSE Cedex FRANCE (*)
Steps 5,6,7 of the synthesis	ROUSSEL UCLAF Plant 3 31, Quai Armand Barbès 69250 Neuville-sur-Saône FRANCE
Blending and micronization of nilutamide	ROUSSEL UCLAF Plant 2 63480 VERTOLAÏE FRANCE

(*) This plant belongs to an outside company acting as a subcontractor for ROUSSEL UCLAF. See self-certification from SNPE regarding compliance with national environmental laws in APPENDIX I.

NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

Environmental Assessment FOI Summary

- Drug product (NILUTAMIDE tablets)

ROUSSEL UCLAF / USIPHAR Plant
Route de Choisy-au-Bac
60205 Compiègne FRANCE

4.5. Environment and surrounding for each manufacturing site

4.5.1. Roussel Uclaf Plant 3, Neuville-sur-Saône

Steps 1,2,3,5,6,7 of nilutamide synthesis

- Site location

Roussel Uclaf plant 3 is located in France by the side of the Saône river at about 15 km north of Lyon city (one of the major cities in France with more than 1 million inhabitants) and in the immediate vicinity of the town of Neuville-sur-Saône (7000 inhabitants). The local climate is of continental type with relatively dry and cold winters and cool to warm and rainy summers. The leading winds are oriented along a northern (Mistral) axis or along a southern axis.

- Topography

The site is located at about 170 m above sea level (average) in the upper part of Rhone River Groove (a long geological ditch of collapsing, stretching from Marseille to north of Lyon city between Alp mountains and Massif Central). The premises are built on a large estate edged by the Saône River. The Saône river is a rather important stream (480-km long) which is the main affluent of the Rhône river, a major river from France and Switzerland. The plant is located at the southern limit of a ground water area (referenced as N° 151e), 72-sq.km large, 5-m to 15-m deep, which is used by Roussel Uclaf plant 3 for industrial water supply.

- Geology

Different geological formations are coexisting on the site :

- . Alluvial deposits originating from post-Würmian Era.
- . Loesses and alluvium from Würmian origin, probably carried here by wind and forming a coat, 0 to 8 m in width.
- . Fallen rocks and deposits resulting from solifluxion, existing on the edge of some hills and corresponding to a discontinuous coat made of clay, loess, and alluvium, including fragments of limestone and all kinds of pebbles.
- . Torrential alluvial cones originating from Würmian Era and consisting of various materials.
- . Stony and clay moraines from Würmian origin.

NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

Environmental Assessment FOI Summary

4.5.2. Roussel Uclaf Plant 2, Vertolaye

Blending and micronization of nilutamide.

- Site location

Roussel Uclaf Plant 2 is located on a 190000 sq.m property near the small town of Vertolaye (620 inhab.) in the Dore valley about 12 km downstream from Ambert (8000 inhab.) and 10 km upstream from Olliergues (1070 inhab.). The average height of the site is about 500 m above sea level. The closest important city is Clermont Ferrand (50-km away : 140000 inhab.). The local climate is continental with cold winters and cool to warm and rainy summers.

- Topography

Roussel Uclaf Plant 2 is located in the north of Massif Central, an old massif dating from Primary Era. The Dore Valley is surrounded by Livardoy mountains and Forez mountains and it ends up in a the larger valley of Limagne. The plant is edged by the Dore River and crossed by the Vertolaye brook, a small affluent of the Dore river. Both of them are used as an industrial water supply by Roussel Uclaf Plant 2.

- Geology

The underground consists mainly of of colluvial deposits with the presence of clay and marn and with alterites in some places. There is no major ground water area in this geological system.

4.5.3. Roussel Uclaf / Usiphar Plant at Compiègne

Manufacture of NILUTAMIDE 50 mg tablets (NILANDRON®)

- Site location

Roussel Uclaf / Usiphar Plant is located at about 80 km north of Paris, in the urban district of Choisy-au-Bac and in the immediate neighborhood of Compiègne (in its northern industrial area), a 45000-inhabitant city. The climate is a temperate one. The leading winds are oriented in the western direction.

- Topography

The site is located in the northern section of Parisian Basin in the southern border of Picardy Province, a part of France generally flat and edged by the sea (the Channel).

NILUTAMIDE 50 mg TabletsENVIRONMENTAL ASSESSMENT REPORTEnvironmental Assessment FOI Summary

The plant lies on a 220000 sq.m property (34 m above sea level) in the immediate vicinity of Compiègne National Forest. The plant is surrounded by two rivers : the Oise River, 700-m away from the site and the Aisne River (an affluent of the Oise River), 50-m away from the site (the Oise is a major river - 302 km long - which crosses the northern part of Parisian Basin before ending in Seine River). The Compiègne Plant is also located above a ground water area (about 1200-m beneath the site). There exists also a water tapping area (from ground water), 1200-m away from the site across the Aisne River.

- Geology

The underground can be divided up in different parts :

- . a part mostly made of sand,
- . a part originating from alluvial layers made mostly from clay and marl,
- . a part made of limestone.

4.6. Location where the products will be disposed of

The Roussel Uclaf plants which are involved in the manufacture of bulk nilutamide and NILUTAMIDE tablets operate with all technical means required to protect, preserve and enhance the quality of the environment as specified in the French law in the fields of environmental protection and occupational hygiene. In addition, each plant is classified and periodically inspected according to regulation from the French department where it is located.

The effluents are submitted to a specific treatment prior to be discharged.

Depending on their quality the solvents are either recycled or destroyed in waste disposal sites agreed by the French Government Authorities (see enclosed listing for each Plant).

The aqueous effluents undergo a treatment adapted to their composition and then are transferred either to biological treatment station or to the incineration facilities.

The solid wastes are transferred to agreed waste disposal sites.

- ROUSSEL UCLAF Plant 1 (Neuville-sur-Saône) and Plant 2 (Vertolaye)

The external waste disposal sites, agreed by French government used by these plants are :

NILUTAMIDE 50 mg TabletsENVIRONMENTAL ASSESSMENT REPORTEnvironmental Assessment FOI SummaryROUSSEL UCLAF Plant 3

Name	Address	Way of reprocessing/ destroying
MOS : DECHARGE DE SATOLAS	29, rue Greuze 69100 Villeurbanne	Delivery on agreed waste disposal site (class 2)
FRANCE DECHETS	Route de Courtry 77270 Villeparisis	Delivery on agreed waste disposal site (class 1)
CIBA GEIGI	Quai L. Aulagne, BP 47, 69191 St-Fons Cedex	Physico-chemical treatment
CIMENTS MONTALIEU	4390 Montalieu	Incineration with power recovery
CIMENTS D'ORIGNY	Usine de Champagnole, 39104 Dôle	Incineration with power recovery
CIMENTS LAFARGE	Usine de Val d'Azerque, 69380 Lozanne	Incineration with power recovery
CUMA(*) DE L'AIN	La sarrazine 01800 St-Maurice de Gourdan	Agricultural development
CUMA(*) DE L'ISERE	Hôtel de Ville, 38460 Crémieu	Agricultural development
PROCIDA	Usine de St Marcel, 13011 Marseille	Development of the product as it is
SOLAMAT	BP57 13340 Rognac	Incineration
TREDI SALAISE	ZI Portuaire 38150 Roussillon	Incineration with power recovery

ROUSSEL UCLAF Plant 2

Name	Address	Way of reprocessing/ destroying
MEUSE ENERGIE	55310 Trouville-en-Barois	Incineration with power recovery
SPEICHIM	BP 41 rue du reclus 43101 Brioude	Development of the product as it is
SOCIETE D'EXPLOITATION LA CHAUVINERE	77100 Le Mans	Incineration
LABO SERVICES	route de la centrale BP 98 69702 Givors	Physico-chemical treatment
SOLAMAT	BP 57 13340 ROGNAC	Incineration with power recovery
SICTOM SUD ALLIER (*)	Bayet 03500 St Pourçain-sur-Sioule	Incineration with power recovery
INCINERATION GENERALE DE CHAUFFE NANCY-ENERGIE	32 avenue du G ^{ral} de Gaulle 54420 Pulnoy	Incineration with power recovery
TREDI SALAISE	ZI portuaire 38150 Roussillon	Incineration with power recovery
SOLAMAT MEREX	13270 Fos-sur-mer BP 57 13340 ROGNAC	Incineration with power recovery
SIVON (**) AMBERT	Décharge du Puyet 63600 Ambert	transfer to an authorized waste management site

NILUTAMIDE 50 mg TabletsENVIRONMENTAL ASSESSMENT REPORTEnvironmental Assessment FOI Summary- ROUSSEL UCLAF / USIPHAR plant at Compiègne

The external waste disposal sites, agreed by French government used by this plants are :

TIRU S.A. (Ivry)	43, rue Bruneseau Paris 75013	Solid wastes (raw materials, rejected finished products etc.)
GEREP	14-16 rue Jacquard 21 du Mitry Compans 77290 Mitry Mory	Used solvents
Lyonnaise des Eaux	24, rue de Senlis Compiègne - Oise	Sludges from biological treatment station

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF PROPOSED ACTION5.1. Drug substance5.1.1. Nomenclature

The name of this new drug substance is nilutamide which is registered as an International Nonproprietary name (INN) and in the USAN (United state Adopted Names).

- IUPAC nomenclature

5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione

- Chemical Abstracts nomenclature

5,5-dimethyl-3-[4-nitro-3-(trifluoroethyl)phenyl]-2,4-imidazolidinedione

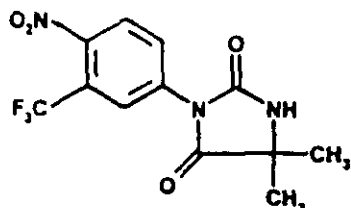
- Laboratory code number : RU 23908 (Roussel uclaf)

- CAS Registry Number : [63612-50-0]

5.1.2. Physico-chemical characteristics

- Molecular formula : $C_{17}H_{16}F_3N_3O$

- Relative molecular mass : 317.25

NILUTAMIDE 50 mg TabletsENVIRONMENTAL ASSESSMENT REPORTEnvironmental Assessment FOI Summary- Structural formula :

- Potential isomerism : there is no asymmetric center in the molecule, hence no potential diastereoisomers. However nitro- and trifluoromethyl- regioisomers can arise from poly-substitution of aromatic ring in the course of nilutamide synthesis, that is why the isomeric purity of starting materials and of key intermediate is regularly controlled.
- Physical form : White to practically white powder
- Polymorphism : only one crystalline form was detected through detection by different analytical methods.
- Melting point : 155-156°C (instantaneous). An endotherm is observed at 154°C by Differential Scanning Calorimetry (DSC).
- Solubility : nilutamide is practically insoluble in water, in aqueous buffer solution, in hexane. It is slightly soluble in isopropyl ether, n-octanol, toluene. It is sparingly soluble in chloroform and 100 p.cent ethanol. It is soluble in dichloromethane, ethyl acetate, methanol. It is freely soluble in acetone.
- Hygroscopicity : nilutamide is not hygroscopic.
- Solvation : solvate formation was never observed during drug development.
- Dissociation constant : nilutamide is weakly acidic on account of a mobile hydrogen atom. However, it was not possible to determine potentiometrically the pKa of the corresponding acidic function, as nilutamide is only slightly dissociated in solution.
- Granulometry : the drug substance was always used in a micronized state owing to its very low solubility in water and to the large size and heterogenousness of nilutamide particles obtained after crystallization.
- n-Octanol/water partition coefficient (POW)

log POW = 2.5 i.e., POW = about 300 (determination performed by HPLC according to : Klein W., Kordel W., Weiss M. and Poręmski H.J.; Chemosphere; Vol 17; N° 2; pp 361-386; 1988).

NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

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5.1.3. Impurities

Impurities in nilutamide are limited to those resulting from chemical synthesis and storage. They are structurally related to nilutamide and do not show abnormal toxicity. Other impurities such as traces of purification solvents and degradation products are routinely controlled in each batch of drug substance and restricted to low levels.

5.2. Drug product : Chemical substances used in the manufacture

The drug product is formulated according to a classical tablet formulation process with well known excipients thoroughly described in pharmaceutical literature. They consist of (in decreasing amounts):

Maize starch USP, lactose USP, povidone USP, talc USP, magnesium stearate USP, docusate sodium USP and additional purified water USP used during formulation and removed during the drying process.

6. INTRODUCTION OF THE SUBSTANCES INTO THE ENVIRONMENT

6.1. Expected production level

As it is intended for treatment of a relatively rare disease (advanced prostate cancer with metastases), NILANDRON® will be produced and marketed only at a limited scale.

6.2. Substances expected to be emitted

6.2.1. At Roussel Uclaf Plant 3, Neuville-sur-Saône

The multi-stage synthesis of nilutamide is performed in this facility. That is why various effluents (mostly liquid) are emitted during these operations.

- Gaseous effluents : they consist mainly of water steam, residual solvents released during drying of various intermediates of nilutamide synthesis. They can also be traces of reaction solvents or reagents. Other effluents resulting from incineration or rejected by the boiler plant are submitted to specific controls before being rejected (see 4.6.3.).

NILUTAMIDE 50 mg Tablets

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- Solid effluents : such as used filter aid or charcoal filter cake, they are transferred to authorized waste management centers (see section 4.6.).
- Liquid effluents : consist mainly of crystallization mother liquors containing small amounts raw materials, intermediates and drug substance. In final stages of nilutamide synthesis these liquors can be recovered and re-extracted. In all cases, these effluents are never directly rejected but they always undergo a biological treatment in a dedicated area of the plant.

liquid effluents such as washing solutions and decontamination mixture (for one chemical step) are passed through biological treatment station as well with appropriate emission controls.

Other effluents (ethanolic mother liquors, washing solvents) that cannot be reprocessed in biological treatment station are totally incinerated in a dedicated area of the plant.

Effluents resulting from use of water for cooling (i.e., with no contact with chemicals) are discharged directly into the Saône river but systematically controlled (see section 6.3.1.).

6.2.4. At Roussel Uclaf Plant 2, Vertolaye

Note : as the operations performed in this plant only consist of blending, micronization and packaging, without further chemical transformation, the emitted effluents are practically negligible and do not have a significant impact on the environment.

- Gaseous effluents : emitted by the micronization, they contain minute amounts of nilutamide dust (< 5 g of dust on a batch of 340 000 g), are passed through a multi-stage filtration system including a final filter operating with an efficiency of 99.9 p.cent.
- Liquid effluents : Approximately 500 liters of water per batch are used for cleaning operations (residual nilutamide dust : 100 g for a batch of 340 000 g). These effluents are sent for biological treatment.

Effluents resulting from use of water for cooling (i.e., with no contact with chemicals) are discharged directly into the river but systematically controlled (see section 6.3.2.).

NILUTAMIDE 50 mg Tablets

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6.2.3. At ROUSSEL UCLAF/USIPHAR Plant at Compiègne

- Gaseous effluents : nilutamide dust emitted during manufacturing of NILANDRON® tablets is trapped through a multi-stage filtration system including a final filter operating with an efficiency of 99.9 p.cent.
- Liquid effluents : The equipment is cleaned up with demineralized water and biodegradable washing agents. The equipment is finally rinsed with demineralized water. The combined effluents containing small amounts of drug substance are systematically transferred to biological treatment station.

6.3. Controls exercised

6.3.1. At Roussel Uclaf Plant 1, Neuville-sur-Saône

- Liquid effluents : they are controlled both by plant analytical department and by an external laboratory agreed by French government. The effluent resulting from biological treatment and the non-contaminated water used for cooling are systematically controlled according to definite criteria before being rejected.

	Effluent after biological treatment	Water used for cooling
Flow-rate / Temperature / pH	continuously	continuously
COD / Suspended matter / Ammoniacal nitrogen	every day	every day
BOD 5 / Total nitrogen	every week	every week
Heavy metals	every day	every week

- Gaseous effluents : the following controls are regularly applied to effluents rejected by the boiler plant or resulting from incineration.

.from boiler plant : oxygen, carbon dioxide, smoke temperature, opacity
 .from incineration : oxygen, carbon monoxide, smoke temperature, opacity, chlorine, dust level

6.3.2. At Roussel Uclaf Plant 2, Vertolaye

- Liquid effluents : they are controlled both by a specialized laboratory and by an external laboratory agreed by French government. The effluents resulting from biological treatment,

NILUTAMIDE 50 mg TabletsENVIRONMENTAL ASSESSMENT REPORTEnvironmental Assessment FOI Summary

the water used for cooling and the rain water are systematically controlled to according to definite criteria before being rejected.

	Effluent after biological treatment	Water used for cooling	Rain water
temperature / pH	continuously	continuously	-
Conductivity	continuously	-	-
Flow-rate / COD	every day	continuously	at each emission
BOD 5 / Suspended matter / Total nitrogen / Ammoniacal nitrogen / salts / heavy metals	every week	-	-

- Gaseous effluents : the following controls are regularly applied to effluents rejected by the boiler plant or resulting from incineration.

.from boiler plant : carbon dioxide, oxygen, temperature, blacking index, temperature (outside)

.from incineration : oxygen, carbon dioxide, dust, chlorine, carbon monoxide, non burnt matter, heavy metals, ascension velocity

6.3.3. At Roussel Uclaf / Usiphar plant at Compiègne

- Liquid effluents : they are periodically controlled both by plant water treatment unit and by an external French government agency.

Plant water treatment unit pH, sludge content, COD, turbidity, chlorides, nitrites, nitrates, ammoniacal nitrogen

French government agency suspended matter, BOD 5, COD, oxidizable matter, total nitrogen, ammonium ions, nitrites, nitrates.

- Gaseous effluents : the smoke produced at the boiler plant is submitted to the following tests : carbon monoxide content and carbon dioxide content.

6.4. Estimation of the quantities and concentrations of substances expected to enter the environment as a result of use and or disposal of products affected by the action

- From disposal of drug product : No substance is expected to be emitted as the wastes are systematically incinerated (see section 4.7.3.).

