

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:NDA 20-892**

**CHEMISTRY REVIEW(S)**

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

**NDA #:** 20-892      **CHEMISTRY REVIEW #:** 5      **REVIEW DATE:** September 9, 1998

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	December 30, 1997	December 31, 1997	January 15, 1998
Major amendment	June 26, 1998	June 29, 1998	June 29, 1998
Amendment (BC)	September 2, 1998	September 8, 1998	September 9, 1998
Amendment (thru fax)	September 9, 1998	September 9, 1998	September 9, 1998

**NAME & ADDRESS OF APPLICANT:**

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

**DRUG PRODUCT NAME:**

Proprietary:  
Nonproprietary/USAN:

Valstar Sterile Solution for Intravesical Instillation  
Valrubicin (This name was adopted by the USAN Council, the publication of 11/30/94, see a copy attached)

Code Name/Number:  
Chem. Type/Ther. Class:

AD 32  
1P

**PHARMACOL. CATEGORY/INDICATION:**

Inhibitor of topoisomerase II and RNA synthesis/  
Treatment of carcinoma in situ of the urinary bladder

**DOSAGE FORM:**

Sterile solution, Single use vial

**STRENGTHS:**

200mg/5ml/vial(40mg/ml)

**ROUTE OF ADMINISTRATION:**

Intravesical Instillation

**DISPENSED:**

Rx       OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):**

CAS Name: (2S-cis)-2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-[(trifluoroacetyl)amino]- $\alpha$ -L-*hxo*-hexapyranosyl]oxy]-2-naphthacenyl]-2-oxoethyl ester, Pentanoic acid

IUPAC Name: (8s,10s)-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)- $\alpha$ -L-*hxo*-hexapyranosyl]oxy]-5,12-naphthacenedione-8-valerate

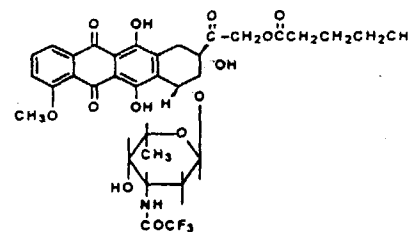
Common Name: N-Trifluoroacetyladriamycin-14-valerate

CAS Number: 56124-62-0

Code Number: AD 32; NSC-246131

M.F.:  $C_{34}H_{36}F_3NO_{13}$

M.W.: 723.65



**SUPPORTING DOCUMENTS:**

INDs:            IND  
DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		6/24/97	manufacture of Valrubicin	Adequate	7/14/98	Reviewed by HFD-150
		5/30/97	Brosilicate tubing vials treated with ammonium sulfate	Adequate	2/20/96	Reviewed by HFD-150
		6/4/97	Rubber stopper	Adequate	5/10/93	Reviewed by HFD-635

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

*EER for* *sites*, submitted on 1/27/98, acceptable recommendation on 4/21/98.  
*Trademark consultation* on 5/5/98, Valstar is accepted (6/11/98)  
*Micro consultation*, initiated on 1/22/98, acceptable on 4/22/98.  
*Environmental assessment*, exemption is requested. Granted.  
*Stability data consultation* on 5/5/98, Eighteen month expiration dating period is recommended (statistical review of 5/28/98)  
*Method validation* will be initiated after satisfactory response to deficiencies regarding method validation.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

Approval of NDA 20-892 is recommended from chemistry viewpoints.

*/S/*

Sung K. Kim, Ph.D.,  
 Review Chemist, HFD-150

cc:

Orig. NDA 20-892  
 HFD-150/Division File  
 HFD-150/S.Kim  
 HFD-150-/A.Staten  
 HFD-150/R.Wood  
 R/D Init. by: \_\_\_\_\_ *9-9-98*  
 filename: N20892.org4

SEP 3 1998

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

**NDA #:** 20-892      **CHEMISTRY REVIEW #:** 4      **REVIEW DATE:** August 31, 1998

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	December 30, 1997	December 31, 1997	January 15, 1998
Major amendment	June 26, 1998	June 29, 1998	June 29, 1998
Amendment	August 24, 1998	August 25, 1998	August 27, 1998

**NAME & ADDRESS OF APPLICANT:**

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

**DRUG PRODUCT NAME:**

Proprietary:  
 Nonproprietary/USAN:

Valstar Sterile Solution for Intravesical Instillation  
 Valrubicin (This name was adopted by the USAN  
 Council, the publication of 11/30/94, see a copy  
 attached)

