CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S18

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-726/S-018

JUN 16 1997

Zeneca Pharmaceuticals, Inc.
Attention: Ms. Kimi F. Denoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
PO Box 15437, 1800 Concord Pike
Wilmington, DE 19850-5437

Dear Ms. Denoble:

Please refer to your pending June 28, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act For Zoladex® (goserelin acetate implant) 1-month Depot, 3.6 mg.

We also refer to your amendment dated May 12, 1997.

We have completed our review of the physician package insert for your submission and have several comments. Revisions have been incorporated directly into the enclosed package insert. Additions have been noted in double underline, deletions have been noted as ~~strikeouts~~. Additional comments requring response are in **14 pt bold face type**.

Please submit your revised package insert as soon as available so that we can continue the evaluation of your NDA.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Revised physician insert

Dunson

NDA 19-726/S-018

FEB 26 1997

Zeneca Pharmaceuticals, Inc
Attention: William J. Kennedy, Ph.D.
Vice President, Drug Regulatory Affairs
1800 Concord Pike, PO Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kennedy:

Please refer to your pending June 28, 1996, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoladex® (goserelin acetate implant) 1-month Depot, 3.6 mg.

To complete our review of the Statistical section of your submission, we request the following:

Study #IL-0022

1. The use of geometric means and a confidence interval on the ratio to compare the treatment groups:

   A brief explanation regarding the distributional reasons is provided in (Vol. 23, Section 2.5.2.). A reference article or further explanation as to why this is appropriate in the efficacy analysis is needed. (Endometrial thickness: SAS file T05a2; Duration of Surgery: SAS file T06a2)

2. Calculation of the Standard Error for the transformation from ranks to the median:

   The statistical analysis section (Vol. 23, Section 2.5.2) does not describe how this transformation is to be carried out. From the SAS command files we can see the mathematical equations used. A description or explanation of why these equations are appropriate for this transformation is needed. (Change in Blood Loss Score: SAS files T03b2, T03b3)

Study #IP-0003

1. Calculation of the confidence interval on the median:

   The analysis section (Vol. 28, Section 2.8.6) describes the method used and provides a reference, *Hollander & Wolfe* (1973). We have this book and understand why this method is applicable. We do not have a SAS command file showing how these values were generated. The SAS command file included in the . only produces the descriptive statistics shown in Table 8.2, not the other statistical

results which also appear in that table. It is possible that these results were generated using other software. Please submit either the SAS command file or a description of the software and commands used for generating these results. (Endometrial Thickness: SAS file T06a)

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 19-726/S-018
HFD-580/Div. Files
HFD-580/CSO/ADunson
HFD-580/KMeaker/LKammerman/LPauls

Drafted by: ADunson/February 4, 1997/n19726st

CONCURRENCES:
KMeaker, LPauls2.4.97/LKammerman2.21.97

INFORMATION REQUEST (IR)

DUNSON

NDA 19-726/S-018

FEB 18 1997

Zeneca Pharmaceuticals, Inc.
Attention: William J. Kennedy, Ph.D.
Vice President, Drug Regulatory Affairs
1800 Concord Pike, PO Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kennedy:

Please refer to your pending June 28, 1996, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoladex® (goserelin acetate implant) 1-month Depot, 3.6 mg.

We have completed our review of the Clinical Pharmacology and Biopharmaceutics section of your submission and have identified the following deficiencies:

In the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** sub-section of the label, the following change in headings should be made:

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 19-726
HFD-580/Div. Files
HFD-580/CSO/ADunson
HFD-580/GBarnette/ADorantes/LPauls
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: ADunson/February 4, 1997/n19726bp

Concurrences:
LPauls2.4.97/GBarnette, ADorantes2.5.97

INFORMATION REQUEST (IR)

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA RAPIFAX AND AIRBORNE EXPRESS

Lisa D. Rarick, M.D.
Division Director
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-45
5600 Fishers Lane
Rockville, MD 20857

JUN 27 1997

Dear Dr. Rarick:

Re: ZOLADEX® (goserelin acetate implant) 3.6 mg Depot
NDA 19-726
Endometrial Thinning Supplement (S-018)

Reference is made to the ZOLADEX® (goserelin acetate implant) supplemental application for use as an endometrial thinning agent prior to endometrial ablation. Please find enclosed a revised copy of the label in portrait format. As discussed in a telephone contact today with Mr. Alvis Dunson and Ms. Kimi F. DeNoble, Zeneca has revised the statement under PRECAUTIONS - General to read: "The pharmacologic action of ZOLADEX on the uterus and cervix may cause an increase in cervical resistance. Therefore, care should be taken when dilating the cervix for endometrial ablation."

Should you have any further questions, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/jr
Enclosure
Desk Copy: Mr. Alvis Dunson, Consumer Safety Officer, HFD 580

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA RAPIFAX AND AIRBORNE EXPRESS

JUN 26 1997

Lisa D. Rarick, M.D.
Division Director
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Re: ZOLADEX® (goserelin acetate implant) 3.6 mg
NDA 19-726
Endometrial Thinning Supplement (S-018)

Reference is made to the Agency's letter of June 23, 1997 providing recommendations to the labeling for the use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to surgical ablation. A three-column label is provided behind Tab A which outlines the revisions to the labeling as follows: the left-hand column represents the current labeling; the middle column represents the labeling submitted to the Agency on June 19, 1997; and the right-hand column represents the changes made in response to the Agency's recommendations of June 23, 1997. In addition, a hard copy of the labeling with the recommended changes is provided behind Tab B in landscape format.

Zeneca provides the following response to the Agency's June 23, 1997 letter:

- Page 1, Zeneca agrees to add the dosage to the title of the label.
- Page 6, under CLINICAL PHARMACOLOGY, Clinical Studies - Endometrial Thinning, Zeneca agrees to delete the word from the first sentence in this subsection as recommended.

In the third paragraph of this same subsection, Zeneca agrees to revise the first sentence to read:

addition, the p-value has been deleted as recommended.

- Page 7, under CLINICAL PHARMACOLOGY, Clinical Studies - Endometrial Thinning, Zeneca agrees to revise the first sentence to read:

In this same paragraph, Zeneca agrees to revise the last sentence to read:

as recommended by the Agency.

- Page 17, under ADVERSE REACTIONS - Endometrial Thinning, Zeneca agrees to revise the second sentence to read:

In addition, Zeneca agrees to delete the sentence,

as recommended by the Agency.

- Page 19, under DOSAGE AND ADMINISTRATION - Endometrial Thinning, Zeneca proposes revising the dosage recommendation to read:

Should you have any additional questions or require clarification on any of the above, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/jr

Desk Copy: Mr. Alvis Dunson, Consumer Safety Officer, HFD No. 580

T:\DENOBLE\FDA\ZOLADEX\19726ENDOTHINSUPS018.DOC

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA RAPIFAX AND AIRBORNE EXPRESS

JUN 18 1997

Lisa D. Rarick, M.D.
Division Director
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Re: ZOLADEX® (goserelin acetate implant) 3.6 mg Depot
NDA 19-726
Endometrial Thinning Supplement (S-018)

Reference is made to the Agency's letter dated June 16, 1997 providing comment on the labeling for a supplement for the use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to surgical ablation. In response, please find enclosed behind Tab A a three column document which outlines the revisions to the labeling as follows: the left-hand column represents the current approved labeling; the middle column represents the changes made to the labeling in support of this supplemental application and responds to the recommendations made by the Agency; and the right-hand column provides comments as applicable.

In addition, provided behind Tab B is a hardcopy of the proposed labeling in landscape format as requested by the Agency. A diskette is also provided which contains this labeling as a WORD document. The enclosed diskette was scanned using the Norton Antivirus and a Virus Definition List dated June 1, 1997. No viruses were detected. (Tab C).