NILUTAMIDE 50 mg Tablets

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- From use of drug product : It has been shown that the excreted metabolites of nilutamide have lost the high antiandrogenic activity displayed by nilutamide.

6.5. Citation of, and statement of compliance with applicable emission requirements

The French government and the concerned French departments where Roussel Uclaf chemical and pharmaceutical plants are located (Rhône, Puy-de-Dôme and Oise) employ responsible agents to assure compliance with national regulations as regards environmental control and occupational exposure.

It is certified that the operations involved in manufacturing, quality control testing, packaging, distribution and disposal of drug substance and drug product comply with national and local regulations.

6.6. Discussion of the effect that approval will have upon compliance with current emission requirements at the production site

As NILANDRON® is prescribed for a relatively rare disease, it is produced on a limited scale and only represents a minor part of total production in the concerned chemical and pharmaceutical plants located in France (1t or less for each plant). Therefore it can be assumed that approval of NILANDRON® will have no adverse effect on the company's compliance with existing French permits and with current emission requirements. Furthermore it is reminded that this drug is already registered in France and in some other countries.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

9. USE OF RESOURCES AND ENERGY

10. MITIGATION MEASURES

11. ALTERNATIVES TO THE PROPOSED ACTION

Items 7. through 11. are not required to be documented

(Rare disease. Cf 21CFR § 25.31 a (b) (3) (ii)).

NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

Environmental Assessment FOI Summary

12. LIST OF PREPARERS

- M. Paul COSTE (Process safety and Environmental Protection at Vertolaye)

Chemical engineer, graduate of the Ecole Nationale Supérieure de Chimie de Clermont-Ferrand, licencié ès Sciences, Docteur-Ingénieur, who had 26 years of professional experience as of January 1, 1991.

- Dr Martine DANAN-DURIEUX (Central Department of Toxicovigilance and Industrial Hygiene)

Medical doctor, graduate of the Faculté de Médecine de Paris, post-Grade studies in clinical and toxicological Pharmacology, who had 17 years of experience in the field of medicine and post-marketing surveillance as of January 1, 1991.

- Mr Jean-Claude GIUDICELLI (Industrial Chemical Control)

Graduate of the Conservatoire National des Arts et Métiers de Paris, who had 26 years of professional experience as of January 1, 1991.

- Mr Jean-Claude GRANEL (Central Department of Environment and Safety)

Chemical engineer, Graduate of the Ecole Nationale Supérieure de Chimie de Montpellier, who had 21 years of professional experience as of January 1, 1991.

- Mr Marcel RICORD (Quality Assurance, Process Safety and Environmental Protection at Neuville-sur-Saône)

Chemical engineer, graduate of the Ecole Nationale Supérieure de Chimie Industrielle de Lyon, who had 26 years of industrial experience as of January 1991.

- Mr Jean-Pierre TORCO (Industrial Development at Compiègne)

Electronic Engineer, who had 21 years of professional experience as of January 1, 1991

At this time Mr TORCO is also in charge of environmental protection.

STE-125-A-42-1

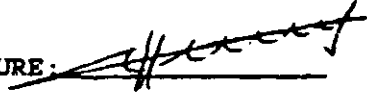
NILUTAMIDE 50 mg Tablets

ENVIRONMENTAL ASSESSMENT REPORT

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13. CERTIFICATION

The undersigned official certifies that the information presented in this document is true, accurate and complete to the best of his knowledge.

SIGNATURE: 

DATE : 15-01-1995

Mr Jean-Claude GRANEL

Head of
Central Department of Environment
of Safety and of Industrial Hygiene
ROUSSEL UCLAF S.A.

ENVIRONMENTAL ASSESSMENT REPORT

Environmental Assessment FOI Summary

14. REFERENCES

- Guidelines

- Environmental Assessment for Proposed Approvals of FDA regulated Products-Format 1. US Code of Federal Regulations (CFR), Title 21, § 25.31 a (a) (Items 1-15) ; April 1991, pp. 207-208.
- Environmental Assessment Technical Assistance Handbook. US Food and Drug Administration and US Department of Commerce, National Technical Information Service (PB87-175345) ; March 1987.
- Environmental Protection Agency (EPA). Code of Federal Regulations (CFR), Title 40.
- Environmental Protection Agency (EPA). Toxic Substance Control Act Test Guidelines. Fed. Reg., 50 (1985) : 39252-39263.
- 1992 Crossley Tracking Survey of the United States Diabetes Market.
- Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA Pharmaceutical Manufacturers Association, Version VII, July 1991 : 1, 9-27, 46-52.

- Publications

- W. Klein, W. Kordel, M. Weiß and H.J. Poreniski : "Updating of the OECD test guidance 107 - Partition coefficient n-octanol/water - OECD laboratory intercomparison test on the HPLC method". Chemosphere, Vol. 17, No 2, pp 361-386 (1988).

FDA Corres

NDA 20-169

AUG 6 1996

Corning Besselaar, Inc.
Attention: Carole Venetianer, R.N., M.S.
Manager, Regulatory Affairs and Biomedical Writing
210 Carnegie Center
Princeton, NJ 08540-16233

Dear Ms. Venetianer:

Please refer to the June 14, 1991, new drug application submitted on behalf of Roussel UCLAF, and your resubmission dated March 7, 1994, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nilandron® (nilutamide tablets).

We also refer to your amendment dated March 15, 1996 submitted in response to our second approvable letter dated February 22, 1996.

We have completed our review of the package insert and ask that you make the following revisions:

CLINICAL PHARMACOLOGY section

WARNINGS section

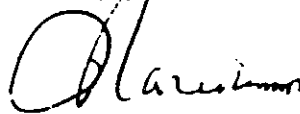
ADVERSE REACTIONS section

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
(301) 443-3510

Sincerely yours,



Lisa D. Rarick, M.D.
Acting Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-169
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls
HFD-580/JFourcroy/HJolson/JEl-Hage

drafted: /August 5, 1996/LPauls/N20169IR.LAB

Concurrences:

JFourcroy, HJolson 08.05.96

INFORMATION REQUEST (IR)

APR 27 1994

G.H. Besselaar Associates
Attention: James Burns, Jr., Ph.D.
Princeton Forrestal Center
103 College Road East
Princeton, NJ 08540-6681

Dear Dr. Burns:

Please refer to your March 7, 1994 new drug application resubmitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Anandron (nilutamide).

We have determined that your application will be filed on May 6, 1994. However, in order to complete our review of the biopharmaceutic section of your submission, we request the following:

1. Dissolution information for the to-be-marketed 50 mg T2 tablets including:
 - a. dissolution profiles in simulated gastric fluid (SGF) without enzyme; and
 - b. dissolution profiles in simulated intestinal fluid (SIF) without enzyme at 5, 15, 30, 45, and 60 minutes using 12 dosage units for each test.

In addition, please provide a pH solubility profile for nilutamide.

2. Clarification as to when blood samples were collected for quantitating nilutamide and its metabolite plasma/serum levels for study 89/1108/CN.
3. Additional data analyses as follows:

Analyses to assess possible relationships between nilutamide and its metabolite plasma/serum levels to the adverse reaction(s) and/or surrogate efficacy/pharmacodynamic endpoints. E.g., PSA and alkaline phosphatase plasma/serum levels (study 89/1108/CN).

In addition, these analyses should attempt to relate covariates such as bodyweight, age, race, patient's hepatic and renal function, and /or degree of disease status.

4. Pharmacokinetic (PK) simulations for predicting steady-state nilutamide and metabolite levels (i.e. steady-state peak, average, and trough plasma/serum levels) in normals and patients for 150 and 300 mg QD dosing regimens based on the PK parameters from the single dose studies. Depending upon the results of these studies, a classic food effect study may be needed.

NDA 28-169

5 OF 6

5. Additional information on the pharmacologic activities of metabolites, including the stereoisomers of metabolites, if available.

Please submit this information as soon as possible so we can continue our evaluation of your NDA.

Should you have any questions, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

JS 4/24/94

Solomon Sobel, M.D.
Director
Division of Metabolism
and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

LJP 4/26/94

cc:

Original NDA

HFC-130/JAllen

HFD-510

HFD-427/AChen/JHunt

HFD-510/JFourcroy

HFD-80/DDIR

HFD-510/LPauls/04.22.94/N20169IR.BPH

INFORMATION REQUEST

NDA 20-169

MAR 10 1994

G.H. Besselaar Associates
Attention: James Burns, Jr., Ph.D.
Princeton Forrestal Center
103 College Road East
Princeton, NJ 08540-6681

Dear Dr. Burns:

We have received your new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Anandron (nilutamide) Tablets, 50 mg

Therapeutic Classification: S

Date of Application: March 7, 1994

Date of Receipt: March 7, 1994

Our Reference Number: NDA 20-169

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 6, 1994, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact:

Lana L. Braithwaite, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

 3/10/94

Enid Galliers
Chief, Project Management Staff
Division of Metabolism
and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

LUB 3/10/94

cc
Orig.
HFC-130/JAllen
HFD-510
HFD-510/JFourcroy/AFleming/YYChiu/AJordan
HFD-510/LBraithwaite/03.10.94/N20169RS.ACK

ACKNOWLEDGEMENT

NDA 20-169

AUG 14 1991

G.H. Besselaar Associates
Attention: James P. Burns, Jr., Ph.D.
Senior Vice President, Regulatory Affairs
103 College Road East
Princeton, NJ 08540-6681

Dear Dr. Burns:

Reference is made to your new drug application dated June 14, 1991, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anandron (nilutamide) Tablets.

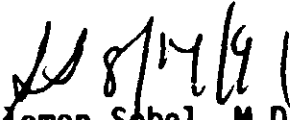
On the basis of our initial review of your NDA referred to above, received on June 17, 1991, and acknowledged on June 21, 1991, we have determined that the application is not acceptable for filing under 21 CFR 314.101. The application is incomplete, because it does not contain on its face information required under section 505(b)(1)(A) of the Act and 21 CFR 314.50(d)(5) of the implementing regulations. Specifically, the application does not contain two adequate and well-controlled studies which are required to provide the data necessary to assess the safety and efficacy of the drug.

Within 30 days of the date of this letter, you may request in writing an informal conference about FDA's refusal to file the application. To file this application over FDA's protest, you must avail yourself to this informal conference.

Although unrelated to our reason for refusing to file the application, we are concerned about the significant toxicity of nilutamide in both animals and man. Without demonstration of considerable efficacy, it is unlikely that the risk/benefit ratio would favor approval of the application. This fact should be taken into consideration in deciding whether to perform a second pivotal clinical trial.

Should you have any questions regarding this action, please contact Ms. Lois Simmons at 301-443-3510.

Sincerely yours,


Solomon Sobel, M.D.
Director

Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch.

HFD-510

HFD-80

HFC-130/JAllen

HFD-426/CBradley/JHunt

HFD-500/LRipper

HFD-713/LPian/ENevius

HFD-510/JFourcroy/GTroendle/ENashed/YChiu/JEl-Hage/AJordan

HFD-511/LSimmons/7.31.91/FT/MMM/8/14/91/n20169rf.fil

Concurrences: JShort/8.07.91/JFourcroy/GTroendle/8.08.91/NNashed/YChiu/8.13.91/
JEl-Hage/AJordan/8.14.91

REFUSE TO FILE

Simmons 14 aug 91

NDA 20-169

G.H. Besselaar Associates
Attention: James P. Burns, Jr., Ph.D.
Senior Vice President, Regulatory Affairs
103 College Road East
Princeton, NJ 08540-6681

JUN 21 1991

Dear Dr. Burns:

We have received your new drug application submitted pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Anandron (nilutamide) Tablets

Date of Application: June 14, 1991

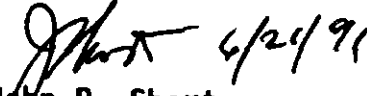
Date of Receipt: June 17, 1991

Our Reference Number: NDA 20-169

Unless we find the application not acceptable for filing, the filing date will be August 15, 1991.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning this NDA, please contact Ms. Lois Simmons at 301-443-3510.

Sincerely yours,


John R. Short
Supervisory Consumer Safety Officer
Division of Metabolism and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch.
HFD-510
HFD-511/LSimmons/6.21.91/FT/MM/6/21/91/n20169.ack
Concurrence:

ACKNOWLEDGEMENT

NDA 20-169

Nilandron® (nilutamide) Tablets

Roussel-UCLAF (Besselaar Associates)

Advertising Material

No advertising material has been submitted.

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Yana Mille, Chair, HFD-600 MPN II

From: Division of Metabolism and Endocrine D. P./ HFD-510
Attention: Xavier Ysern Phone: 301 443-3510

Date: 28-APR-1994

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: ANANDRON NDA #: 20-169

Established name, including dosage form: Nilutamide tablets 50 mg
Chemical name: 5,5-dimethyl-3-[(4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione CAS 63612-50-0

Other trademarks by the same firm for companion products: _____

Indications for Use (may be a summary if proposed statement is lengthy): Treatment of metastatic prostate cancer in combination with chemical castration with an LHRH agonist or following surgical castration. Nilutamide is nonsteroid antiandrogen that blocks by competition, the binding of androgens with their receptors

Initial comments from the submitter (concerns, observations, etc.): See attached (marketing approvals and submissions, pages 93 and 94 of the original submission) the footnote regarding the comment of the "Committee for Proprietary Medicinal Products".

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

NILUTAMIDE FOR PROSTATE CANCER
NDA APPLICATION SUMMARY

PART C: FOREIGN MARKETING HISTORY
[314.50(c)(2)(iii)]

1. MARKETING APPROVALS

Nilutamide (RU 23 908) has been approved for metastatic prostate cancer in combination with surgical or chemical castration (LHRH agonists) by the regulatory authorities in the following countries:

COUNTRY	DATE OF APPROVAL
<u>EUROPEAN COUNTRIES</u>	
Belgium ^a	August 1990 ^b
Finland	December 1992 ^b
France	July 1986
Iceland	March 1991
Luxembourg ^a	January 1991 ^b
Netherlands	May 1990 ^b
Norway	December 1992 ^b
Portugal	November 1987
Sweden	December 1990 ^b
<u>EASTERN EUROPEAN COUNTRIES</u>	
Czechoslovakia	July 1990
Poland	October 1991
Russia	January 1992
Yugoslavia	January 1992
<u>AMERICAN COUNTRIES</u>	
Argentina	November 1989
Brazil	May 1989
Canada	December 1991 ^c
Chile	August 1991
Guatemala	December 1989
Peru	January 1990
Uruguay	May 1991
Venezuela	July 1990
Colombia	January 1990
Trinidad and Tobago	July 1992
<u>OTHERS</u>	
India	December 1992
New Zealand	April 1992
Egypt	August 1992
Iraq	March 1992
Morocco	December 1992

- ^a EEC Procedure, CPMP negative opinion in May 1989
^b Flare-Up
^c 300 mg daily in combination with surgical castration

000093

Nilutamide has not been withdrawn from marketing in any country for any reason relating to safety or effectiveness. There are no significant safety or effectiveness problems.

2. SUBMISSIONS

Nilutamide has been submitted for approval for the above indication to the regulatory authorities of the following countries:

COUNTRY	SUBMISSION DATE	PRESENT STATUS
Denmark*	October 1988	Unfavorable opinion issued June 1989. Additional submission in "FLARE UP" made in February 1993.
W. Germany*	October 1988	Application withdrawn. ⁴
Greece*	October 1988	Application withdrawn. ⁴
Ireland*	October 1988	Clinical objections raised in April 1989 and March 1992; dossier withdrawn. ⁴
Italy*	October 1988	Italian regulatory authorities adhered to the C.P.M.P. unfavorable opinion (June 1989). ⁴
Spain*	October 1988	Negative position (1989). ⁴
U.K.*	October 1988	Objections by the Committee on Safety of Medicines (July 1989). Answers filed in February 1991. Final hearing with the CSM on September 1991 giving rise to a negative advice. ⁴
Switzerland	December 1988	Objections mainly based on risk/benefit evaluation. Rejected October 1989. New submission: September 1993.

* New submission planned (1994), mainly based on new pivotal clinical studies (CTR 606 and CTR FF/86/90861) metaanalysis and prognostic factors.

* Standard dossier (with preliminary limited clinical data) submitted in October 1988 through the EEC MULTI-STATE PROCEDURE (laid down by the EEC 83/570 Directive) in 9 Member-States. Objections raised by some Member-States were referred to the Committee for Proprietary Medicinal Products (C.P.M.P.) at its meeting of 24 May 1989, resulting in the following C.P.M.P. opinion: "the Committee for Proprietary Medicinal Products considers that the proprietary medicinal product does not satisfy the requirements of Art. 5 of Directive 65/65 EEC, as the clinical documentation does not demonstrate an acceptable benefit/risk ratio concerning therapeutic effect/adverse reactions. In addition, adequate quality was not assured."

000094

1.0/46

Consult #300 (HFD-510)

ANANDRON

Nilutamide Tablets 50 mg

A review revealed several names which look or sound like the proposed name: Anadrol-50, Anayodin, Anarol, Anabolin, Amrinone, Ananase, and Ondansetron (Sertraline).

The name of greatest concern was Anadrol (Syntex - Oxymetholone Tablets) since it is also available as a 50 mg tablet. The Committee was particularly concerned about potential confusion between these two products since Anadrol is an anabolic steroid which is contraindicated in carcinoma of the prostate while Anandron is an antiandrogen used to treat metastatic prostate cancer. It was felt that the consequences of a medication error involving these two products would be serious. For this reason the Committee found the proposed name misleading as defined in 21 CFR 201.10(c)(5).

It was also noted that the name appears to be derived from the medical "anandria" meaning loss of masculinity or virility. While this is appropriate and meaningful for this anti-androgen product, such a name could be considered misleading due to its fanciful nature [21 CFR 201.10(c)(3)] particularly if the name implies an effectiveness greater than the product exhibits. Since the Committee does not have information pertaining to product effectiveness, it was felt Division reviewers should make the final determination with regard to this aspect of the name.

