CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-892

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # 20-892 SUPPL # N.A.

Trade Name Valstar™ Generic Name AD-32 (VALRUBICIN)

Applicant Name Anthra HFD # 150

Approval Date If Known 9-25-98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

d) **Did the applicant request exclusivity?**

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Seven years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not

independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

A9301 / A9302 _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /X/ ! NO /___/ Explain: _____

_____

Investigation #2

IND # YES /Y/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

/S/

Signature

6-22-98

Date

Title: Project Manager

/S/

Signature of Office Director

9/24/98

Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

(NDA)/BLA # 20-892 Supplement # N.A. Circle one: SE1 SE2 SE3 SE4 ~~SE5 SE6~~

HFD-150 Trade and generic names/dosage form: valrubicin 5mL single-use vials Action: AP AE (NA)

Applicant Anthra Pharmaceuticals, Inc. Therapeutic Class Cytotoxic

Indication(s) previously approved none

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application intravesical use in the treatment of patients with biopsy-proven carcinoma in situ of the urinary bladder who are refractory to BCG immunotherapy.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. 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.

X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. See above proposed indication

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/ Project Manager 4/22/98

Signature of Preparer and Title Date

cc: Orig (NDA)/BLA # 20-892
HFD-150 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

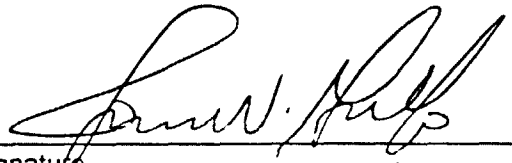
(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Debarment Certification

Anthra Pharmaceuticals, Inc. represents and warrants that Anthra, its consultants and contractors has neither been debarred nor is subject to debarment and that it has not used in any capacity any person who has been debarred pursuant to section 306 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 335a, or who is or has been the subject of a conviction described in such section.

For Anthra Pharmaceuticals, Inc.



Signature

Joseph V. Gulfo

Printed Name

Executive Vice President & COO

Title

December 15, 1997.

Date

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Dan Boring, Ph.D., Chair
Division of Antiviral Drug Products, HFD-530, CDER

FROM: Sung K. Kim, Ph.D., Reviewing Chemist (Phone: 827-1522) SKK 5-5-98
Through Rebecca H. Wood, Ph.D., Chemistry Team Leader, DNDC I RHW for RHW 5-5-98
Division of Oncology Drug Products, HFD-150, CDER

DATE: May 5, 1998

Subject: Request for Assignment of a Trademark for a Proposed Drug Product

---

Proposed Trademark: **Valstar™** Sterile Solution for Intravesical Instillation NDA # 20-892

Established name, including dosage form: Valrubicin Sterile Solution

Other trademarks by the same firm for companion products:
Not available

Indications for Use:
Carcinoma in situ of urinary bladder

Initial comments from the submitter: (concerns, observations, etc.)
Valrubicin is a semi-synthetic anthracycline derivative, chemically related to daunorubicin and doxorubicin. One of our team's comment—"-star" in the proposed trademark connotes a superiority over other therapies.

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.

cc:
Original NDA # 20-892
HFD-150/Div. File
HFD-150/SKim
HFD-150/AStaten
HFD-150/RWood
HFD-530 / DBoring

PATENT INFORMATION

AD 32 (valrubicin) is not covered by any patents.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-892

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

STATEN

Food and Drug Administration
Rockville MD 20857

NDA 20-892

JAN 23 1998

Anthra Pharmaceuticals, Inc.
103 Carnegie Center, Suite 102
Princeton, New Jersey 08540

Attention: Timothy P. Urschel
Manager, Regulatory Affairs

Dear Mr. Urschel:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: AD-32 (valrubicin)

Therapeutic Classification: Priority

Date of Application: December 30, 1997

Date of Receipt: December 31, 1997

Our Reference Number: 20-892

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 March 1, 1998 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Ann Staten, Project Manager, at 301-594-5770.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ 1/20/98