Zeneca provides the following response to the recommended changes as noted in the Agency's June 16, 1997 letter, a copy of which is provided behind Tab D. The page numbers cited below correspond to the Agency's letter of June 16, 1997:

- In general, formatting changes to bold cross references throughout the labeling have been made as recommended by the Agency. Zeneca requests that the other formatting changes to remove the indentations and to italicize the subsections be addressed separately. The format currently used by Zeneca is standard for all Zeneca product prescribing information and would require significant effort to revise.

- Page 4, under CLINICAL PHARMACOLOGY - Pharmacokinetics section, Zeneca agrees to delete the subsection title and replace with the subtitle and add the statement as recommended by the Agency.

- Pages 8 - 10, under CLINICAL PHARMACOLOGY - Clinical Studies section, Zeneca agrees to add to the subsection heading as recommended. Zeneca proposes retaining the descriptor for accuracy in that two pivotal trials (9393IL/0022 and 9393IP/0003), one supportive trial (ZX1600/9001), and seven other trials were conducted to support this application and were included in the supplemental application.

  Zeneca agrees to re-order this section as recommended such that the methods for Trial 0022 are presented followed by the study results and the methods for Trial 0003 are presented followed by these study results. In addition, the surgical procedures used and the median endometrial thicknesses achieved in each of these studies have been added as recommended.

  Zeneca proposes to retain the p-value for the comparison in amenorrhea for patients receiving ZOLADEX when compared to placebo. Zeneca believes the addition of p-values supplement the statement by providing a frame of reference as to the degree of benefit achieved. Zeneca agrees to include the following sentence:

  as recommended.

  Zeneca proposes to retain the discussion on the percentage of patients with hypomenorrhea and normal menses as it is believed that this additional information may be useful to the physician in assessing patient outcome for those patients that did not achieve amenorrhea. Zeneca proposes the following:

- Page 10, under INDICATIONS AND USAGE - Prostatic Carcinoma section, Zeneca agrees to delete the statement:

  Zeneca agrees to delete the word in this paragraph as recommended.

- Page 11, under INDICATIONS AND USAGE - Endometrial Thinning, Zeneca accepts the addition of to the indication as recommended by the Agency.

- Page 24, under ADVERSE REACTIONS - Endometrial Thinning, Zeneca accepts the recommendation to include only adverse events reported for Trial 0022. A revised table of adverse events entitled has been added. This table provides only the percent of adverse events for the ZOLADEX and placebo treatment groups.

- Page 27, under DOSAGE AND ADMINISTRATION - Endometrial Thinning, Zeneca proposes to revise the dosing recommendation to:

  Zeneca believes this dosing recommendation is supported by the results of Trial 0022 in which two depots were used prior to surgery. The additional advantage conferred by using two depots and performing surgery up to 2 weeks after the second depot is a 16% increase in amenorrhea rate. This is believed to be the result of continued down regulation for an additional two weeks following surgery during the healing phase.

Should you have any additional questions or require clarification on any of the above, please do not hesitate to contact us.

Sincerely,

Kimi F. DeNoble

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/lmc

Desk Copy: Mr. Alvis Dunson, Consumer Safety Officer, HFD No. 580, Room No. 17B-45

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

COPY 2

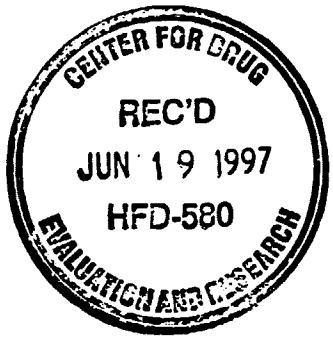
DUPLICATE

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA RAPIFAX AND
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

ORIG AMENDMENT

JUN 16 1997



Lisa D. Rarick, M.D.
Division Director
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Re: ZOLADEX® (goserelin acetate implant) 3.6 mg Depot
NDA 19-726
Endometrial Thinning Supplement (S-018)

Reference is made to the Agency's letter dated June 16, 1997 concerning an efficacy supplement for the use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to endometrial ablation. Zeneca is currently reviewing the Agency's comments and will provide a response shortly.