The Committee finds the proposed name unacceptable for the reasons described above.

CDER Labeling and Nomenclature Committee

Yana Mills, Chair 5/31/94

COMPLETED

6/1/94

Co. Corres

210 Carnegie Center
Princeton, NJ 08540-6233
609.432.8550
609.432.9375 Fax

ORIGINAL

ORIGINAL AMENDMENT

FOR APPROVAL
8/14/96

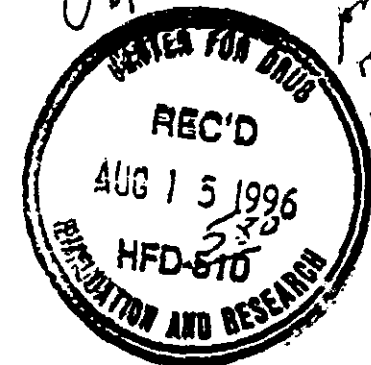
14 August, 1996

Lisa D. Rarick, M.D.
Acting Director
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Labeling is acceptable
for drug approval
Khalil
8/28/96

CORNING Besselaar

Accepted for approval
8/28/96
Notice
Information
provided
reviewed
on 8/28/96
#4 (14-1)
and
submitted
N.A.T.
X. Y. 525
8/23/96



Re: NDA 20-169; NILANDRON™ (nilutamide) Tablets ✓

Dear Dr. Rarick:

Reference is made to the Agency's approvable letter for the above-referenced NDA, dated 7 March 1995, our response to this letter dated 15 August 1995, the Agency's subsequent approvable letter dated 22 February 1996, our response dated 15 March 1996, the Agency's letter dated 6 August 1996, and our response dated 7 August 1996. In addition, reference is made to a telephone call on 13 August 1996 from Ms. Lana Pauls to Corning Besselaar requesting that the sponsor make the naming of the drug product consistent among the package insert, carton label, and blister label. On behalf of the sponsor, Roussel UCLAF of Romainville, France, we are submitting a revised package insert to address this concern.

Please note the following:

- Nilandron™ is the brand name,
- Nilutamide is the established generic name, and
- Tablet is the dosage form.

Therefore, we have changed the first page of the package insert to be consistent with the carton and blister labels. The drug name will now read "NILANDRON™ (nilutamide)", followed by the dosage form "Tablets".

In addition, we are submitting revised carton labels that include the addition of instructions to open the child-resistant packaging and a change in location of copy from the back panel to the side panel.

For your convenience, we are resubmitting the blister labels.

14/8/96

Page 2

If you have any questions or require additional information we would be pleased to respond.

Sincerely yours,



Carole L. Venetianer, R.N., M.S.
Project Director

Copy to: J. T. Zenno
B. D. Mooney
R. J. Wojnar, Ph.D.
C. Michel, Ph.D

A. de Gery (Roussel)
A. Deslauriers (Roussel)
C. Kirk-Yourtee (HMR)
FDA Log/Archives

ref: 00814sob.doc

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I. ☐ MEMO
CSO INITIALS	DATE

Corning Besselaar, Inc.
210 Carnegie Center
Princeton, NJ 08540-6233
609.452.8550
609.452.9375 Fax

17 September, 1996

CORNING Besselaar

Lisa D. Rarick, M.D.
Acting Director
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-169; NILANDRON™ (nilutamide) Tablets
Labeling Commitment

Dear Dr. Rarick:

Reference is made to a telephone conversation of September 16, 1996 between Corning Besselaar and Ms. Lana Pauls regarding labeling for NILANDRON™. During this conversation it was suggested that the sponsor be allowed to implement the change requiring the addition of the word in Nilandron carton packaging components (physician sample carton and commercial carton) at the printing immediately following launch.

The sponsor is requesting that the launch materials already produced be exempted from the requirement of adding to the front panel of the cartons. We understand that the blister packs do not require the additional text.

A mock-up of each component (physician sample and commercial cartons) carrying the additional labeling copy as suggested will be submitted to the Agency tomorrow. The additional text is, This text will immediately follow the proprietary and established names on the front panels of the carton.

17/9/96

Page 2

We would appreciate your circulating this request to the appropriate reviewers and letting us know if this is an acceptable proposal. If you have any questions or require additional information we would be pleased to respond.

Sincerely yours,



Carole L. Venetianer, R.N., M.S.
Project Director

Copy to: M.J. Losi, Ph.D.
B. D. Mooney
R. J. Wojnar, Ph.D.
C. Michel, Ph.D

A. de Gery (Roussel)
A. Massey (Roussel)
C. Kirk-Yourtee (HMR)
FDA Log/Archives

ref: 00916sob.doc

Corning Besselaar, Inc.
210 Carnegie Center
Princeton, NJ 08540-6233
609.452.8550
609.452.9375 Fax

ORIG AMENDMENT

7 August, 1996

CORNING Besselaar

Lisa D. Rarick, M.D.
Acting Director
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-169 (Nilandron™; Nilutamide)

Dear Dr. Rarick:

Reference is made to the Agency's approvable letter for the above-referenced NDA, dated 7 March 1995, our response to this letter dated 15 August 1995, the Agency's subsequent approvable letter dated 22 February 1996, our response dated 15 March 1996, and the Agency's letter dated 6 August 1996. On behalf of the sponsor, Roussel UCLAF of Romainville, France, we are submitting a revised package insert that complies with the Agency's requested wording for the CLINICAL PHARMACOLOGY, WARNINGS, and ADVERSE REACTIONS sections.

If you have any questions or require additional information we would be pleased to respond.

Sincerely yours,

A handwritten signature in cursive script, appearing to read 'Carole L. Venetianer'.

Carole L. Venetianer, R.N., M.S.
Project Director

Copy to: J. T. Zenno
B. D. Mooney
R. J. Wojnar, Ph.D.
C. Michel, Ph.D.

A. de Gery (Roussel)
A. Deslauriers (Roussel)
C. Kirk-Yourtee (HMR)
FDA Log/Archives

ref: 0807sob.doc

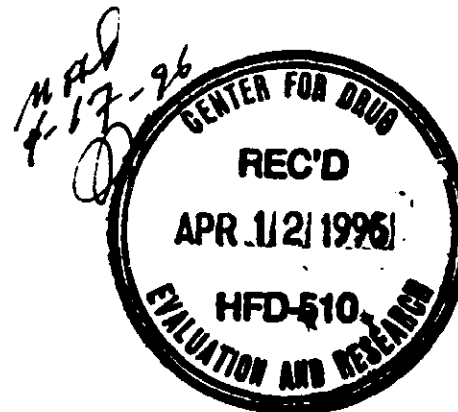
Corning Besselaar, Inc.
210 Carnegie Center
Princeton, NJ 08540-6233
609.452.8550
609.452.9375 Fax

04-11-96
CORNING BESSELAAR

11 April, 1996

CORNING Besselaar

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-169 (Nilandron™; Nilutamide)

Dear Dr. Sobel:

Reference is made to the Agency's approvable letter for the above-referenced NDA, dated 7 March 1995, our response to this letter dated 15 August 1995, the Agency's subsequent approvable letter dated 22 February 1996, and our response dated 15 March 1996, at which time a revised package insert and carton and container labels were submitted. On behalf of the sponsor, Roussel UCLAF of Romainville, France, we are submitting additional documentation to support minor proposed changes to the **HOW SUPPLIED** section of the package insert and to the carton and container labels. Reference is made to a telephone conversation between Ms. Lana Pauls, CSO and Corning Besselaar at which time it was discussed that these changes were minor and could probably be reviewed in parallel to the 15 March 1996 submission.

The sponsor proposes to change the present individual blister card of 20 tablets and the to-be-marketed package count of 100 (5x20 ct) to the preferred U.S. sales and sample package of an individual blister card of 15 tablets and the to-be-marketed package count of 90 (6x15 ct).

In addition, the sponsor proposes to change the aluminum foil lidding by adding polyester and paper to the outer surface to insure the required function for providing child resistance.

These changes do not impact the blister cavity cell size, the surface to volume ratio, the product contact material, or the aluminum foil thickness, and therefore, do not represent a substantial change to the packaging of the drug product. The sponsor commits to place the first three lots on stability and report the data to the NDA after approval.

11/4/96

Page 2

Attached please find the following information.

- Attachment 1 Supportive documentation for the above-referenced changes to the packaging.
- Attachment 2 A revised HOW SUPPLIED section to the package insert submitted on 15 March 1996 to incorporate the above-referenced changes.
- Attachment 3 Revised carton and container labels to incorporate the above referenced changes.

If you have any questions or require additional information we would be pleased to respond.

Sincerely yours,



Carole L. Venetianer, R.N., M.S.

Copy to: J. T. Zenno
B. D. Mooney
R. J. Wojnar, Ph.D.
C. Michel, Ph.D.

A. de Gery (Roussel)
A. Deslauriers (Roussel)
C. Kirk-Yourtee (HMR)
FDA Log/Archives

ref: 0329sob.doc

REVIEWS COMPLETED	
ACTION:	
ENTER	☐ N.A.I. ☐ MEMO
CSO INITIALS	DATE

Corning Besselaar, Inc.
210 Carnegie Center
Princeton, NJ 08540-6233
609.452.8550
609.452.9375 Fax

ORIGINAL

~~CONFIDENTIAL~~

PZ

15 March, 1996

CORNING Besselaar

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Handwritten notes:
"not attached" (with arrow pointing to the stamp)
"3-26-96" (with arrow pointing to the date)
"memo" (with arrow pointing to the word)
"Noted" (with arrow pointing to the stamp)
"See comments" (with arrow pointing to the stamp)
"4/11/96" (with arrow pointing to the stamp)
"JF"

Re: NDA 20-169 (Nilandron™; Nilutamide)

Dear Dr. Sobel:

Reference is made to the Agency's approvable letter for the above-referenced NDA, dated 7 March 1995, our response to this letter dated 15 August 1995, and the Agency's subsequent approvable letter dated 22 February 1996. On behalf of the sponsor, Roussel UCLAF of Romainville, France, we are responding to the Agency's request for additional information necessary for approval of the NDA.

Environmental Assessment

Attachment 1 provides the additional information requested to fulfill the requirements for the Environmental Assessment. As noted in the Agency's letter of 22 February 1996, we are only providing replacement pages and/or addendums for the Agency to incorporate into the previously submitted version.

Biopharmaceutics

Attachment 2 provides the sponsor's response to the Agency's request to change the dissolution specifications to:

USP Apparatus II (Paddle), 50 rpm
900 mL water at 37°
Q = $\bullet$ % in $\bullet$ min

Handwritten notes:
"From the same sample"
"Q = 75% is acceptable"
"Graph from dissolution"
"change of apparatus"
"signature"
"acceptance"
"X-1500"
"4/12/96"

In view of the results presented in *Attachment 2*, the sponsor prefers to remain with Q = $\bullet$ %. The sponsor commits to the timely submission of dissolution profiles (up to $\bullet$)

15/3/96

Page 2

min) on three batches (12 tablets per batch) in simulated intestinal fluid on batches that are within the expiration date.

Package Insert

Attachment 3 provides a revised version of the package insert that responds to the Agency wording received with the 22 February 1996 approvable letter. This attachment consists of two documents. The first document (*Attachment 3a*) is formatted to provide the Agency suggested wording of 22 February 1996 with the Roussel-proposed revisions. Deletions to the Agency wording are shown by strike-through and additions are double-underlined.

Attachment 3b provides a clean copy of the entire text of the draft package insert as proposed by Roussel.

It is apparent upon review that there is very close agreement on the draft package insert. While Roussel has accepted most of the Agency's modifications to the original package insert, minor modifications and editorial changes have been made. Those issues requiring additional discussion are provided below:

CLINICAL PHARMACOLOGY;
Pharmacokinetics-Distribution, Metabolism,
Elimination

WARNINGS; Hepatitis

WARNINGS; Pregnancy

PRECAUTIONS; Animal Pharmacology and Toxicology

ADVERSE REACTIONS

HOW SUPPLIED

Safety Update

Reference is made to the submission of 5 February 1996. This submission referenced the submission of 15 August 1995 at which time a Safety Update was submitted that provided all data cleaned as of 2 May 1995 for ongoing clinical trials. The pivotal studies, FF/86/908/01 and GHBA-606, have a limited number of patients continuing to participate in the studies and these studies are monitored and the data cleaned on a yearly basis, with the exception of deaths, serious adverse experiences, and adverse experiences resulting in discontinuation. (15 patients continue to participate in FF/86/908/01 and 19 in GHBA-606.) The 15 August 1995 submission provides all pooled safety data that is available in house from these two ongoing studies.

Attached please find additional reports of deaths, serious adverse experiences, and adverse experiences resulting in discontinuation for which information has become available subsequent to the 15 August 1995 submission (*Attachment 4a*). Also attached is additional post-marketing surveillance information that has become available (*Attachment 4b*). **(This information has previously been submitted on 5 February 1996 and is being resubmitted for ease of review.)**

The information provided does not alter the statements of contraindications, warnings, precautions, or adverse reactions contained in the proposed package insert.

Carton and Container Labels

Attachment 5 provides mock-up labels for both commercial and sample packages.

We would like to make the Agency aware that after approval the NDA will be transferred to Hoechst Marion Roussel, Inc. who will market Nilandron tablets in the United States. The contact person will be Ms. Cynthia Kirk-Yourtee (Telephone No. 816-966-5076 and Fax No. 816-966-6790).

If you have any questions or require additional information we would be pleased to respond.

Sincerely yours,



Carole L. Venetianer, R.N., M.S.
Manager, Regulatory Affairs and Biomedical Writing

REVIEWS COMPLETED	
☐ N.A.I.	☐ MEMO
CSC INITIALS	DATE

Copy to: J. T. Zenno
B. D. Mooney
R. J. Wojnar, Ph.D.
C. Michel, Ph.D

A. de Gery (Roussel)
A. Deslauriers (Roussel)
C. Kirk-Yourtee (HMR)
FDA Log/Archives

ref: 0226asob.doc

STUDY N° FF/86/908/01

MEDIAN TIMES (months)	NDA 20169 CUTOFF 30 Aug. 1989				UPDATE CUTOFF 31 Dec. 1992				UPDATE CUTOFF 31 Dec. 1994			
	ORCHIECTOMY				ORCHIECTOMY				ORCHIECTOMY			
	Nilutamide	Placebo	p. *		Nilutamide	Placebo	p. *		Nilutamide	Placebo	p. *	
<i>Objective progression</i>												
Evaluable patients	19.0	14.9	0.008		21.2	14.7	0.0038		21.2	14.7	0.0024	
All patients	18.9	14.9	0.009		21.8	14.9	0.0089		21.1	14.9	0.0045	
<i>Cancer survival</i>												
Evaluable patients	NR	27.5	0.058		35.4	30.0	0.0416		35.4	30.0	0.0353	
All patients	NR	27.5	0.049		37.0	29.8	0.0135		37.0	29.8	0.0133	
<i>Overall survival</i>												
Evaluable patients	28.3	23.2	0.145		27.2	24.2	0.1283		27.2	24.2	0.0635	
All patients	28.3	22.8	0.144		27.3	23.8	0.0586		27.3	23.8	0.0328	

NR = Not Reached

* Based on a Logrank test

ROUSSEL UCLAF

Nilutamide versus Placebo in

Orchiectomized Patients

FF/06/908/01

Investigator : Combined

CUTOFF DATE : 31.12.95

TABLE 12
NUMBER OF PATIENTS WITH OBJECTIVE PROGRESSION OF PROSTATE CANCER
BY TIME INTERVAL
(Evaluable patients)

Time interval	Orchiectomy +		Orchiectomy +		p-value **
	N*	Nilutamide	N*	Placebo	
0-6 months	202	20	208	38	
7-12 months	173	27	160	36	
13-18 months	137	22	118	37	
19-24 months	105	29	75	15	
25-30 months	66	15	66	8	
31-36 months	48	4	43	10	
37-42 months	43	8	28	6	
43-48 months	33	2	21	1	
49-54 months	29	2	20	2	
55-60 months	24	2	17	3	
61-66 months	21	3	14	2	
67-72 months	-	-	11	-	
73-78 months	17	2	10	1	
79-84 months	13	2	7	1	
85-90 months	6	1	4	1	
> 91 months	5	-	-	-	
TOTAL		139		161	

Progression Free
Actuarial Rate

Month 6	88.7	81.0
Month 12	75.1	62.2
Month 18	62.5	42.1
Month 24	44.3	33.3
Month 30	34.1	26.3
Month 36	31.2	21.4
Month 42	25.2	16.8
Month 48	23.6	16.0
Month 54	22.0	14.3
Month 60	20.2	11.8
Month 66	17.3	10.0
Month 72	-	10.0
Month 78	16.3	8.8
Month 84	12.8	7.0
Month 90	10.2	3.5

Median Time to Progression
(months)

21.2

14.7

0.0024

* Numbers of patients at risk at beginning of time interval

** Based on a Logrank test

ROUSSEL UCLAF
Nilutamide versus Placebo in
Orchiectomized Patients
FF86/908/01
Investigator : Combined

CUTOFF DATE : 31.12.94

TABLE 13
NUMBER OF PATIENTS WITH OBJECTIVE PROGRESSION OF PROSTATE CANCER
BY TIME INTERVAL
(All patients)

Time interval	Orchiectomy +		Orchiectomy +		p-value **
	N*	Nilutamide	N*	Placebo	
0-6 months	225	24	232	42	
7-12 months	185	30	180	39	
13-18 months	146	24	133	41	
19-24 months	112	29	86	17	
25-30 months	70	15	63	10	
31-36 months	62	5	49	13	
37-42 months	48	9	31	6	
43-48 months	35	2	24	2	
49-54 months	31	2	22	2	
55-60 months	27	6	19	3	
61-66 months	21	3	16	2	
67-72 months	-	-	12	-	
73-78 months	17	2	11	1	
79-84 months	13	2	8	1	
85-90 months	8	1	5	2	
> 91 months	5	-	-	-	
TOTAL		153		151	