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20892
HFD-150/Div. Files
HFD-150/CSO/AStaten
HFD-150/OOdujinrin/GWilliams
HFD-150/WMcGuinnw/PAndrews
HFD-150/SKim/RWood
HFD-150/EMishina/ARahman
HFD-150/GChen/TKoutsoukos
DISTRICT OFFICE

Drafted by: AStaten/January 7, 1998/wpfiles/NDA/20892/letters/ack.ltr
R/D init. by DPease/1-16-98
Final: AStaten/1-16-98

ACKNOWLEDGEMENT (AC)

DUPLICATE ORIG AMENDMENT

BC

thra

PHARMACEUTICALS, INC.

Clinical Offices:
103 Carnegie Center • Suite 102 • Princeton, NJ 08540 • 609-514-1060 Fax: 609-514-0534

Research Offices:
P.O. Box 41361 • Memphis, TN 38174 • 901-448-4584 Fax: 901-448-4587

September 9, 1998

Ms. Ann Staten
CSO/Project Manager
Food and Drug Administration
Division of Oncology Drug Products
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 20,892
Serial Number 34 (Minor Amendment)
Valstar™ (valrubicin, AD 32)

Dear Ms. Staten:

Reference is made to New Drug Application (NDA) 20,892; submitted on December 31, 1997 by Anthra Pharmaceuticals, Inc.

Anthra is submitting this minor amendment to the NDA in response to the telefaxes received on September 8, 1998 regarding the reviewing chemist's comments on the vial label for Valstar. Anthra agrees to and commits to the following;

(a) We will print on the vial label the following three statements:

1. "For Intravesical Use Only"
2. "Not for IM or IV Use"
3. 200 mg/5ml(40mg/ml)

(b) In addition, Anthra will replace, with, "Sterile Solution for IV Instillation" on both the vial and carton label.

In order to print the above statements, Anthra will remove the dosage information; and if needed for spacing reasons, the name of the distributor from the vial label will also be removed as suggested by the reviewing chemist.

This amendment is submitted in duplicate. If you have any questions or concerns regarding this submission, please contact me at (609) 514-1060 extension 3982.

Sincerely,

Timothy Urschel

Timothy Urschel
Assistant Director, Regulatory Affairs

Copy: J. Gulfo, M.D.
N. Murray
A. Thunberg, Ph.D.
D. Webber
C. Rini - Medeva

fda\amcnd34-9-09-98

Anthra

PHARMACEUTICALS, INC.

Clinical Offices:
103 Carnegie Center • Suite 102 • Princeton, NJ 08540 • 609-514-1060 Fax: 609-514-0534

Research Offices:
P.O. Box 41361 • Memphis, TN 38174 • 901-448-4584 Fax: 901-448-4587

June 26, 1998

Ms. Ann Staten
CSO/Project Manager
Division of Oncology Drug Products
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 20,892
Major Amendment – Volume 2.1
Valstar [AD 32 (N-Trifluoroacetyladriamycin-14-Valerate)]

Dear Ms. Staten:

Reference is made to New Drug Application (NDA) 20,892 submitted on December 31, 1997 and to the post-ODAC meeting conducted on June 19, 1998 between Anthra, the Oncology Division (Drs. Justice, Williams, Odujinrin, and White), Dr. Temple (Director of ODE 1) and Dr. Scher (ODAC member).

Anthra is submitting this major amendment providing an approvable basis of valrubicin, as proposed and discussed by Drs. Temple, Justice and Williams during the post-ODAC meeting, in patients with BCG-refractory carcinoma in situ in whom cystectomy is medically contraindicated. The primary purpose of this amendment is to define such a population.

The submission contains the following: 1) a literature-based discussion of medical contraindications to major surgery, in general, with emphasis on radical cystectomy, including copies of all cited references; 2) an evaluation of the comorbid conditions of patients in the A9301/02 studies who did not undergo cystectomy; 3) a revised package insert; and 4) minutes of the June 19 post-ODAC meeting.