Should you have any questions, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/jr

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA RAPIFAX AND
AIRBORNE EXPRESS

JUN 10 1997

Mr. Alvis Dunson
Consumer Safety Officer
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-20
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Dunson:

Re: ZOLADEX® (goserelin acetate implant) 3.6 mg Depot
NDA 19-726
Endometrial Thinning Supplement (S-018)

Reference is made to our telephone conversation of June 9, 1997 in which the package labeling for ZOLADEX® (goserelin acetate implant) 3.6 mg Depot were requested. In response, please find attached copies of the labeling for the carton and pouch for ZOLADEX.

Should you require any additional information, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/jr
Enclosures

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

DUPLICATE
COPY 2

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

ORIG AMENDMENT
SE1-018

SENT VIA RAPIFAX (Tab A only) AND
AIRBORNE EXPRESS

MAY 12 1997

Mr. Alvis Dunson
Consumer Safety Officer
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-20
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Dunson:

Re: ZOLADEX® (goserelin acetate implant) 3.6 mg Depot
NDA 19-726
Endometrial Thinning Supplement (S-018)

Reference is made to our telephone conversation of May 9, 1997 concerning the draft labeling for supplement S-018 for the use of ZOLADEX® (goserelin acetate implant) 3.6 mg depot as an endometrial thinning agent prior to endometrial ablation. As requested, provided behind Tab A is the draft labeling for supplement S-018 in portrait format which incorporates the proposed text for the endometrial thinning indication into the current labeling for ZOLADEX (64102-00, Rev C 04/96).

Please note that a Changes Being Effected supplement (S-019) was submitted on September 11, 1996 to add language concerning hypersensitivity reactions. These changes are reflected in the current labeling for ZOLADEX which is provided (Tab A). In addition, formatting changes to the Clinical Pharmacology section of the proposed labeling for supplement S-018 have been made as recommended by the Biopharmaceutics Reviewer in a correspondence dated February 18, 1997.

Provided on diskette are two WORD 7.0 documents (ZOLN024EndometrialThinning.doc and ZOL3CN75.doc). These documents are, respectively, the draft labeling in portrait format as described above, and draft labeling in a three column landscape format which identifies the

proposed changes to the current prescribing information. For ease in review, a hardcopy of the three-column document is provided behind Tab B. The diskette has been scanned using the Norton Antivirus for Windows 95 (95.0.b). No viruses were detected (Tab C).

Should you have any questions or require additional information, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/car
Enclosures

ORIGINAL

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

COPY 1

MAR 7 1997

3/19/97

Noted 3/19/97

SUPPL NEW CORRESP

SENT VIA RAPIFAX

Lisa D. Rarick, M.D.
Division Director
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-45
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS 3/10/97 DATE

Dear Dr. Rarick:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Endometrial Thinning Supplement (S-018)

The purpose of this communication is to confirm receipt of the Agency's letter dated February 26, 1997 with regard to the June 28, 1996 supplemental new drug application (S-018) for the use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to endometrial ablation. A response is currently being formulated and will be provided shortly.

Sincerely,

8-19-97

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/car

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 13 1997
HFD-580

ORIG AMENDMENT ORIGINAL

COPY 1

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

Not in Box

mailed copy 3/6/97

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

ORIG AMENDMENT

Mr. Alvis Dunson
Consumer Safety Officer
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-45
5600 Fishers Lane
Rockville, MD 20857

FEB 26 1997

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
AD 3/6/97
CSO INITIALS DATE

Dear Mr. Dunson:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Endometrial Thinning Supplement (S-018) - Four Month Safety Update

Reference is made to our telephone conversation of February 21, 1997 concerning the Four Month Safety Update for Zeneca's supplemental NDA (sNDA) for the use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to endometrial ablation. In our discussion, it was agreed that Zeneca would submit the Four Month Safety Update in hardcopy format only. This Four Month Safety Update will not be provided as a update or as WordPerfect files unless specifically requested by FDA.