Progression Free
Actuarial Rate

Month 6	88.6	81.2	
Month 12	73.7	63.0	
Month 18	60.9	43.1	
Month 24	44.2	34.2	
Month 30	34.6	28.8	
Month 36	31.2	20.7	
Month 42	24.9	18.6	
Month 48	23.4	15.2	
Month 54	21.9	13.8	
Month 60	17.8	11.6	
Month 66	15.3	10.0	
Month 72	-	10.0	
Month 78	13.5	8.9	
Month 84	11.3	7.4	
Month 90	9.0	0.0	
Median Time to Progression (months)	21.1	14.9	0.0045

* Numbers of patients at risk at beginning of time interval

** Based on a Logrank test

ROUSSEL UCLAF

CUTOFF DATE : 31.12.94

Nilutamide versus Placebo in

Orchiectomized Patients

PF/86/08/01

Investigator : Combined

TABLE 14
NUMBER OF PATIENTS WHO DIED BECAUSE OF PROSTATE CANCER
BY TIME INTERVAL
 (Evaluable patients)

Time interval	Orchiectomy +		Orchiectomy +		p-value **
	N*	Nilutamide	N*	Placebo	
0-6 months	207	5	218	11	
7-12 months	197	23	197	28	
13-18 months	163	12	163	19	
19-24 months	144	23	140	23	
25-30 months	113	18	109	17	
31-36 months	90	9	90	17	
37-42 months	74	12	65	8	
43-48 months	64	3	55	7	
49-54 months	50	3	43	3	
55-60 months	46	2	38	8	
61-66 months	39	1	31	2	
67-72 months	35	3	27	2	
73-78 months	31	1	22	1	
79-84 months	26	1	16	2	
85-90 months	18	3	10	1	
> 91 months	8	1	1	-	
TOTAL		120		146	

**Progression Free
 Actuarial Rate**

Month 6	97.6	94.7
Month 12	86.7	81.0
Month 18	79.3	71.4
Month 24	66.1	59.3
Month 30	55.4	49.9
Month 36	49.6	39.9
Month 42	41.1	36.1
Month 48	38.7	31.2
Month 54	36.4	28.9
Month 60	34.7	24.3
Month 66	33.8	22.7
Month 72	30.8	20.9
Month 78	29.8	19.8
Month 84	28.7	16.8
Month 90	23.0	11.2

Median Time to Progression (months)	35.4	30.0	0.0353

* Numbers of patients at risk at beginning of time interval

** Based on a Logrank test

ROUSSEL UCLAF
Nilutamide versus Placebo in
Orchiectomized Patients
FF/86/908/01
Investigator : Combined

CUTOFF DATE : 31.12.94

TABLE 16
NUMBER OF PATIENTS WHO DIED BECAUSE OF PROSTATE CANCER
BY TIME INTERVAL
(All patients)

Time interval	Orchiectomy +		Orchiectomy +		p-value **
	N*	Nilutamide	N*	Placebo	
0-6 months	225	7	232	12	
7-12 months	211	25	212	31	
13-18 months	174	12	173	20	
19-24 months	155	24	149	26	
25-30 months	121	18	115	18	
31-36 months	97	9	95	19	
37-42 months	81	13	67	6	
43-48 months	60	3	57	7	
49-54 months	55	3	45	3	
55-60 months	50	3	39	6	
61-66 months	42	1	32	2	
67-72 months	38	3	28	2	
73-78 months	34	1	23	1	
79-84 months	28	1	17	2	
85-90 months	19	3	10	1	
> 91 months	8	1	1	-	
TOTAL		127		156	

Progression Free
Actuarial Rate

Month 6	98.8	94.7
Month 12	84.9	80.4
Month 18	78.9	71.0
Month 24	66.2	56.2
Month 30	56.1	49.0
Month 36	50.7	38.6
Month 42	42.1	35.0
Month 48	39.9	30.4
Month 54	37.7	28.3
Month 60	35.3	23.9
Month 66	34.4	22.3
Month 72	31.6	20.7
Month 78	30.7	18.6
Month 84	29.5	16.7
Month 90	24.1	11.1

Median Time to Progression (months)	37.0	29.8	0.0133

* Numbers of patients at risk at beginning of time interval
** Based on a Logrank test

ROUSSEL UCLAF

Nilutamide versus Placebo in

Orchiectomized Patients

FF/86/008/01

Investigator : Combined

CUTOFF DATE : 31.12.94

TABLE 16
NUMBER OF PATIENTS WHO DIED BECAUSE OF ANY CAUSE
BY TIME INTERVAL
(Evaluable patients)

Time Interval	Orchiectomy +		Orchiectomy +		p-value **
	N*	Nilutamide	N*	Placebo	
0-6 months	207	10	216	19	
7-12 months	197	33	197	34	
13-18 months	183	18	163	23	
19-24 months	144	31	140	31	
25-30 months	113	21	109	18	
31-36 months	90	12	90	22	
37-42 months	74	15	65	8	
43-48 months	54	4	55	8	
49-54 months	50	3	43	4	
55-60 months	46	4	38	6	
61-66 months	39	2	31	4	
67-72 months	36	4	27	4	
73-78 months	31	1	22	2	
79-84 months	26	1	18	2	
85-90 months	18	4	10	2	
> 91 months	8	1	1	-	
TOTAL		164		187	

Progression Free
Actuarial Rate

Month 6	95.2	91.2	
Month 12	79.2	76.5	
Month 18	70.4	64.8	
Month 24	55.3	50.5	
Month 30	44.9	42.1	
Month 36	38.8	31.8	
Month 42	30.6	27.6	
Month 48	28.3	23.4	
Month 54	26.6	21.2	
Month 60	24.2	17.8	
Month 66	22.9	15.6	
Month 72	20.3	13.2	
Month 78	19.8	11.9	
Month 84	18.8	10.1	
Month 90	13.8	8.1	
Median Time to Progression (months)	27.2	24.2	0.0635

* Numbers of patients at risk at beginning of time interval

** Based on a Logrank test

ROUSSEL UCLAF

Nilutamide versus Placebo in

Orchiectomized Patients

FF/86/908/01

Investigator : Combined

CUTOFF DATE : 31.12.94

TABLE 17
NUMBER OF PATIENTS WHO DIED BECAUSE OF ANY CAUSE
BY TIME INTERVAL
(All patients)

Time Interval	Orchiectomy +		Orchiectomy +		p-value **
	N*	Nilutamide	N*	Placebo	
0-6 months	225	14	232	20	
7-12 months	211	36	212	39	
13-18 months	174	18	173	24	
19-24 months	155	32	149	34	
25-30 months	121	22	115	19	
31-36 months	97	12	95	24	
37-42 months	81	16	87	8	
43-48 months	60	4	67	8	
49-54 months	55	3	45	5	
55-60 months	50	6	39	6	
61-66 months	42	2	32	4	
67-72 months	39	4	29	4	
73-78 months	34	1	23	2	
79-84 months	29	2	17	2	
85-90 months	19	4	10	2	
> 91 months	8	1	1	-	
TOTAL		176		201	

Progression Free
Actuarial Rate

Month 6	93.8	91.4
Month 12	77.7	74.8
Month 18	69.7	64.2
Month 24	65.2	49.6
Month 30	45.1	41.3
Month 36	39.4	30.6
Month 42	31.3	26.9
Month 48	29.1	22.9
Month 54	27.5	20.4
Month 60	24.7	17.2
Month 66	23.4	15.1
Month 72	21.0	12.9
Month 78	20.3	11.7
Month 84	18.9	10.0
Month 90	14.0	5.0

Median Time to Progression
(months)

27.3

23.6

0.0326

* Numbers of patients at risk at beginning of time interval

** Based on a Logrank test

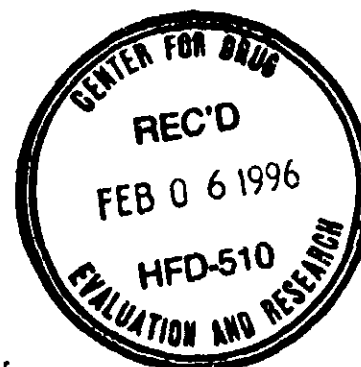
Corning Besselaar
210 Carnegie Center
Princeton, NJ 08540-6233
609.452.8550
609.452.9375 Fax

00000000000000000000

5 February, 1996

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CORNING Besselaar



Re: NDA 20-169 (Nilandron™; Nilutamide)
Response to a Request for Information

Dear Dr. Sobel:

On behalf of the sponsor, Roussel-UCLAF, we are responding to a request from Ms. Lana Pauls, CSO, for a final Safety Update before approval of the above-referenced NDA. Reference is made to the submission of 15 August 1995 at which time a Safety Update was submitted that provided all data cleaned as of 2 May 1995 for ongoing clinical trials. The pivotal studies, FF/86/908/01 and GHBA-606, have a limited number of patients continuing to participate in the studies and these studies are monitored and the data cleaned on a yearly basis, with the exception of deaths, serious adverse experiences, and adverse experiences resulting in discontinuation. (15 patients continue to participate in FF/86/908/01 and 19 in GHBA-606.) The 15 August 1995 submission provides all pooled safety data that is available in house from these two ongoing studies.

Attached please find additional reports of deaths, serious adverse experiences, and adverse experiences resulting in discontinuation for which information has become available subsequent to the 15 August 1995 submission (*Attachment 1*).

Also attached is additional post-marketing surveillance information that has become available (*Attachment 2*).

The information provided does not alter the statements of contraindications, warnings, precautions, or adverse reactions contained in the proposed package insert.

Reference is made to a telephone conversation of 17 January 1996 between Corning Besselaar and Dr. Albert Chen (Biopharmaceutics) requesting additional dissolution data for

5 February 1996

Page 2

recently manufactured batches. Please note this information was faxed to Dr. Chen on 23 January 1996 and is being included in this submission (*Attachment 3*).

If you have any questions or require additional information we would be pleased to respond.

Sincerely yours,

Carole Venetianer

Carole L. Venetianer, R.N., M.S.
Manager, Regulatory Affairs and Biomedical Writing

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER

☐ N.A.I.

CSO INITIALS

DATE

Corning Besselaar, Inc.
210 Carnegie Center
Princeton, NJ 08540-6233
609.452.8550
609.452.9375 Fax

ORIGINAL
24
GPO 1987-1-457

13 December, 1995

CORNING Besselaar

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-169, NILANDRON™
Nilutamide Tablets

Dear Dr. Sobel:

Reference is made to the Agency's approvable letter dated 7 March 1995 for the above-referenced New Drug Application (NDA). Reference is also made to our submission dated 15 August 1995 on behalf of the sponsor, Hoechst Marion Roussel, Inc., responding to the Agency's request for additional information necessary for approval of the NDA. With this submission, we are supplying updated information that was referenced in the 15 August 1995 submission.

Please find attached a revised version of the proposed package insert for NILANDRON. This version contains two changes to the labeling. At the request of the Division, the sponsor has now added a subsection **Animal Pharmacology and Toxicology** to the **PRECAUTIONS** section (page 6 of revised package insert). The wording of this subsection is consistent with the Agency's recommended wording received with the approvable letter.

The second revision is to the **DOSAGE AND ADMINISTRATION SECTION** (page 12 of revised package insert). The sponsor has deleted the sentence that nilutamide

To support this change in the labeling, the sponsor is submitting the final report for the food interaction study referenced in the response to the approvable letter. Please find attached the final report for Protocol No. ZA/95/908/12 ("Effect of Food on Bioavailability of Nilutamide After Single Oral Administration of 300 mg to Healthy Male Volunteers"). Also attached is Report No. 95/7844/CN which contains the pharmacokinetic results and methods for this study.

13/12/95

Please note that minor editorial changes have been made to page 1 (**DESCRIPTION**) of the revised package insert and the doses of the nilutamide administered to rats for 18 months has been slightly altered to reflect the correct doses (**PRECAUTIONS--Carcinogenesis, Mutagenesis, Impairment of Fertility**, page 7).

If you have any questions, or require additional information, we would be pleased to respond.

REVIEWS COMPLETED

Sincerely yours,

CSO ACTION:

Carole Venetianer

☐ LETTER

☐ N.A.I.

Carole Venetianer, R.N., M.S.
Manager, Regulatory Affairs and Biomedical Writing

CSO INITIALS

DATE

15 August 1995

CORNING Besselaar

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-169, NILANDRON®;
Nilutamide Tablets

Dear Dr. Sobel:

Reference is made to the Agency's approvable letter dated 7 March 1995 for the above-referenced New Drug Application (NDA). On behalf of the sponsor, Roussel UCLAF, we are responding to the Agency's requests for additional information necessary for approval of the NDA. This submission consists of 25 volumes; for ease of review a table of contents follows this letter. Each request is presented in italics followed by the sponsor's response.

Biopharmaceutics:

1. *A pharmacokinetic/bioavailability study should be conducted to assess the effect of food on this tablet and to support the labeling recommendation that Nilandron be administered prior to breakfast with a glassful of water. This study should include at least twelve healthy subjects and utilize a standard high-fat breakfast. Please contact Dr. Albert Chen in the Division of Biopharmaceutics for further information regarding the study design.*

Reference is made to a sponsor submission of 13 April 1995 that included a draft protocol (ZA/95/908/12) for a pharmacokinetic/bioavailability study. Reference is also made to a telephone conversation between Dr. Albert Chen in the Division of Biopharmaceutics and Corning Besselaar on 28 April 1995 at which time Dr. Chen outlined his suggested revisions to the draft protocol (these revisions are enumerated in a Division letter dated 2 June 1995). A final protocol that contained all the requested changes was submitted on 24 May 1995. Reference is made to

15 August 1995

the Division's letter dated 2 June 1995 stating that approval of Nilandron® may be granted prior to the completion of the study and the recommendation that the study be initiated as soon as possible and the results submitted in a timely manner. The sponsor indicates that the study began on 22 June 1995; the results will be submitted as soon as they are available. For your reference a copy of the final protocol is provided in Attachment A.

2. *Between-study analyses should be conducted relating nilutamide plasma levels with efficacy and safety parameters. For example, is the difference in the number of patients who reported impaired adaptation to darkness and were receiving nilutamide in conjunction with either surgical or chemical castration (13% vs. 56%) related to differences in drug plasma levels?*

The requested analyses are provided in Attachment A.

3. *The following dissolution method/specification should be implemented:*

*USP Apparatus II (Paddle), 50 rpm
900 mL USP pH 7.5 simulated intestinal fluid (SIF) without enzymes
at 37°C
Q = 75% in 15 min*

Before this method is finalized, however, dissolution profiles (up to 15 min) must be provided for the biobatches (12 tablets per batch) used in the pharmacokinetic studies as well as the batches used in the two pivotal clinical studies (Nos. FF/86/908/01 and GHBA 606).

Attachment A contains a document entitled: Nilutamide 50 mg Tablets (NILANDRON®), Additional Information, STE-125-A-40-1, July 1995. The document provides a comparative dissolution study between water and SIF media and the sponsor's proposal to maintain the water method with Q = 75% at 15 min.

Environmental Assessment:

1. *The environmental assessment document will be releasable under the Freedom of Information Act; therefore, confidential data and information*

15 August 1995

that were pertinent to the environmental review of the proposed action must be submitted separately as a confidential section. However, this information must be summarized in the environmental assessment document to the extent possible. In addition, the appropriate information from [REDACTED] must be included in the environmental assessment document.

Attachment B provides a revised version of the environmental assessment document. This document is provided in two parts: 1) Confidential version (STE-125-A-18-2) and 2) Nonconfidential version (STE-125-A-42-1) that will be available to be releasable under the Freedom of Information Act. The revised environmental assessment report is prepared in accordance with the format and content requirements outlined in 21CFR, 40CFR, and the FDA Assistance Handbook.

All information concerning subcontractor [REDACTED] is provided in a confidential Drug Master File (DMF [REDACTED]) previously submitted to the FDA.

2. *The environmental assessment document omits Sections 7 through 11, citing an exemption under 21 CFR 25.31a(b)(3). However, no information is provided in Section 4 to justify the exemption. The environmental assessment document should be treated as a stand-alone document; therefore the brief description of the requested approval and need for action should contain sufficient information on the use of nilutamide to justify the requested exemption.*

Section 4 (page 8) has been revised to provide a brief description of the requested approval and the need for the action of nilutamide as treatment for advanced prostate cancer. Nilandron® is prescribed for a relatively rare disease and is to be manufactured on a limited scale, therefore justifying the exemption for Section 7-11.

3. *Section 4 (description of the proposed action) should be revised as follows:*
 - a. *The document should contain a brief description of the requested approval and of the need for action.*

Section 4 has been revised to provide this information (Sections 4.1 and 4.2, page 8).

- b. The complete address should be included for the subcontractor*

The revised version of the environmental assessment document provides the complete address for (Section 4.5, page 12).

- c. The environments at, and surrounding, each facility should be described in sufficient detail to allow evaluation of the environmental impact of the proposed action, i.e., urban, suburban, rural*

The revised document describes the environments at and surrounding the Usiphar Plant at Compeigne, Plant 3 at Neuville S/Saone, and Plant 2 at Vertolaye (Section 4.6, page 13).

- d. The document should include a description of the expected locations of use of the drug product.*

The expected location for the use of nilutamide is now provided in the revised document (Section 4.3, page 8).

- e. The identity, location, and permit numbers should be included for any facilities involved with the recycling and/or disposal of wastes from manufacturing, formulation, and packaging activities.*

The requested information has been added to the revised document (Section 4.7, page 18, 19, 26, and 30).

- 4. Section 5 (identification of chemical substances) should be revised to include a physical description of the drug substance as well as identification of the impurities.*

Section 5 has been revised to provide a physical description of the drug substance for nilutamide as well as identification of potential impurities (Section 5.1.2, pages 40 and 47 and Section 5.1.3, page 55).