In consultation with our expert consultant urologists, pending discussions with the Agency, we propose to also include patients who refuse cystectomy in the revised claim.

The following changes have been incorporated in the package insert for valrubicin (AD 32), which includes the following changes:

- The drugname (Valstar™), which was not available when the NDA was submitted, has been included throughout the package insert.

- The section "Clinical Trials" was revised to reflect the most up-to-date efficacy information from study A9301/02. These data were submitted to the agency in Minor Amendment 16 (April 29, 1998) and Minor Amendment 24 (June 11, 1998).

- "Indications and Usage" was revised:

- "Disease Progression/Recurrance" was revised to reflect the most up-to-date failure and cystectomy results in study A9301/02. These data were submitted to the agency in Minor Amendment 16 (April 29, 1998).

- An error was corrected in the section "Adverse Reactions: Intravesical Use." The original package insert indicated that 7 of 145 patients did not receive the scheduled course of six doses. The correct numbers are 7 of 143 patients.

- A sentence concerning the use of PVC tubing was added to "Administration Precautions" paragraph.

This amendment is submitted in duplicate. If you have any questions or concerns regarding this submission, please contact me at (609) 514-1060 extension 3982.

Sincerely,

Timothy Urschel
Asst. Director, Regulatory Affairs

Copy: J. Gulfo

DUPLICATE

hra

PHARMACEUTICALS, INC.

Clinical Offices:
103 Carnegie Center • Suite 102 • Princeton, NJ 08540 • 609-514-1060 Fax: 609-514-0534

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ORIG AMENDMENT
BM

May 29, 1998

Ms. Ann Staten
CSO/Project Manager
Division of Oncology Drug Products
HFD-150, 1451 Fishers Lane
Rockville, MD 20857

Re: NDA 20,892
Serial Number 023 (Minor Amendment)
AD 32 (N-Trifluoroacetyladriamycin-14-Valerate)

Dear Ms. Staten:

Reference is made to New Drug Application (NDA) 20,892; submitted on December 31, 1997 by Anthra Pharmaceuticals, Inc.

Anthra is submitting this minor amendment to the NDA to provide a response to the Medical Reviewer's comments received in the telefax dated May 19, 1998 regarding consultation review of specimens obtained during the study (A9301/A9302) by the reference Pathologist at AFIP. Attached, please find the AFIP review for the three cases, #30203, #440201, #670201 requested by the Medical Reviewer. These include specimens for the baseline and failure evaluations. Please note the protocol did not require consultation review of the cystectomy pathology.

This amendment is submitted in duplicate. If you have any questions or concerns regarding this submission, please contact me at (609) 514-1060 extension 3982.

Sincerely,

Timothy Urschel

Timothy Urschel
Assistant Director, Regulatory Affairs

Enclosure

Copy: J. Gulfo
D. Webber

FDA\Amend23-5-29-98

DUPLICATE

hra

PHARMACEUTICALS, INC.

Clinical Offices:
103 Carnegie Center • Suite 102 • Princeton, NJ 08540 • 609-514-1060 Fax: 609-514-0534

Research Offices:
P.O. Box 41361 • Memphis, TN 38174 • 901-448-4584 Fax: 901-448-4587

ORIG AMENDMENT
BM

May 28, 1998

Ms. Ann Staten
CSO/Project Manager
Division of Oncology Drug Products
HFD-150, 1451 Fishers Lane
Rockville, MD 20857

Re: NDA 20,892
Serial Number 022 (Minor Amendment)
AD 32 (N-Trifluoroacetyladriamycin-14-Valerate)

Dear Ms. Staten:

Reference is made to New Drug Application (NDA) 20,892; submitted on December 31, 1997 by Anthra Pharmaceuticals, Inc.

Anthra is submitting this minor amendment to provide responses for the questions received from the Medical Reviewer in the telefax received May 26, 1998. These data were provided to the agency previously as Minor Amendment 16 (April 29, 1998).