Should you have any questions or require additional information, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 28 1997
HFD-580

KFD/lmc

T:\DENOBLE\FDA\ZOLADEX\19726ETS.DOC

3/6/97 Copy

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

COPY 1

SENT VIA AIRBORNE EXPRESS

FEB 26 1997

Lisa D. Rarick, M.D.
Division Director
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-45
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
AT 3/6/97
CSO INITIALS DATE

Dear Dr. Rarick:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Four Month Safety Update - Endometrial Thinning Supplement (S-018)

Reference is made to Zeneca's supplemental NDA (sNDA; S-018), submitted on June 28, 1996, which presented data to establish the safe and efficacious use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to endometrial ablation. Reference is also made to the correspondence dated July 3, 1996 between Zeneca and the division in which the timelines for the submission of this update were established.

The enclosed Safety Update provides the FDA with the following safety information: additional safety data collected from the pivotal trial (Study 9393IL/0022) by means of a postcard 12 months following surgery; and safety data from other sources obtained through Zeneca's worldwide database called SECURE. With the exception of the additional data collected by postcard for Study 9393IL/0022, all trials were completed at the time of the sNDA submission, therefore, no additional safety data is available from those trials. This Safety Update incorporates data which has been collected from December 31, 1995 through June 8, 1996 for Study 9393IL/0022. Safety data obtained from other sources were collected from December 31, 1995 to November 18, 1996.

The data contained herein are consistent with the data submitted in the NDA, and no new safety issues have arisen.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 28 1997
HFD-580

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

ZENECA
Pharmaceuticals
A Business unit of Zeneca Inc.

JAN 31 1997

SENT VIA AIRBORNE EXPRESS

COPY 1

Craig S. Cropp, M.D.
Medical Officer
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Cropp:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Supplement (S-018) - Endometrial Thinning WordPerfect Document Diskettes

Reference is made to our telephone conversation of January 30, 1997 in which Zeneca agreed to provide you with WordPerfect versions of the documents provided in the [illegible] for the ZOLADEX® (goserelin acetate implant) endometrial thinning supplement. In that regard, please find enclosed two diskettes containing the text and image documents discussed. Also provided behind Tab A, is a listing of the document directories, document names and document descriptions. In addition, a detailed table of contents for the Integrated Summary of Efficacy and Integrated Summary of Safety is provided behind Tab B.

The enclosed diskettes have been scanned using the Norton Antivirus Version 3.0 and a Virus Definition List dated January 1, 1997. No viruses were detected. Zeneca certifies that the diskettes are clean of known viruses.

Should you have any questions or require any further information, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble
Assistant Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
CSO INITIALS DATE 2/7/97

Enclosures and Attachments

Desk Copies: Mr. Alvis Dunson, HFD No. 580
Mr. David M. Moss, HFD No. 070

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 03 1997
HFD-580

...DA\ZOLADEX\19726END.DOC

SUPPL NEW CORRESP
SNC 018

ZENECA Pharmaceuticals

A Business Unit of Zeneca Inc.

COPY 1

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

Noted Receipt 08/30/96

Noted M Jenkins 9/27/96

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

AUG 2 3 1996

Ms. Lana Pauls
Chief, Project Management Staff
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-04
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D AUG 30 1996 HFD-580

Dear Ms. Pauls:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Supplement (S-018) - Endometrial Thinning Indication

Reference is made to the supplemental New Drug Application submitted on June 28, 1996 for the use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to endometrial ablation. Reference is also made to our telephone conversation of August 13, 1996 in which clarification was requested as to whether providing the data by means of a obviated the need for a SAS Data Disk. This is to confirm that, based on our discussion, no SAS Data Disk will be provided for this submission. Further, the Statistical Reviewer has been provided access to the ZOLADEX as well as training on the Text and Imaging, and Data review facilities.

Should you have any further comments or concerns, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble

Kimi F. DeNoble
Senior Regulatory Specialist, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/lmc/4566/67

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.L. ☐ MEMO

CSO INITIALS 10/2/96 DATE

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

COPY

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA AIRBORNE EXPRESS

COPY 2

AUG 13 1996

Dr. Lee Ping Pian
Mathematical Statistician
Division of Biometrics II
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 715, Room No. 17B-20
5600 Fishers Lane
Rockville, MD 20857

Dr. Pian:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Endometrial Thinning Supplement (S-018) - CANDA User's Guide

Reference is made to the supplement filed on June 28, 1996 for the use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to endometrial ablation. Reference is also made to our meeting on August 12, 1996 in which Zeneca provided training on the use of the ZOLADEX During that meeting, Zeneca committed to providing you a current version of the User's Guide. In that regard, please find enclosed one copy of the Zeneca Pharmaceuticals User's Guide.