5. *Section 6 (introduction of substances into the environment) should be revised as follows:*

- a. *Each chemical that is anticipated to be in the effluent, waste, or emission from each process step should be identified. In addition, an anticipated concentration should be provided.*

The requested information is now provided in the revised document (Section 6.2.1, page 64, Section 6.2.2, page 72, and Section 6.2.3, page 73).

- b. *A table should be included showing the estimates for production levels for five years.*

The requested table is provided in the revised document (Section 6.1, page 63).

- c. *The description of environmental controls at Compiègne should be expanded to include dust emissions from the tableting process.*

The description has been expanded in the revised document to include dust emissions from the tableting process (Section 6.2.3, page 73).

- d. *The efficiency of each emission control step should be included for all facilities.*

The requested information is now provided in the revised document (Section 6.3.1, page 74, Section 6.3.2, page 76, and Section 6.3.3, page 79).

- e. *Section 6.3 should reference the inspection report for Compiègne.*

A recent inspection report is now provided in the revised document (Section 6.5, page 84).

15 August 1995

- f. The document should include sufficient information for each facility to allow confirmation of the statement that approval of the proposed action will have no adverse effect on compliance with existing permits.*

The requested information has been provided in the revised document (Section 6.6, page 159).

- g. The document should provide an estimate of the maximum yearly market volume of the drug product and a calculation of Estimated Expected Emitted Concentration.*

The requested information is now provided in the revised document (Section 6.1, page 63 and Section 6.4.2, page 82).

- h. The document should describe the method of disposal of returned or expired drug product.*

The requested information is now provided in the revised document (Section 4.7.3, page 30).

- 6. Section 14 (references) should be revised to include the citations for all material referred to and used in the preparation of the environmental assessment.*

The requested information has been provided in the revised document (Section 14, page 167).

Labeling:

A revised package insert is provided in Attachment C that incorporates minor textual and format changes made by the sponsor as well as suggested revisions outlined in the approvable letter of 7 March 1995 and subsequent fax dated 23

15 August 1995

March 1995. An annotated version of the initial package insert provided with the NDA resubmission of 7 March 1994 is also provided in Attachment C. This annotated version outlines the changes that have been made from the initial package insert to the current revised version. A description of how each request is addressed by the sponsor is provided below and also appended to the revised package insert.

DESCRIPTION section

The second sentence of the fourth paragraph should be deleted from this section. This information, however, may be moved to the HOW SUPPLIED section.

The requested information has been deleted and additional information on the physical properties of nilutamide have been added to this section.

CLINICAL PHARMACOLOGY section

- a. *Under the subsection Mechanism of Action, the phrase*
should be deleted from the last sentence. This sentence
should now read:

The sponsor has deleted the requested phrase

Complete peripheral antiandrogen activity has been demonstrated in animal pharmacology studies regardless of the method of castration.

The sponsor has deleted the word from the sentence but has
opted to keep the word to be consistent with the labeling for flutamide.

The sponsor has modified the sentence that begins

Please note also, the sponsor has added the mean elimination half life (56hrs) in patients after the administration of the usual dosage (150 mg) in the "Elimination" subsection of the "Pharmacokinetics" section.

Under the subsection Clinical Studies, the last sentence should be revised to place emphasis on the trial performed by orchiectomy patients (i.e., the study order should be reversed). Therefore, the last sentence should read:

The sponsor proposes to delete mention to the leuprolide study and only present results for the orchiectomy study in this section for consistency with the "INDICATIONS" section.

- c. *Under the same subsection, Clinical Studies, the entire second paragraph that currently begins should be deleted and replaced with the following paragraph that reads:*

INDICATIONS and USAGE section

CONTRAINDICATIONS section

- The sponsor has added the requested information to the hepatic impairment contraindication but proposes to keep the wording for severe impairment. The justification is presented in Annex 2 appended to the revised package insert in Attachment C. The sponsor proposes adding a sentence in the "PRECAUTION -

Information for Patients" section indicating that patients presenting with symptoms of hepatitis should advise their physicians promptly.

The sponsor also proposes to keep the contraindication in women and to add children to the contraindications to strengthen the impact of this section.

WARNINGS section

Appropriate subheadings have been added as requested.

- b. A new sentence should be added as the last sentence of the current first paragraph. This sentence should read:***

The sponsor proposes to modify the requested sentence to

The justification for this change is presented in Annex 3 appended to Attachment C.

The sponsor has also added possible additional signs and symptoms that may be present at the onset of interstitial pneumonitis.

The sponsor proposes to retain the wording for all

- c. The last sentence of the current second paragraph that begins should be deleted.***

This sentence has been deleted as requested.

- d. *In the penultimate paragraph, the number 3 should be changed to the number 2 and the order of the last two words reversed. Therefore, this paragraph should now read as follows:*

The sponsor proposes to keep the reference to transaminases to 3 times the upper limit of normal in keeping with the contraindication of severe hepatic impairment.

PRECAUTIONS section

The requested change has been made.

- b. *In the same subsection, Information for Patients, the third paragraph should be in bold-face type.*

This paragraph is now in bold-face type.

- c. *The subsection Laboratory Tests, should be revised to read:*

15 August 1995

The sponsor proposes to delete the information is now provided in the section.

subsection. The appropriate subsection and in the

Please note also that the hepatic microsomal enzyme sysytem has been specified as the liver cytochrome P-450 isoenzyme system in the "Drug Interaction" subsection.

- d. The first paragraph of the subsection Carcinogenesis, mutagenesis, impairment of fertility should be revised to read:*

The requested information has been revised as requested.

- e. The second paragraph of the same subsection should be revised to read:*

The sponsor proposes to slightly alter the suggested wording to provide a simpler format.

15 August 1995

Page 13

- f. In the same subsection, the last sentence that currently reads:
should be revised to read as follows:

The wording has been changed as requested.

- g. The entire Pregnancy subsection should be revised to read:

This subsection has been revised as requested.

- h. A new subsection entitled "Animal pharmacology and toxicology"
should be added to the end of this section. This new subsection
should read as follows:

The sponsor proposes that this subsection is not necessary for inclusion in the revised labeling in order to give instructions for safe and effective use of the drug in humans. Annex 4 appended to Attachment C provides a statement from an American consultant pathologist on the interpretation of the toxicology studies in dogs and rats to justify the omission of this subsection.

ADVERSE REACTIONS section

- a. This section should remain basically as written.*

15 August 1995

The "ADVERSE REACTIONS" subsection remains basically as written but provides updated adverse event rates as substantiated by the Safety Update Report contained in Attachment D of this submission. A sentence has been added below each table to provide the overall adverse event rate for all patients in each treatment group.

- b. *The last three sentences of the fourth paragraph that begins should be deleted.*

The sponsor proposes to retain these sentences in order to inform the physician that adverse events reported in $\leq 5\%$ of patients treated with nilutamide are usually observed in elderly patients or in patients with metastatic prostate cancer (the exceptions being interstitial pneumonitis and alcohol intolerance).

Please note that in the "DOSAGE AND ADMINISTRATION" section the sponsor has deleted

CARTON and CONTAINER LABELS

All carton and container labels must be submitted.

Attachment C provides mock-up copies of revised carton and container labels. If these are acceptable, the sponsor will submit copies with graphics and physical dimensions.

15 August 1995

In addition, a safety update as provided for by 21 CFR 314.50(d)(5)(vi)(b) must be submitted.

Attachment D provides a safety update report for nilutamide. This report provides cumulative integrated adverse experience and laboratory safety information for nilutamide and focuses on the two pivotal studies, FF/86/908/01 and GHBA-606. The updated adverse event rates are reflected in the ADVERSE REACTIONS section of the revised package insert. Also included is an update of the deaths, serious adverse experiences, and adverse experiences that resulted in discontinuation for the supportive clinical studies. Case report forms are provided for patients who died or discontinued for an adverse experience since the last safety update of 13 October 1994.

Introductory promotional material will be submitted for review, at a subsequent time, prior to use by the sponsor.

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,



Carole L. Venetianer, R.N., M.S.
Manager,
Regulatory Affairs and Biomedical Writing

ref: g:\gc\venetian\lrr\0629sobe.ltr

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USA
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Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

27 January 1995

SELAAR

Re: NDA 20-169; nilutamide tablets
Response to a Request for Information



Dear Dr. Sobel:

At the request of Dr. J. El Hage, reviewing pharmacologist, we are submitting supplemental summary tables for the 30-day oral toxicity study in dogs (89/1376/TX) and the 26-week oral toxicity study in dogs (299 TCC) contained in the above-referenced NDA.

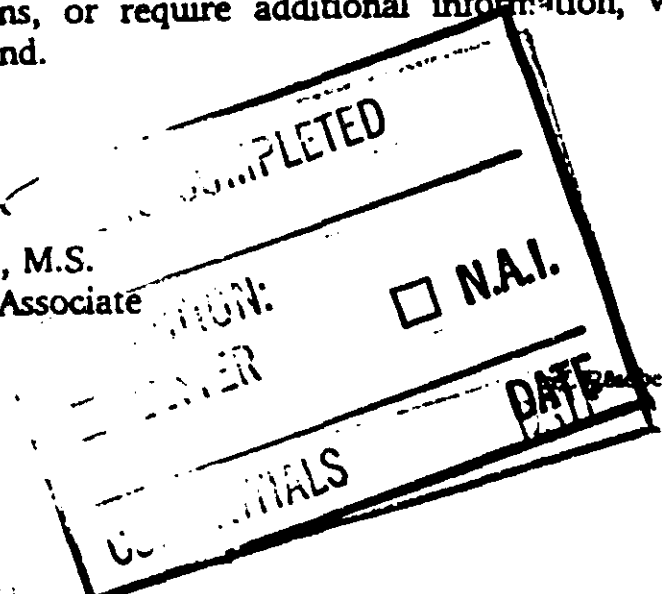
If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,

Carole L. Venetianer

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:egd



VIEWS COMPLETED	
ACTION:	
LETTER	☐ N.A.I.
INITIALS	DATE

Princeton, USA
Nashville, USA
Radnor, USA
Madison, USA
West Palm Beach, USA
Walnut Creek, USA
Sydney, Australia
Tokyo, Japan

Brussels, Belgium
Maidenhead, U.K.
Leeds, U.K.
Munich, Germany
Zurich, Switzerland
Paris, France
Stockholm, Sweden
Dublin, Ireland

G H Besselaar Associates
210 Carnegie Center
PRINCETON, NJ 08540-6233
USA
Phone (609) 452 8550
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BC

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ORIGINAL

SELAAR

Solomon Sobel, M.D.

27 January 1995

Director

Division of Metabolism and Endocrine

Drug Products, HFD-510

Food and Drug Administration

Center for Drug Evaluation and Research

5600 Fishers Lane

Rockville, MD 20857

Re: NDA 20-169: Nilutamide Tablets;
Response to a Request for Information

RECEIVED
ACTION:

REGISTER

NOTES

☐ MAY

CENTER FOR DRUG

RECEIVED

JAN 30 1995

HFD-510

Dear Dr. Sobel:

With this submission, we are responding to the draft deficiency letter dated 22 December 1995 for additional information to supplement the chemistry, manufacturing, and controls section of the above-referenced NDA.

Attached please find the sponsor's (Roussel-UCLAF) reply. Each deficiency point pertaining to drug substance and drug product is followed by the sponsor's response. For the request pertaining to labeling, the sponsor has submitted the name nilutamide, an International Nonproprietary Name (INN), to the United States Adopted Name (USAN) Council on 13 December 1994 and indicated that Nilandron is the proposed tradename.

Princeton, USA
Nashville, USA
Radnor, USA
Madison, USA
West Palm Beach, USA
Walnut Creek, USA
Sydney, Australia
Tokyo, Japan

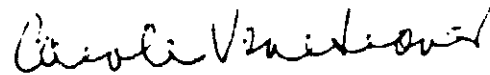
Brussels, Belgium
Maidenhead, UK
Leeds, UK
Munich, Germany
Zurich, Switzerland
Paris, France
Stockholm, Sweden
Dublin, Ireland

Page 2

27 January 1995

If you have any questions or require additional information, we would be pleased to respond.

Sincerely yours,

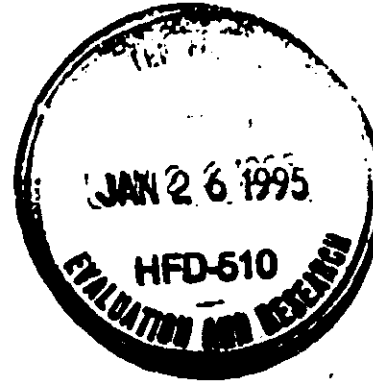
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Carole L. Venetianer
Senior Regulatory Affairs Associate

CLV:egd
0512aobcl.ltr

Bm

Case 1:12-cv-00002



25 January 1995

55ELAAR

ORIGINAL

Dear Dr. Sobel:

Attached please find the following information, supplied by the sponsor, Roussel UCLAF: 1) Categories of Prostatic Specific Antigen values for baseline and at the end of 12 weeks for the two pivotal clinical studies; and 2) Updated survival and progression information for the two pivotal studies.

and 2) Updated survival and progression in
studies.

TESTING COMPLETED

☐ **DATE**

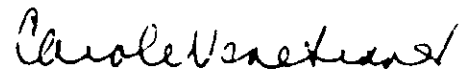
☐ **N.A.I.**

Princeton, USA
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Sydney, Australia
Tokyo, Japan

Brussels, Belgium
Maidenhead, UK
Leeds, UK
Munich, Germany
Zurich, Switzerland
Paris, France
Stockholm, Sweden
Delft, The Netherlands

If you have any questions or require additional information, we would be pleased to respond.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Carole Venetianer".

Carole L. Venetianer
Senior Regulatory Affairs Associate

CLV:egd
0512aobel.ltr

G H Besselaar Associates
210 Carnegie Center
PRINCETON, NJ 08540-6233
USA
Phone (609) 452 8550
Fax (609) 452 9375

B?

ORIGINAL-26-95

SELAAR

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

20 January 1995

Re: NDA 20-169;
nilutamide tablets
Nonclinical Toxicology

REVIEWS COMPLETED

REVISION:

☐ LETTER ☐

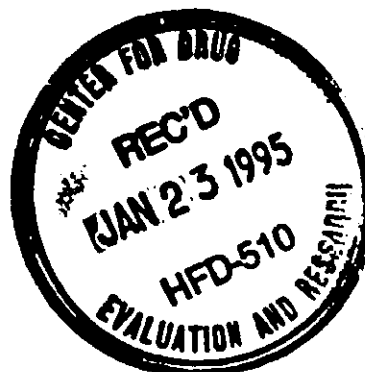
Dear Dr. Sobel:

In response to a request from Dr. El Hage, pharmacologist, we are submitting the following supplements to the 1-year dog and 78-week rat chronic toxicity studies:

- Supplement to Study 1042 TCC: Toxicity Study in Beagle Dogs by Oral Administration for 52 Weeks, May 1990.
- Supplement to Study 20: Toxicity Study in Rats by Repeated Dietary Administration for 78 weeks, May 1990.

This information has previously been submitted to IND
No. 090).

(Serial



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St. Louis, USA

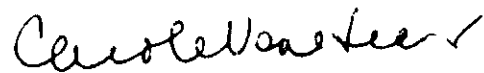
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Munich, Germany
Zurich, Switzerland
Paris, France
Stockholm, Sweden

Page 2
Dr. Solomon Sobel

20 January 1995

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,

A handwritten signature in cursive script, reading "Carole L. Venetianer", followed by a checkmark.

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:egd

ref.200120-169.nda

G.H. Besselaar Associates
210 Carnegie Center
PRINCETON, NJ 08540-6233
USA
Phone (609) 452 8550
Fax (609) 452 9375

BB

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

18 January 1995

ORIGINAL

ELAAR

Re: NDA 20-169; (nilutamide tablets)
Response to a Request for Information

Dear Dr. Sobel:

With this submission we are responding to requests, dated 2 January and 3 January 1995, from Dr. Albert Chen, biopharmaceutics reviewer, requesting additional information pertaining to the above referenced NDA. Each request is followed by the sponsor's (Roussel-UCLAF) response.

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,

Carole Venetianer

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:gl

Ref:030sobel.ltr

REVIEWS COMPLETED

CCO ACTION:

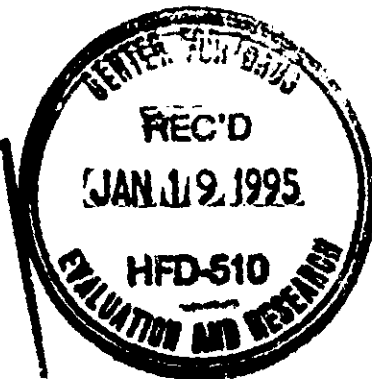
☐ LETTER

☐ N.A.I.

CCO INITIALS

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Nashville, USA
Radnor, USA
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Walnut Creek, USA
Sydney, Australia

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Leeds, UK
Munich, Germany
Zurich, Switzerland
Paris, France
Stockholm, Sweden



5 December 1994

Page 2

If you have any questions or require additional information, we would be pleased to respond.