In response to Question 1, the attached table provides summary data for patients in studies A9301/02 who have not died. The table contains the following information:

- Date of disease recurrence or failure (ie, "Off Study Date")
- Clinical stage of disease at failure
- Date of the last follow-up visit
- Date of cystectomy, if applicable
- Pathologic stage of disease at cystectomy
- Type of treatment received post AD 32 treatment, if applicable

Please note that protocol section 12.0 defines the criteria for evaluation and endpoint definitions. Following completion of AD 32 treatment, disease evaluation took place approximately six weeks following treatment (primary disease evaluation) and at three months intervals thereafter in the "on study" phase. Upon failure or disease recurrence following AD 32 treatment, the clinical stage at failure was noted and the patients were followed periodically (every 6 months) for status and survival. These long-term follow-up evaluations were performed via chart reviews, phone calls, contact with other urologists for referral patients, etc.

The protocol definition of "on study" mandates following patients by visits and data collection to show that there is no undue risk of progression of bladder cancer in addition to gathering efficacy and safety data. Once the patient is in the "off study" phase following failure or recurrence (ie, long term follow up), the patient is now returned to the care of the urologist. There are no protocol-specified follow up requirements other than the periodic check of status and survival in the "off study" phase. The patient may or may not receive additional IVe therapy post AD 32 treatment in the off study phase. This is determined by the practicing urologist.

Patients with locally advanced disease can be derived from the A9301/A9302 database of the cystectomy pathologic stages. These data provide the extent of bladder disease at the time of cystectomy for those patients who underwent bladder removal post AD 32 treatment.

The only patients known to have metastatic disease following AD 32 treatment were the 4 patients who died with bladder cancer provided in the NDA update (Minor amendment 016). Aside from this, the extent of metastatic disease can be tracked by noting those patients who in long term follow up have gone on to receive systemic chemotherapy following AD 32. In the original NDA, one patient was known to have received systemic chemotherapy. Since the NDA update, there are no patients who have gone on to receive systemic chemotherapy.

In response to Question 2, there are 48 of 90 (53%) patients who had 2 or more sites of Tis at baseline. Sixty-three of 90 (70%) patients had $\geq$ 2 courses of BCG prior to AD 32 treatment.

This amendment is submitted in duplicate. If you have any questions or concerns regarding this submission, please contact me at (609) 514-1060 extension 3982.

Sincerely,

Timothy Urschel

Timothy Urschel
Asst. Director, Regulatory Affairs

Copy: J. Gulfo
D. Webber

ORIGINAL

hra

P H A R M A C E U T I C A L S, I N C.

Clinical Offices:
103 Carnegie Center • Suite 102 • Princeton, NJ 08540 • 609-514-1060 Fax: 609-514-0534

Research Offices:
P.O. Box 41361 • Memphis, TN 38174 • 901-448-4584 Fax: 901-448-4587

May 13, 1998

ORIG AMENDMENT

[redacted]

BM

CENTER ... REC'D MAY 1 4 1998 HFD-150 EVALUATION AND RESEARCH

Ms. Ann Staten
CSO/Project Manager
Division of Oncology Drug Products
HFD-150, 1451 Fishers lane
Rockville, MD 20857

Re: NDA 20,892
Serial Number 018 (Minor Amendment)
AD 32 (N-Trifluoroacetyladriamycin-14-valerate)

Dear Ms. Staten:

Reference is made to New Drug Application (NDA) 20,892; submitted on December 31, 1997 by Anthra Pharmaceuticals, Inc.

Anthra is submitting this minor amendment to the NDA to provide clarification requested by the Agency via telefax regarding patient   dated May 12, 1998.

This amendment is submitted in duplicate. If you have any questions or concerns regarding this submission, please contact me at (609) 514-1060 extension 3982.

Sincerely,

Timothy Urschel

Timothy Urschel
Assistant Director, Regulatory Affairs

Copy: J. Gulfo
D. Webber

c:\fda\amend18-5-13-98