Should you have any questions or require any further information, please do not hesitate to contact us.

Sincerely,

Kimi F. DeNoble
Senior Regulatory Specialist, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/jr/4565/67
Enclosure

Desk Copy: Ms. Lana L. Pauls, HFD No. 580, Room No. 17B-04

COPY 1

NDA SUPP AMEND

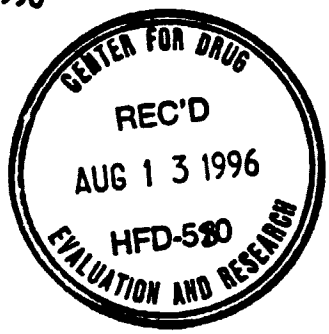
ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

ORIGINAL

AIRBORNE EXPRESS

AUG 12 1996



Lisa D. Rarick, M.D.
Division Director
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 17B-20
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Supplement (S-018) - Endometrial Thinning Indication

Reference is made to the supplemental New Drug Application submitted on June 28, 1996 for the use of ZOLADEX® (goserelin acetate implant) as an endometrial thinning agent prior to endometrial ablation. In the cover letter accompanying the supplement, we stated that the non-confidential version of the Environmental Assessment (EA) would be provided under separate cover. In that regard, please find enclosed the non-confidential version of the Environmental Assessment to be included as part of this supplement (S-018). A confidential version of the EA was included in the June 28, 1996 submission as part of the Chemistry, Manufacturing and Controls technical review section.

Should you have any questions or require any further information, please do not hesitate to contact me.

Sincerely,

Sandra L. Acquaviva

Sandra L. Acquaviva
Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-2192
(302) 886-2822 (fax)

SLA/KFD/lmc/4557/67
Enclosure

Desk copy: Ms. Lana Pauls, HFD No. 580, Room No. 17B-20

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

DUPLICATE

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

COPY 2

JUL 3 1996

Ms. Lana L. Pauls
Project Leader
Division of Reproductive
and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 14B-04
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Pauls:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Supplement (S-018) - Endometrial Thinning Indication

Reference is made to our telephone conversation June 12, 1996 concerning the timing for the submission of the Four Month Safety Update for the ZOLADEX® (goserelin acetate implant) supplemental New Drug Application (sNDA). The supplement was filed on June 28, 1996. This is to confirm that, based on our discussion, Zeneca will provide a safety update for this supplemental filing four months prior to the twelve month User Fee date, in other words, eight months post submission. Zeneca plans to establish timelines for the production of the Four Month Safety Update based on the timings discussed and submit the additional data accordingly. No pre-approval safety update will be provided following the submission of the Four Month Safety Update unless specifically requested by FDA.

Should you have any further comments or concerns, please do not hesitate to contact me.

Sincerely,

Kimi F. DeNoble

Kimi F. DeNoble
Senior Regulatory Specialist, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-4079
(302) 886-2822 (fax)

KFD/jr/4457/67

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

JUN 2 8 1996

HAND DELIVERED

Dr. Lisa D. Rarick
Division Director
Divison of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 580, Room No. 14B-04
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Rarick:

Re: ZOLADEX® (goserelin acetate implant)
NDA 19-726
Supplement - Endometrial Thinning Indication

Zeneca PLC, Macclesfield, Cheshire, England, owner of the patent, safety and efficacy information for ZOLADEX® (goserelin acetate implant) hereby submits a supplemental application. The application conforms to the content and format requirements established under 21 CFR 314.50. The application presents data to establish the safe and effective use of ZOLADEX as an endometrial thinning agent prior to endometrial ablation. This sNDA consists of a total of 38 volumes and includes a blue (archival) copy and review copy for each applicable technical section of the sNDA. Each technical review section includes a copy of the application summary. A confidential version of the Environmental Assessment (EA) is included in this submission in the Chemistry, Manufacturing and Controls (CMC) technical review section. A non-confidential version of the EA will be provided under separate cover.