Sincerely yours,



Carole I. Venetianer
Senior Regulatory Affairs Associate

CLV:egd
0512sobel.ltr

G.H. Besselaar Associates
Princeton Forrestal Center
103 College Road East
PRINCETON, NJ 08540-6681
USA
Phone (609) 452 8550
Fax (609) 452 9375

BB

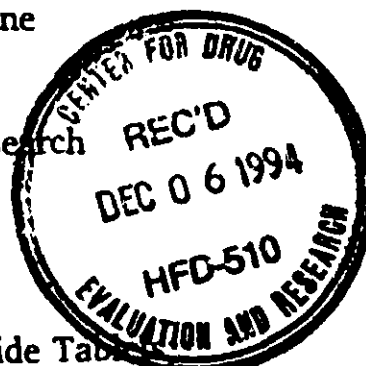
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12-9-94
JF

ORIGINAL

5 December 1994

SELAAR

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

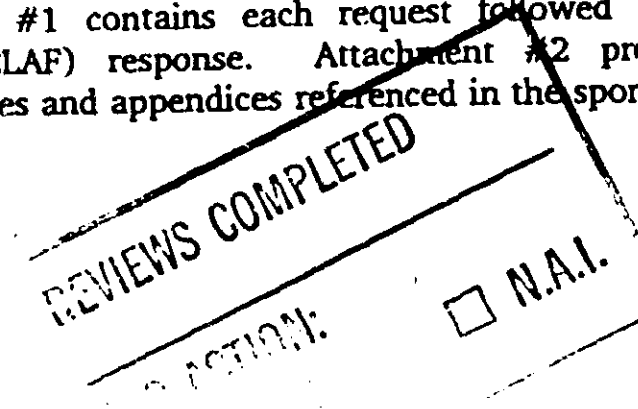


Re: NDA 20-169: Nilutamide Tablets
Response to a Request for Information

Dear Dr. Sobel:

With this submission, we are responding to requests dated 18 October, 20 October, 21 October, 24 October, and 28 October 1994 from Dr. Albert Chen requesting additional biopharmaceutic information pertaining to the above-referenced NDA.

Attachment #1 contains each request followed by the sponsor's (Roussel-UCLAF) response. Attachment #2 provides additional tables, figures and appendices referenced in the sponsor's replies.



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Paris, France
Stockholm, Sweden

C
G.H. Besselaar Associates
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Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

11 November 1994

ORIGINAL



Re: NDA 20-169; Nilutamide tablets
Preapproval Inspection

SELAAR

Dear Dr. Sobel:

On behalf of the sponsor, Roussel UCLAF, we are submitting a copy of the responses to FDA Form 483, generated by the FDA inspectors during the preapproval inspection of the Roussel facilities at Compiègne and Romainville. This information has also been submitted to the International Inspection Program and Technical Support Branch (HFC-134).

If you have any questions, or require additional information, we would be pleased to respond.

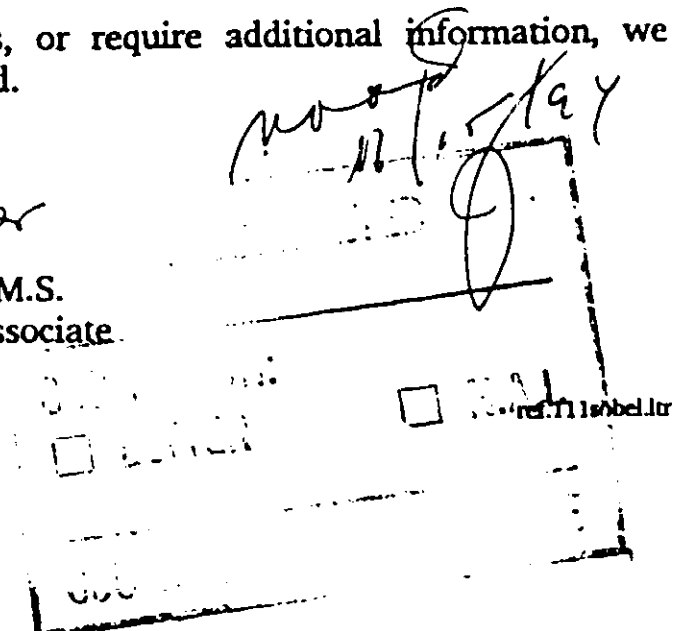
Sincerely yours,

Carole L. Venetianer

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:egd

attachment
enclosure



*Noted
11-16-94
JG/Hug*

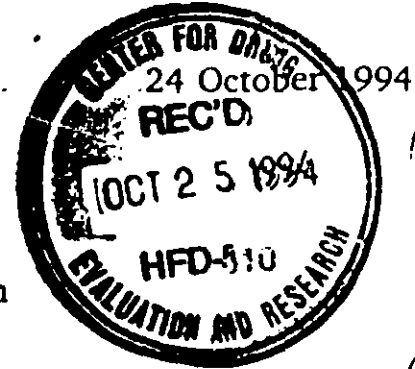
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Osaka, Japan

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ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



*Noted
10-27-94
JGH/HSC*

*Moss
10-24-94*

SSELAAR

Re: NDA 20-169: Nilutamide tablets
Response to a Request for Additional Information

Dear Dr. Sobel:

With the submission we are responding to a request from Dr. Albert Chen, biopharmaceutics reviewer, for additional information. On 27 September we submitted analysis to assess the relationship between nilutamide plasma levels and prostatic specific antigen (PSA) and alkaline phosphatase (ALP). We are now providing mean values for PSA and ALP at specified time points.

*noted
JGH/HSC
29 Oct 1994*

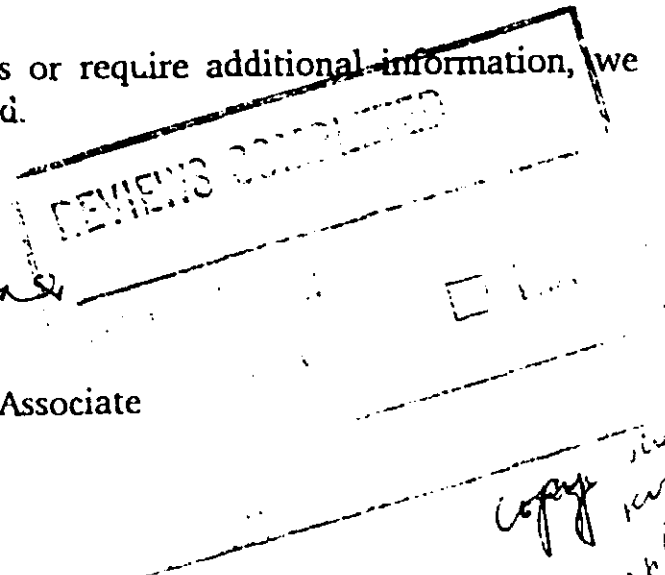
If you have any questions or require additional information, we would be please to respond.

Sincerely yours,

Carole L. Venetianer

Carole L. Venetianer
Senior Regulatory Affairs Associate

CLV:jab:dch
sobell 012

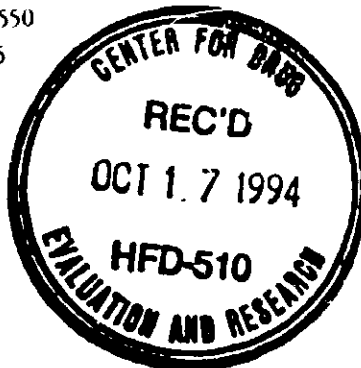


*copy should be
recovered by
Biopharm (Biller)
x1 10/27/94*

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103 College Road East
PRINCETON, NJ 08540-6681
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Phone (609) 452 8550
Fax (609) 452 9375



ORIGINAL

*noted
11-7-94
RTH*

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

13 October 1994

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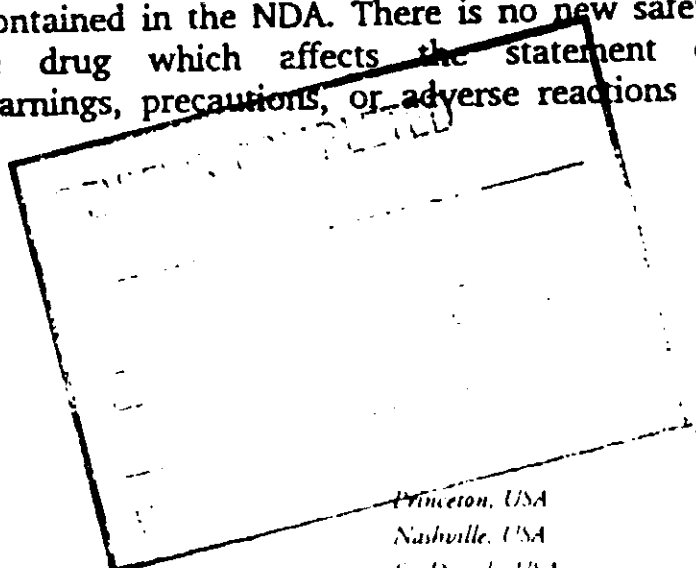
Re: NDA 20-169: Nilutamide Tablets; Safety Update

*noted
Kysen*

Dear Dr. Sobel:

On behalf of the sponsor Roussel UCLAF and in compliance with 21 CFR 314.50(d)(vi)(b), we are submitting a safety update for the above-referenced NDA submitted on 7 March 1994 and filed by the Agency on 6 May 1994. 19 OCT 1994

The submission consists of 66 volumes and contains updated safety information for the two primary studies, FF/86/908/01 and GHBA-606, as well as information on deaths, serious adverse experiences, and adverse experiences resulting in withdrawal for supportive studies contained in the NDA. There is no new safety learned about the drug which affects the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling.



Princeton, USA
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West Palm Beach, USA
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Leeds, UK
Munich, Germany
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Stockholm, Sweden

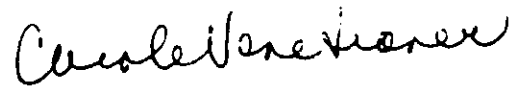
ESSELAAR

Page 2

13 October 1994

If you have any questions or require additional information, we would be pleased to respond.

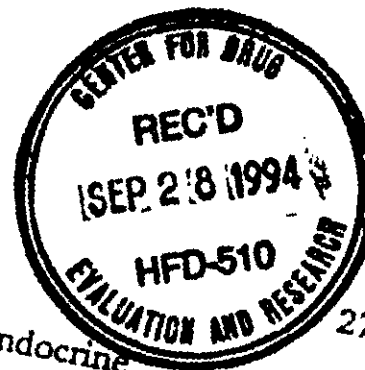
Sincerely yours,

A handwritten signature in cursive script, reading "Carole L. Venerianer".

Carole L. Venerianer
Senior Regulatory Affairs Associate

CLV:egd
sobel.ltr

G.H. Besselaar Associates
Princeton Forrestal Center
103 College Road East
PRINCETON, NJ 08540-6681
USA
Phone (609) 452 8550
Fax (609) 452 9375



B2

27 September 1994

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

ISELAAR

ORIGINAL

Re: NDA 20-169
(Nilutamide tablets)
Response to a Request for Additional Information

Dear Dr. Sobel:

With this submission we are responding to a Division request dated 27 April 1994 for additional information to supplement the biopharmaceutics section of the above-referenced NDA. The Division request for information appears in italics followed by the sponsor's response.

Request 3

Additional data analyses as follows:

Analyses to assess possible relationships between nilutamide and its metabolite plasma/serum levels to the adverse reaction(s) and/or surrogate efficacy/pharmacodynamic endpoints. E.g., PSA and alkaline phosphatase plasma/serum levels (study 89/1108/CN).

In addition, these analyses should attempt to relate covariates such as bodyweight, age, race, patient's hepatic and renal function, and/or degree of disease status.

REVIEWS COMPLETED	
ACTION:	
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CSO INITIALS	
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Princeton, USA
Nashville, USA
Madison, USA
West Palm Beach, USA
Sydney, Australia
Lima, Peru

Brussels, Belgium
Maidenhead, UK
Leeds, UK
Munich, Germany
Zurich, Switzerland
Paris, France
Geneva, Switzerland

Page 2

27 September 1994

Attachment please find the above-requested analyses. In addition, these analyses have also been performed using the data from the two primary studies, FF/86/908/01 and GHBA-606.

STAT {

Also enclosed at the request of Dr. David Hoberman, statistician, is a diskette containing the predictive marker analysis including all patients (intent-to-treat approach). Evaluable patients are flagged with "0" and not evaluable with "1". Also included are Karnofsky and pain scores for time points up to Month 18 (Visit 6).

CHEM {

In addition, on behalf of the Sponsor, Roussel UCLAF, we would like to submit the proposed tradename NILANDRON, for the above-referenced NDA, to the nomenclature committee.

✓
XY

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:gml/egd
Ref. LTRS/1054

G.H. Besselaar Associates
Princeton Forrestal Center
103 College Road East
PRINCETON, NJ 08540-6681
USA
Phone (609) 452 8550
Fax (609) 452 9375

EB

Noted
9/16/94
JETH

2 September 1994

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

noted
9-8-94
JETH

ESSELAAR

Re: NDA 20-169; (nilutamide tablets)
Response to a Request for Information

Dear Dr. Sobel:

With this submission we are responding to a Division request dated 27 April 1994 for additional information to supplement the biopharmaceutics section of the above-referenced NDA. The Division request for information appears in italics followed by the sponsor's response.

noted
X-150m
9/16/94

Request 2

Clarification as to when blood samples were collected for quantitating nilutamide and its metabolite plasma/serum levels for study 89/1108/CN.

Attached is clarification for the timing of collection of blood samples for study 89/1108/CN

In addition, at the request of Dr. Albert Chen, biopharmaceutics reviewer, we are enclosing a diskette, formatted in Wordperfect 5.1, of the Human Biopharmaceutics Summary Document contained in the Application Summary volume of the NDA.



Princeton, USA	Brussels, Belgium
Nashville, USA	Maidenhead, UK
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Tokyo, Japan	Stockholm, Sweden
	Dublin, Ireland

Page 2

2 September 1994

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,

Carol Weston

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:seh

attachment
enclosure

Reviews Associate

REVIEWS COMPLETED

COSY [] NMA

[] []

COSY [] DATE

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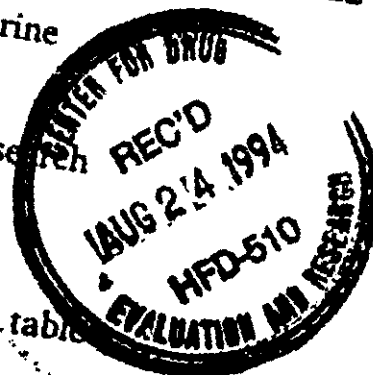
G.H. Besselaar Associates
Princeton Forrestal Center
103 College Road East
PRINCETON, NJ 08540-6681
USA
Phone (609) 452 8550
Fax (609) 452 9375

BC

ORIGINAL

22 August 1994

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



ESSELAAR

Re: NDA 20-169; nilutamide tablets
Additional Information

Dear Dr. Sobel:

On behalf of the sponsor, Roussel UCLAF, we are submitting additional stability data for nilutamide 50 mg tablets to support an extension of the shelf-life from 2 years to 3 years.

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,

Carole Venetianer
Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:egd
ref.228sobel.ltr

see chemistry
review #1
2-nov-1994
X Yarn

REVIEWS COMPLETED	
CSO ACTION:	
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CSO COMMENTS	
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Tokyo, Japan

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Maidenhead, UK
Leeds, UK
Munich, Germany
Zurich, Switzerland
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Stockholm, Sweden
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G.H. Besselaar Associates
Princeton Forrestal Center
103 College Road East
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USA
Phone (609) 452 8550
Fax (609) 452 9375

BS (Diskette w/ Stat copy)

ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

2 August 1994



ESSELAAR

Re: NDA 20-169; nilutamide tablets
Response to a Request for Information

Dear Dr. Sobel:

At the request of Dr. David Hoberman, reviewing statistician, we are submitting a revised diskette of the data sets for the predictive marker analysis contained in the above-referenced NDA. A desk copy for Dr. Hoberman has been submitted under a separate cover directly to Dr. Hoberman.

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,

Carole Venetianer

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:egd

ref.028sobel.ltr

Noted X Y Gen 10/6/94

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I.
CSO INITIALS	DATE

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BB

ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

12 July 1994



BSELAAR

Re: NDA 20-169;
(nilutamide tablets)
Response to a Request for Additional Information

noted
X 4 sent
7/25/94

Dear Dr. Sobel:

With this submission we are responding to a Division request dated 27 April 1994 for additional information to supplement the biopharmaceutics section of the above-referenced NDA. The Division request for information appears in *italics* followed by the sponsor's response.

Request 1

Dissolution information for the to-be-marketed 50 mg T₂ tablets including:

- dissolution profiles in simulated gastric fluid (SGF) without enzyme; and*
- dissolution profiles in simulated intestinal fluid (SIF) without enzyme at 5, 15, 30, 45, and 60 minutes using 12 dosage units for each test.*

In addition, please provide pH solubility profile for nilutamide.

REVIEWS COMPLETED	
CSO ACTION:	☐ N.A.I.
☐ LETTER	DATE
CSO INITIALS	

Princeton, USA
Nashville, USA
St. Louis, USA
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West Palm Beach, USA
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Tokyo, Japan

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Leeds, UK
Munich, Germany
Zurich, Switzerland
Paris, France
Stockholm, Sweden
Dublin, Ireland

12 July 1994

Attachment # 1 provides the requested dissolution and pH solubility profile information for nilutamide tablets.

Request 4

Pharmacokinetic (PK) simulations for predicting steady-state nilutamide and metabolite levels (i.e. steady-state peak, average, and trough plasma/serum levels) in normals and patients for 150 and 300 mg QD dosing regimens based on the PK parameters from the single dose studies. Depending upon the results of these studies, a classic food effect study may be needed.

Attachment #2 provides a discussion of the feasibility of performing pharmacokinetic simulations for prediction of steady-state nilutamide and metabolite levels and a discussion to support the lack of a food effect with nilutamide.

Request 5

Additional information on the pharmacological activities of metabolites, including the stereoisomers of metabolites, if available.

Attachment # 3 provides the requested additional information on the pharmacological activity of the metabolites and stereoisomers of the metabolites.

In addition, at the request of Dr. Albert Chen, biopharmaceutics reviewer, we are attaching a revised "Attachment B" to Volume 1.25, page 21-22 to accurately reflect the AUC and $T_{1/2}$ for Study No. 90/2053/CN (Attachment #4).

We will submit additional information for requests 2 and 3 of the 27 April 1994 letter in the near future.

Page 3

12 July 1994

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Carole L. Venetianer".

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Assistant

CLV:egd

ref.236aobel.ltr

G.H. Besselaar Associates
Princeton Forrestal Center
103 College Road East
PRINCETON, NJ 08540-6681
USA
Phone (609) 452 8550
Fax (609) 452 9375

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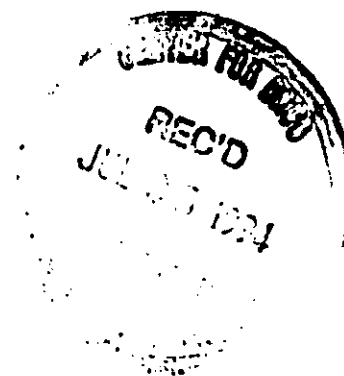
ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

1 July 1994

ELAAR

Re: NDA 20-169
Nilutamide Tablets



Dear Dr. Sobel:

In response to a request from Dr. Fourcroy, medical reviewer, we are enclosing diskettes, formatted in Word Perfect 5.1, for the text of the following sections of the above-referenced NDA:

- Application Summary
- Clinical Trial Report for GHBA-606 (leuprolide study)
- Clinical Trial Report for FF/86/908/01 (orchiectomy study)
- Clinical Data Section - Efficacy Data
- Clinical Data Section - Safety Data

A description of the contents of each diskette follows this letter.

We are aware of Dr. Fourcroy's request for the safety and efficacy data bases for the two primary studies to be submitted, formatted in Excel. We are working to provide this information and hope to submit these diskettes shortly.

Princeton, USA
Nashville, USA
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Madison, USA
West Palm Beach, USA
Sydney, Australia
Tokyo, Japan

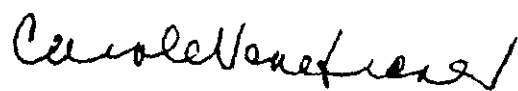
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Stockholm, Sweden

Page 2

1 July 1994

If you have any questions, or require additional information, we would be pleased to respond.

Sincerely yours,



Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Associate

CLV:egd
ref.156nda.ltr

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER

☐ N.A.I.

CSO INITIALS

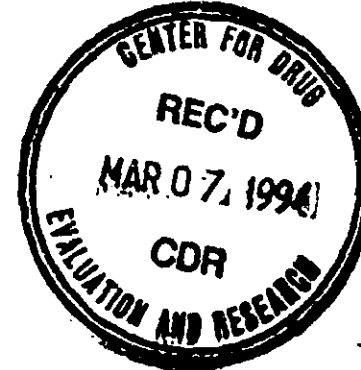
DATE

G.H. Bessehaar Associates
Princeton Forrestal Center
103 College Road East
PRINCETON, NJ 08540-6681
USA
Phone (609) 452 8550
Fax (609) 452 9375



March 1994

(28)
Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857



BESSELAAR

Re: NDA 20-169
(Nilutamide; Anandron)
Resubmission

Dear Dr. Sobel:

ORIGINAL

On behalf of the sponsor, Roussel-UCLAF of Romainville, France we are resubmitting NDA 20-169 (ANANDRON; nilutamide tablets) indicated for the treatment of Stage D₂ metastatic prostate cancer. It is intended that nilutamide will be used either in combination with chemical castration with an LHRH agonist or following surgical castration.

The above-referenced NDA was initially submitted on 14 June 1991 and contained 349 volumes, numbered Volume 1.1 through Volume 1.349.

Reference is made to your refusal-to-file letter dated 14 August 1991. On the basis of feedback received from your Division following our informal refusal-to-file meeting held on 19 December 1991, and your letter of 14 July 1992, we are resubmitting NDA 20-169 in a new format that we believe will be acceptable for filing under 21 CFR 314.101. The resubmission contains two pivotal trials, FF/86/908/01 (orchiectomy study) and GHBA-606 (leuprolide study), to support the approval of the NDA.

REVIEW'S COMPLETED

CSO ACTION:

☐ LETTER

☐ NDA

CSO INITIALS

DATE

Princeton, USA
Nashville, USA
St. Davids, USA
Madison, USA
West Palm Beach, USA
Sydney, Australia
Tokyo, Japan

Brussels, Belgium
Maidenhead, UK
Leeds, UK
Munich, Germany
Zurich, Switzerland
Paris, France
Stockholm, Sweden
Dublin, Ireland

Solomon Sobel, M.D.
7 March 1994

Page 2

Nilutamide is now approved for marketing in over 25 countries, including Canada. The resubmission of the NDA is part of a planned worldwide submission to make nilutamide available to the population of prostate cancer patients who will most benefit from treatment and as an alternative therapy for patients who are intolerant to flutamide. The increased extended exposure to nilutamide since the initial submission has not resulted in any increased risk or change in the incidence or spectrum of adverse events.

In addition to the above-mentioned developments, an application for Orphan Drug Designation was submitted to the Agency on 8 December 1993 for a population with newly diagnosed Stage D₂ metastatic prostate cancer.

Finally, reference is made to our letter of 18 August 1992 to Dr. Fourcroy outlining the strategy for the revisions to be made to the NDA when resubmitted and to a telephone conversation between Carole Venetianer of Besselaar and Dr. Fourcroy on 4 November 1992 in which Dr. Fourcroy agreed to the proposed strategy.

Based on our communications with the Division during the last several months, this submission includes:

- Addenda to the reports of what are now the two pivotal studies, GHBA-606 and FF/86/908/01, which will contain analyses of the predictive value of the markers prostate specific antigen (PSA) and alkaline phosphatase (ALP) for progression-free interval and survival time. These analyses will be based on updated data for progression and survival for GHBA-606 and FF/86/908/01.

- Description of the statistical methodology used in the surrogate endpoint analysis, are added to the Statistical Section of the NDA.
- Revised Integrated Summary of Safety (ISS); this has been revised to emphasize safety summaries for each of the two pivotal studies using the safety data that exists in the NDA submitted previously.
- Revised Integrated Summary of Efficacy (ISE); this has been revised to include discussion of both GHBA-606 and FF/86/908/01 and how the use of ALP values at baseline can be used to select a subset of patients who should most benefit from treatment with nilutamide and PSA normalization at Month 3 which can be used to support efficacy and continuation of treatment (an electronic database is also provided which includes data on PSA and ALP in Volume 2.1 of the blue archive copy and tan medical review copy).

Revised tables of all studies.

- Items in the Application Summary that also were to be revised to reflect these new data to include:

Solomon Sobel, M.D.
7 March 1994

Page 4

Part A	-	Labeling
Part B	-	Scientific Rationale
Part C	-	Foreign Marketing History
Part H.2	-	Overview of Clinical Studies
Part H.3	-	Controlled Clinical Studies
Part H.4	-	Uncontrolled Clinical Studies
Part H.5	-	Other Studies
Part H.6	-	General Safety Conclusions
Part I	-	Discussion of Benefit/Risk Relationship

An analysis of all previously reported pulmonary adverse experiences occurring during development in nilutamide-treated patients has been prepared by Roussel and is included in this resubmission. We are also submitting a protocol to conduct a post-marketing study of the effect of nilutamide on driving impairment.

In addition to the above-mentioned revisions, we are appending the Chemistry, Manufacturing and Controls sections to include updated stability data and a current samples list and lot numbers. For completeness, an addendum to the Nonclinical Pharmacology and Toxicology section will contain new reports of toxicity studies relevant to the safety profile of nilutamide. We are also providing a revised study report (1042 TCC) for the 1-year dog toxicity study to respond to Dr. El-Hage's request for tables formatted to present summary data by week for each variable. This additional information will also be reflected in the updated Application Summary.

We have revised the Index in Volume 1.1, incorporating the new information, and reorganized the order of the studies to reflect the reformatting of the NDA. An outline is attached to this letter to reflect the new information and new location in the present NDA submission. We plan to keep the same volume numbers in the new submission as in the 14 June 1991 submission (Volume 1.1 to Volume 1.349). When an existing volume contains new or revised

Solomon Sobel, M.D.
7 March 1994

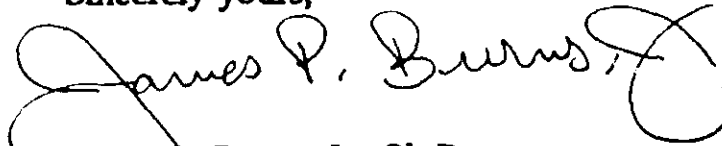
Page 5

information or documents, we plan to replace the entire volume. The numbering of the replacement volumes will begin with Volume 2.1.

We are submitting review copies for the medical reviewer, chemistry reviewer, biopharmaceutics reviewer, and the statistical reviewer. It is our understanding from Dr. El-Hage, the pharmacologist, that she has the review copy from the initial submission and therefore, we will submit only updated or replacement volumes for her review.

Thank you for your guidance on this application. We look forward to continued cooperation with you as we both strive to find the best way to bring an important new therapeutic product to that patient population who would most benefit.

Sincerely yours,

A handwritten signature in cursive script, reading "James P. Burns, Jr.", with a large, stylized flourish at the end.

James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB:CV:egd

ref.1050

G.H. Besselaar Associates
Princeton Forrestal Center
103 College Road East
PRINCETON, NJ 08540-6681
USA
Phone (609) 452 8550
Fax (609) 452 9375

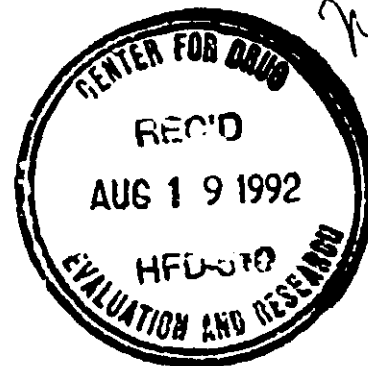
ORIGINAL

18 August 1992

Jean L. Fourcroy, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
5600 Fishers Lane
Rockville, MD 20857

SELAAR

Re: NDA 20-169
(Nilutamide; Anandron)



Dear Dr. Fourcroy:

Reference is made to the telephone conversation of 26 June 1992 between John Short of your division and Carole Venetianer of Besselaar wherein Mr. Short outlined the administrative procedures required to re-submit the NDA as well as the specific requests you had for the re-organization of the data in the NDA. Reference is also made to the letter of 14 July 1992 from Dr. Sobel requesting the submission of revised information to support approval of the NDA for Anandron (nilutamide).

In keeping with these requests, we are proposing to submit the following documents for your review:

- 1) Addenda to the reports of, what are now, the two pivotal studies, GHBA 606 and GHBA 608/610, which will contain analyses of the predictive value of the surrogate markers prostate specific antigen (PSA) and alkaline phosphatase (ALP) for progression-free interval and survival time. These analyses will be based on the data already submitted in the NDA.

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER

☒ N.A.I.

[Signature]
CSO INITIALS
1/11/93
DATE

Noted *Kit*
1-1-93

Princeton, USA
Nashville, USA
St Davids, USA
Madison, USA
West Palm Beach, USA
Sydney, Australia
Tokyo Japan

Brussels, Belgium
Maidenhead, UK
Leeds, UK
Munich, Germany
Zurich, Switzerland
Paris, France
Stockholm, Sweden

18 August 1992

- 2) Description of the statistical methodology used in the surrogate endpoint analysis which will be added to the Statistical Section of the NDA.
- 3) Revised Integrated Summary of Safety (ISS); this will be revised to include separate safety summaries for each of the two pivotal studies using the safety data as exists in the NDA submitted previously.
- 4) Revised Integrated Summary of Efficacy (ISE); this will be revised to include discussion of both GHBA 606 and GHBA 608/610 and how the use of surrogate endpoints can be used to support efficacy (an electronic database will also be provided which will include data on the surrogate markers PSA and ALP).
- 5) Items in the Application Summary which will also need to be revised to reflect this new data to include:

Part A	-	Labeling
Part B	-	Scientific Rationale
Part H.2	-	Overview of Clinical Studies
Part H.3	-	Controlled Clinical Studies
Part H.5	-	Other Studies
Part H.6	-	General Safety Conclusions
Part I	-	Discussion of Benefit/Risk Relationship

We believe that the re-organization of the data as outlined here meets your stated requirements for presentation for initial review toward the goal of having a "complete" NDA package that is acceptable for filing with the FDA.

18 August 1992

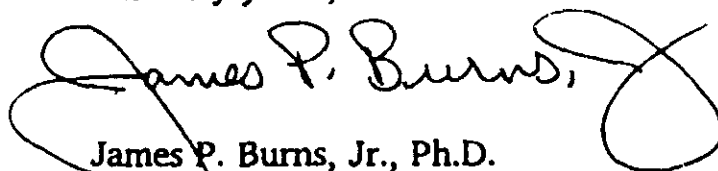
In addition to the above, we will also be submitting a report on the occurrence of pulmonary adverse experiences and a proposed protocol for studying the effect of Anandron on driving ability impairments.

We want to move forward on this effort as soon as possible but are at this time soliciting your acceptance of the approach as outlined above before proceeding. We are available to meet with you or to discuss this matter by telephone at your convenience.

I will be in contact with you shortly to obtain any initial comments you may have about our proposed plans and to determine if you see any need for a meeting and/or teleconference to help expedite matters.

Thank you for your guidance on this application. We look forward to continued cooperation with you as we both strive to find the best way to bring an important new therapeutic product to that patient population who would most benefit.

Sincerely yours,



James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB:pac

cc: P. A. Blaine
J. I. Drayer, M.D.
N. L. Heyden
G. M. Hockel, Ph.D.
M. Johnson
P. F. Kosmoski
M. J. Losi, Ph.D.
T. J. Newman, M.D.
C. M. Pennise
C. L. Venetianer

Dr. A. Ulmann (Roussel-UCLAF)
A. de Gery (Roussel-UCLAF)
Client File
FDA Log

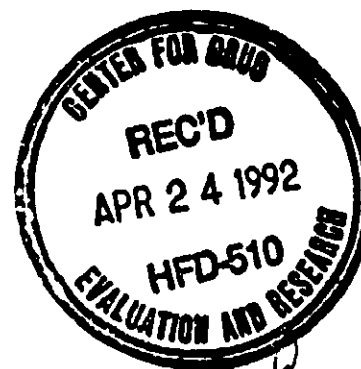
**G.H. Besselaar
Associates**

CONSULTANTS TO THE INTERNATIONAL PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES
PRINCETON FORRESTAL CENTER / 103 COLLEGE ROAD EAST / PRINCETON, NEW JERSEY 08540 - 6681
TELEPHONE: (609) 452 - 8550 / TELEFAX: (609) 452 - 9375

ORIGINAL

ORIGINAL

23 April 1992



Erica McNeilly
Consumer Safety Officer
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-169 Nilutamide (Anandron, RU 23 908)

Dear Ms. McNeilly:

We refer to our submission of 4 March 1992 that responds to the Division's concerns about the prognostic value of prostatic specific antigen (PSA) in the outcome of treatment for prostatic cancer. We also refer to our telephone conversation of 23 April 1992 about a new journal article that supports the use of PSA as a surrogate efficacy endpoint. At your request we are enclosing extra copies of this new publication for the reviewers:

J. I. Miller, et.al. *The Clinical Usefulness of Serum Prostate Specific Antigen After Hormonal Therapy of Metastatic Prostate Cancer.* J of Urology 1992; 147: 956-961

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER

☒ NAL

CSO INITIALS

DATE

GHBA PRINCETON, USA • NASHVILLE, USA • BRUSSELS, BELGIUM • MUNICH, GERMANY • MAIDENHEAD, ENGLAND
ZOLLIKON, SWITZERLAND • DANDERYD, SWEDEN • PARIS, FRANCE • DUBLIN, IRELAND • EPPING, AUSTRALIA • TOKYO, JAPAN
GHBA / HAZLETON CLINICS: LEEDS, ENGLAND • MADISON, USA • WEST PALM BEACH, USA
GHBA / PACT: ST. DAVIDS, USA • MAIDENHEAD, ENGLAND

Erica McNeilly
Food and Drug Administration
Page 2
23 April 1992

We look forward to a positive response to our submission of 4 March 1992. If you have any questions about this submission, please contact us.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Carole L. Venetianer".

Carole L. Venetianer, R.N., M.S.
Senior Regulatory Affairs Assistant

CLV:jmn
Enclosure
ref.92278

ORIGINAL

**E.H. Besselaar
Associates**

CONSULTANTS TO THE INTERNATIONAL PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES
PRINCETON FORRESTAL CENTER / 103 COLLEGE ROAD EAST / PRINCETON, NEW JERSEY 08540 - 6681
TELEPHONE (609) 452 - 8550 / TELEFAX (609) 452 - 9375

4 March 1992

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-169 Anandron (Nilutamide)

Dear Dr. Sobel:

I refer to our meeting of 19 December 1991 to discuss your refusal to file the New Drug Application (NDA) for Anandron (nilutamide) Tablets, NDA 20-169, and to my letter to you of 21 January 1992 informing you of our intention to respond formally to the issues discussed at the 19 December meeting. We are at this time submitting our response for your review and consideration.

This response addresses the following issues:

1) PSA prognostic value as a surrogate efficacy endpoint

- statistical analysis strategy as it relates to a) the justification for selecting the month 3 PSA values as the best predictor of treatment outcome, b) the justification for the cut-off point being the upper limit of the normal range for PSA values as having significance for predicting outcome of treatment, and c) comparability on entry of patients with and without a PSA assay at month 3.
- PSA assays -- methods, with normal ranges; sample handling techniques; reasons for lack of samples from all patients.
- literature support for use of PSA as a predictive marker.

CSO INITIALS
DATE

CSO ACTION:
☐ LETTER ☐ N.A.I.

REVIEWING COMPLETED

Solomon Sobel, M.D.
Food and Drug Administration
4 March 1992
Page 2

- 2) Discussion of possible reasons for the difference in patient response between the orchiectomy study (FF/86/908/01) and the leuprolide study (GHBA 606).

We believe the responses provided should now allow for the filing of NDA 20-169.

We remain convinced that an objective review of the data will show that Anandron is an effective therapy for the treatment of metastatic cancer of the prostate which, with appropriate instructions to the physician, can be used in a manner which would allow for an acceptable benefit/risk ratio.