ZOLADEX is a synthetic agonist analogue of the naturally occurring gonadotrophin-releasing hormone (GnRH). By acting on the pituitary receptors of the hypothalamic-pituitary-ovarian axis, ZOLADEX causes an initial stimulatory effect followed by down-regulation of the receptors and a reduction in the secretion of gonadotropins. In women, the diminished concentrations of circulating estrogen results in atrophy of the endometrium. This pharmacological effect of ZOLADEX has potential for use as adjunctive treatment for women undergoing hysteroscopic ablation as treatment for condition such as dysfunctional uterine bleeding.

This application provides evidence of the efficacy and safety for the use of ZOLADEX as an endometrial thinning agent prior to endometrial ablation.

Reference is made to the following discussions and submissions between the Agency and Zeneca Pharmaceuticals concerning the use of ZOLADEX as an endometrial thinning agent. These include the following items:

- In a meeting held April, 1993, the FDA accepted the beneficial role of thinning the endometrium prior to an ablative procedure, ZOLADEX as an endometrial thinning agent, and the concept of ablation as a surgical technique.

- At an End-of-Phase II meeting held on February 4, 1994, Zeneca's proposed Phase III Clinical Trial Program was presented. The FDA agreed to the structure, end-points, dosing, time of surgery, and blinding of Trial 9393IL/0022. Following the meeting, the FDA agreed to accept the ZOLADEX arm of Trial 9393IP/0003 as the second, adequate and well-controlled trial to support the claim.

- In a communication dated May 3, 1994, Zeneca submitted a proposal for the statistical analysis of the ZOLADEX arm of Trial 9393IP/0003.

- In a correspondence dated January 12, 1995, Zeneca requested clarification on whether the FDA required bone mineral density data in this clinical trial program. The FDA provided a response dated April 20, 1995 which stated that collection and analysis of bone mineral density data was not required for this program.

- At a pre-NDA meeting held on October 26, 1995, the FDA accepted the proposed indication for ZOLADEX as an endometrial thinning agent prior to endometrial ablation, the use of Trials 9393IL/0022 and 9393IP/0003 as the pivotal studies, the statistical plans, a submission and the dosing recommendation of two depots administered 28 days apart with surgery timed within two weeks after the second depot.

Zeneca conducts clinical trials according to operating procedures which incorporate the key requirements for Good Clinical Practice (GCP) as documented in the guidelines of the US Food and Drug Administration and the European Committee for Proprietary Medicinal Products (CPMP), as well as requirements of the Declaration of Helsinki. Zeneca does not use the services of any person debarred under section 306 (a) or (b) of the US Food, Drug and Cosmetic Act, or any other such regulatory authority listing. Zeneca undertakes a GCP audit programme to ensure compliance with its procedures, and to asses the adequacy of its quality control procedures. Audits are performed by an International GCP Group within Zeneca operating independently of the trial monitors. The audit program is directed towards clinical trial files, investigator sites and clinical trial reports.

The US agent for this application representing Zeneca PLC will be Zeneca Pharmaceuticals Group, a Business Unit of Zeneca Inc., Wilmington, Delaware 19897. The appropriate letter of authorization is enclosed.

Zeneca considers all information contained in this supplemental NDA, except for the published articles, to be trade secrets and therefore, confidential, and hereby requests that the FDA treat this information accordingly. Confidentiality of this information is claimed under Provisions 21 USC Section 331(j) and/or 18 USC, Section 1905.

Should you have any questions regarding this application, please do not hesitate to contact me, or in my absence, Ms. Kimi F. DeNoble at (302) 886-4079.

Sincerely,

Sandra L. Acquaviva
Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-2192
(302) 886-2822 (fax)

SLA/KFD/car/4437/68
Enclosure