We look forward to a positive response to this submission and stand ready to work with you in developing acceptable labeling.

Sincerely yours,



James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB:pac
Ref: 043

Attachment

**G.H. Besselaar
Associates**

CONSULTANTS TO THE INTERNATIONAL PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES
PRINCETON FORRESTAL CENTER / 103 COLLEGE ROAD EAST / PRINCETON, NEW JERSEY 08540 - 6681
TELEPHONE: (609) 452 - 8550 / TELEFAX: (609) 452 - 9375

ORIGINAL

21 January 1992

ORIGINAL NEW CORR

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



1-30-92

Re: NDA 20-169 Anandron (Nilutamide)

Dear Dr. Sobel:

Thank you for the opportunity to meet with you and your colleagues on 19 December 1991 to discuss the New Drug Application (NDA) for Anandron (nilutamide) Tablets, NDA 20-169.

Based on the discussion at this meeting, we believe there may be the possibility of producing an NDA package that could be acceptable for filing under 21 CFR 314.101.

We are focusing on the issues raised by your reviewers at this meeting and are preparing a response that will be submitted within a month. This response will provide information concerning the following:

- PSA plasma samples -- reasons for lack of samples from all patients; sample handling conditions; assay techniques, with specifications
- literature support for predictive value of PSA marker
- statistical analysis strategy
- justification for selection of month 3 PSA values

REVIEWS COMPLETED

DISPOSITION:

LETTER

☐ **NAL**

DISPOSITION INITIALS

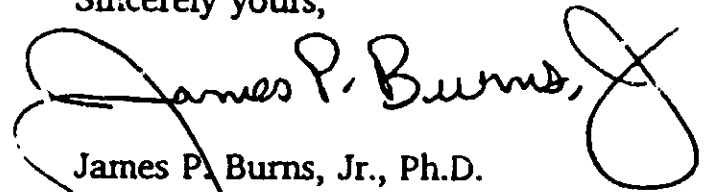
DATE

Solomon Sobel, M.D.
Food and Drug Administration
21 January 1992
Page 2

- that no selection bias was introduced into the subgroup of patients evaluated at month 3 for PSA values, i.e. the month 3 subpopulation is representative of the original population
- that there can be enhanced safe use of nilutamide by evaluating the need for continued use after 3 months, especially for orchiectomized patients
- baseline characteristics of patients for both studies 606 and 608/610 to support reason for difference in response

From the above, we believe appropriate labelling can be constructed to inform the physician about the safe use of Anandron so that this important new therapy can be made available for those patients for which there is no approved product or for whom current therapy is ineffective or not tolerated.

Sincerely yours,


James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB:pac
Ref: 015

G.H. Besselaar Associates

CONSULTANTS TO THE INTERNATIONAL PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES
PRINCETON FORRESTAL CENTER • 103 COLLEGE ROAD EAST / PRINCETON NEW JERSEY 08540 • 0681
TELEPHONE (609) 452 • 8550 / TELEFAX (609) 452 • 9375

6 December 1991

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-169 (Nilutamide/RU23 908, Anandron)

Dear Dr. Sobel:

In preparation for our NDA conference scheduled for 10:00 a.m. on Thursday, 19 December 1991, we are submitting at this time a list of attendees (Attachment #1) and 12 copies of background material for this meeting (Attachment #2).

The background material contains additional efficacy analyses provided by the sponsor, Roussel-Uclaf, of the data obtained from studies FF/86/908/01 (GHBA 608/610, orchiectomy) and GHBA 606 (leuprolide). These analyses were made to define subgroups of patients who might derive a greater benefit from treatment. Recently shown by several authors, a rapid decrease in prostatic specific antigen (PSA) plasma level after induction of endocrine therapy was a good predictor of response to endocrine treatment. Therefore, for these analyses, patients were divided into two groups based on the status of prostatic specific antigen (PSA) plasma levels after three months of treatment. One group comprised patients for whom PSA had normalized within 3 months of treatment; a second group comprised the patients for whom PSA remained elevated after this period. The analyses showed that, for both studies, the progression-free interval and survival time were statistically significantly longer for patients who had normalized PSA levels after 3 months of treatment. In addition, in both studies the number of patients who had normal PSA at month 3 was statistically significantly higher ($p < 0.001$) in the nilutamide groups.

Solomon Sobel, M.D.
Food and Drug Administration
6 December 1991
Page 2

These results indicate that total androgen blockade with nilutamide increases the chance for a given patient to have a normal PSA value after 3 months, hence a higher probability of a longer progression-free interval and survival (as demonstrated in study FF/86/908/01-GHBA 608/610).

The data indicate that study FF/86/908/01-GHBA 608/610 has clearly demonstrated an objective and significant impact of nilutamide over placebo (orchiectomy) on median time to progression ($p=0.005$), median survival time ($p=0.07$), and best response to treatment ($p<0.001$), which has been further confirmed when patients were grouped according to PSA levels at 3 months of treatment. Furthermore, in study GHBA 606, nilutamide was shown to cause a statistically significant increase in the number of patients with normalized PSA after 3 months as compared to leuprolide alone which was associated with a statistically significant improvement in the progression-free interval ($p<0.001$) and the actuarial rate survival ($p=0.005$). Given the above, we believe a case can be made to allow for approval of nilutamide, which is consistent with regulatory needs and the stated policy most recently enunciated by the Commissioner, Dr. Kessler, that the agency is committed to expediting approval of drugs for the treatment of life-threatening diseases, of which nilutamide would certainly qualify.

Based on the above, the package insert would be revised to change the indication to treatment following both medical and surgical castration in patients with stage D₂ prostatic cancer. Importantly, the dosage and administration section would also be revised to advise physicians that continuation of the dosing would be contingent on the physician's judgement, including PSA improvement, after three months of treatment, thus reducing the unnecessary risk of exposure unless appropriate benefit is demonstrated.

In addition, Roussel is planning to conduct a study to determine the impact of nilutamide-induced visual disturbances on driving ability (Attachment #3) and will have an expert pneumologist review the cases of interstitial pneumonitis.

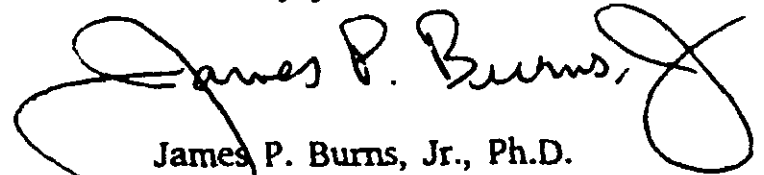
In summary, recognizing that stage D₂ prostate cancer represents a life-threatening condition, we strongly believe that the results from the new analyses indicate that NDA 20-169 should be filed with the results of FF/86/908/01 (GHBA 608/610), which provides strong support for treatment with nilutamide following orchiectomy for which, presently, no prescription treatment is indicated and GHBA 606, which supports the efficacy of

Solomon Sobel, M.D.
Food and Drug Administration
6 December 1991
Page 3

nilutamide in combination with leuprolide, now being viewed as the two adequate and well-controlled studies demonstrating the efficacy of nilutamide for total androgenic blockade in metastatic prostate cancer. Thus, a full range of treatment might be available for a life-threatening condition.

We look forward to discussing these matters on December 19 and to exploring how the available data can satisfy your regulatory needs to the ultimate benefit of patients who could have access to this drug by its approval.

Sincerely yours,

A handwritten signature in black ink, appearing to read "James P. Burns, Jr.", with a large, stylized flourish at the end.

James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB:pac
Ref:226

REVIEWS COMPLETED

ORIGINAL

G.H. Besselaar
Associates

CSO ACTION

☐ LETTER

☒ N.A.

CSO INITIALS

DATE

4 September 1991

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Product, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-169/Anandron (nilutamide) Tablets

Dear Dr. Sobel:

Reference is made to our New Drug Application dated 14 June 1991 and your letter of 14 August 1991, in which you state the subject New Drug Application is not acceptable for filing under 21 CFR 314.101. Also stated in your letter is the opportunity to request, in writing, an informal conference to discuss your refusal to file the application.

Thus, we are hereby requesting (within the 30-day time limit) that such an informal conference be held at your earliest convenience.

We will contact Ms. Lois Simmons to confirm receipt of this letter and assist in the organization of the conference.

Sincerely,

James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB/GMH/mm

cc: C. Bertagna, M.D. (Roussel)
J. I. Drayer, M.D.
N. L. Heyden
G. M. Hockel, Ph.D.

M. J. Losi, Ph.D.
C. M. Pennise
C. L. Venetianer
J. T. Zenno

CRIG NEW CORRES

ORIGINAL

C

G.H. Besselaar
Associates

REVIEW IS COMPLETED

CONSULTANTS TO THE INTERNATIONAL PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES
PRINCETON FORRESTAL CENTER / 103 COLLEGE ROAD EAST / PRINCETON, NEW JERSEY 08540 - 6681
TELEPHONE (609) 452 - 8550 / TELEFAX (609) 452 - 9375

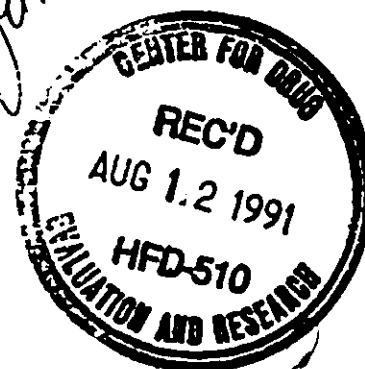
CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS _____ DATE _____

6 August 1991

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA-20-169: Nilutamide (Anandron)

Dear Dr. Sobel:

On behalf of the sponsor, Roussel UCLAF of Romainville, France, we are writing concerning our plans for the 4-month safety update which we expect to submit on or about 14 October 1991 in compliance with 21 CFR 314.50 (d) (5) (vi) (b). NDA 20-169 for nilutamide was submitted on 14 June 1991.

Our most current safety analysis of all adverse experiences, regardless of relationship to study medication, that have occurred in the primary study FF/86/908/01, and in GHBA-606, a major supportive study for safety, indicate that there has been no unexpected increase in the frequency of any adverse experience as compared to the frequencies reported in the NDA submission. With respect to laboratory values, our analysis also indicates that the findings reported in the NDA regarding the numbers of nilutamide and placebo patients with laboratory values outside of predefined limits are essentially unchanged. In addition, no new, previously unreported, clinical or laboratory adverse experience has occurred in any study during the time period between the NDA data cut-off dates for the reporting of adverse experiences (31 March 1990 for FF/86/908/01, 31 August 1990 for GHBA-606, and 31 October 1989 for all other studies) and the cut-off dates for this submission (30 April 1991 for GHBA-606 and 31 January 1991 for all other studies).

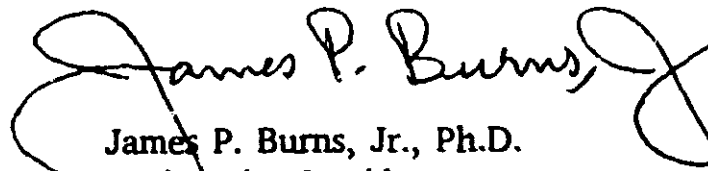
Solomon Sobel, M.D.
Food and Drug Administration
Page 2

06 August 1991

Since there are no new safety information learned about the drug which may reasonably affect the statement of contraindications, warnings, precautions or adverse reactions in the draft labeling, we are not planning to submit a new integrated safety summary. We plan instead to submit the incidence of all adverse experiences in studies FF/86/908/01 and GHBA-606 while focusing our 4-month safety update on the more serious adverse experiences that occurred during the time period between the NDA data cut-off dates and our current data cut-off dates mentioned above. These adverse experiences are clinical and laboratory adverse experiences resulting in death or discontinuation from the study, and all other serious adverse experiences. We propose to present patient data listings and corresponding narrative discussions of these adverse experiences for nilutamide and placebo patients (sample formats attached). We will provide copies of the Case Report Forms for patients with adverse experiences resulting in death or discontinuation.

Please let us know if this proposal is acceptable to the division.

Sincerely,


James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB:amb

Attachments

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☒ N.A.I.

LEJ 19 Aug 91
CSO INITIALS DATE

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ORIGINAL

**G.H.Besselaar
Associates**

CONSULTANTS TO THE INTERNATIONAL PHARMACEUTICAL AND MEDICAL DEVICE INDUSTRIES
PRINCETON FORRESTAL CENTER / 103 COLLEGE ROAD EAST / PRINCETON, NEW JERSEY 08540 - 6681
TELEPHONE (609) 452 - 8550 / TELEFAX: (609) 452 - 9375

REVIEWS COMPLETED

CSO ACTION:

25 June 1991

☐ LETTER ☐ N.A.I.

Solomon Sobel, M.D. CSO INITIALS DATE
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-169 Nilutamide (Anandron)

Dear Dr. Sobel:

Pursuant to a telephone request from Ms. Lois Simmons, Consumer Safety Officer, on 25 June 1991, we are enclosing the diskette containing the medical summary for NDA 20-169 (nilutamide), submitted on 14 June 1991. Dr. Fourcroy, Supervisory Medical Officer, has confirmed this request.

Enclosed are the following labelled disks formatted in WordPerfect® 5.0:

- H1: Clinical Pharmacology
- H2: Overview of Clinical Studies
- H3: Controlled Clinical Studies
- H4: Uncontrolled Clinical Studies
- H5: Other Studies and Information
- H6: Safety Summary - General Safety Conclusions

These summaries are contained in Volume 1.1A of the NDA. The Clinical Pharmacology Summary (H1) contains four figures which are not part of the disk, but which are available on pages 17-20 of Volume 1.1A.

Solomon Sobel, M.D.
Food and Drug Administration
Page 2

25 June 1991

If there are any questions concerning the enclosed information, we would be pleased to respond.

Sincerely yours,

A handwritten signature in cursive script, reading "James P. Burns Jr / cm6".

James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB/jdf
ref.500

Copy to: Ms. Lois Simmons (FDA)
Dr. Jean Fourcroy (FDA)

NDA 28-169

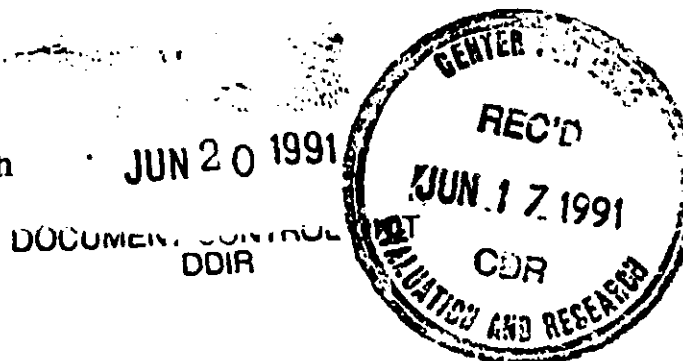
6 OF 6

G.H.Besselaar Associates

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TELEPHONE (609) 452-8550 / TELEFAX: (609) 452-9375

14 June 1991

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-169: Nilutamide (Anandron)

Dear Dr. Sobel:

On behalf of the sponsor, Roussel-UCLAF of Romainville, France, and pursuant to 21 CFR 314.50, we hereby submit, in duplicate, a New Drug Application for nilutamide (Anandron) for the treatment of metastatic cancer of the prostate (stage D₂). This NDA consists of 349 volumes numbered 1.1 through 1.349 and represents collective experience with nilutamide of over 11 years. The NDA consists of 20 clinical pharmacology studies, eight double-blind, placebo-controlled studies, two uncontrolled studies and nine studies in which nilutamide was used for indications other than previously untreated metastatic prostate cancer in orchiectomized patients. As of the data cutoff date for this submission, (31 August 1989 for the primary study, FF/86/908/01, and seven other controlled studies to be used as supportive studies and 28 February 1990 for study GHBA-606, another major supportive study for safety) 3,195 patients or subjects had been treated in the clinical program for nilutamide; of these 3,102 had prostate cancer. Of the 3,195 patients/subjects, 2,261 received nilutamide.

We are filing at this time for approval for treatment of metastatic prostate cancer with nilutamide in combination with surgical castration (bilateral orchiectomy). Our primary study, FF/86/908/01 (also known as GHBA-608/610) included 457 previously untreated patients who were surgically castrated prior to initiation of treatment with either nilutamide or placebo (225/232). Results show that patients treated with nilutamide, in combination with surgical castration, had better complete or partial tumor regression, fewer early progressions of prostate cancer, longer median time to progression and greater median survival time for cancer-related deaths than placebo treated

Solomon Sobel, M.D.
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Page 2

14 June 1991

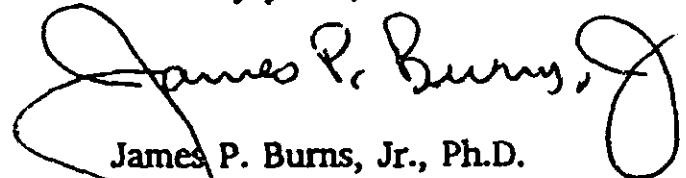
patients. Study CDN/83/908/05 provides strong supportive data to the primary study.

This NDA is based on data from one controlled study with positive efficacy results (GHBA-608/610) and strong supportive data from study CDN/83/908/05. This is based on discussions at our pre-NDA meeting of 28 November 1990, at which meeting we understood from you that approval could be based on one study showing positive results for improvement in median time for survival with supportive efficacy data from other studies. We also reference the NIH/FDA Commentary, published 17 March 1989, that discussed efficacy parameters other than survival which could be used to support approval of anti-cancer drugs.

Please be advised that our 4-month safety update will contain additional safety data from all studies and updated median times to progression and survival for the primary study.

We feel that this NDA supports the use of nilutamide plus orchiectomy in the treatment of prostate cancer stage D₂. We will be pleased to answer any questions that arise during the review of this NDA.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "James P. Burns, Jr.", with a large, stylized loop at the end.

James P. Burns, Jr., Ph.D.
Senior Vice President
Regulatory Affairs

JPB:CMP:pac
Ref.366