Code Name/Number:  
 Chem. Type/Ther. Class:

AD 32  
 1P

**PHARMACOL. CATEGORY/INDICATION:**

Inhibitor of topoisomerase II and RNA synthesis/  
 Treatment of carcinoma in situ of the urinary bladder

**DOSAGE FORM:**

Sterile solution, Single use vial

**STRENGTHS:**

200mg/5ml/vial(40mg/ml)

**ROUTE OF ADMINISTRATION:**

Intravesical Instillation

**DISPENSED:**

Rx       OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):**

CAS Name: (2S-cis)-2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-[(trifluoroacetyl)amino]- $\alpha$ -L-*h*xo-hexapyranosyl]oxy]-2-naphthacetyl]-2-oxoethyl ester, Pentanoic acid

IUPAC Name: (8s,10s)-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)- $\alpha$ -L-*h*xo-hexapyranosyl]oxy]-5,12-naphthacenedione-8-valerate

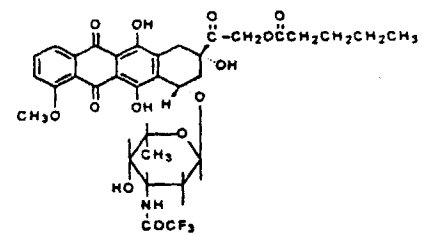
Common Name: N-Trifluoroacetyladrriamycin-14-valerate

CAS Number: 56124-62-0

Code Number: AD 32; NSC-246131

M.F.: C<sub>34</sub>H<sub>36</sub>F<sub>3</sub>NO<sub>13</sub>

M.W.: 723.65

**SUPPORTING DOCUMENTS:**

INDs: IND

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		6/24/97	manufacture of Valrubicin	Adequate	7/14/98	Reviewed by HFD-150

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		5/30/97	Brosilicate tubing vials treated with ammonium sulfate	Adequate	2/20/96	Reviewed by HFD-150
		6/4/97	Rubber stopper	Adequate	5/10/93	Reviewed by HFD-635

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

*EER for* sites, submitted on 1/27/98, acceptable recommendation on 4/21/98.  
*Trademark consultation* on 5/5/98, Valstar is accepted (6/11/98)  
*Micro consultation*, initiated on 1/22/98, acceptable on 4/22/98.  
*Environmental assessment*, exemption is requested. Granted.  
*Stability data consultation* on 5/5/98, Eighteen month expiration dating period is recommended (statistical review of 5/28/98)  
*Method validation* will be initiated after satisfactory response to deficiencies regarding method validation.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

Approval of NDA 20-892 is recommended from chemistry viewpoints. The following comment should be included in an action letter to be prepared:

An expiration dating period of 18 months is granted at this time. The expiration dating period could be updated based on real-time stability data obtained from three batches of the drug product which is manufactured using drug substance (e.g batches 515-44-0004 and 515-44-0005 and one more batch). However, an expiration dating period of 24 months is granted if the drug product to be marketed is manufactured using OmniChem's drug substance.

/S/

\_\_\_\_\_  
Sung K. Kim, Ph.D.,  
Review Chemist, HFD-150

cc:

Orig. NDA 20-892  
HFD-150/Division File  
HFD-150/S.Kim  
HFD-150-/A.Staten  
HFD-150/R.Wood  
R/D Init. by: \_\_\_\_\_  
filename: N20892.org3

9-1-98

STATE

AUG 13 1998

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

**NDA #:** 20-892      **CHEMISTRY REVIEW #:** 3      **REVIEW DATE:** August 12, 1998

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	December 30, 1997	December 31, 1997	January 15, 1998
Major amendment	June 26, 1998	June 29, 1998	June 29, 1998
Amendment	July 24, 1998	July 28, 1998	July 30, 1998
Amendment	July 27, 1998	July 28, 1998	July 30, 1998

**NAME & ADDRESS OF APPLICANT:**

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

**DRUG PRODUCT NAME:**

Proprietary:  
Nonproprietary/USAN:

Valstar Sterile Solution for Intravesical Instillation  
Valrubicin (This name was adopted by the USAN Council, the publication of 11/30/94, see a copy attached)

Code Name/Number:  
Chem. Type/Ther. Class:

AD 32  
1P

**PHARMACOL. CATEGORY/INDICATION:**

Inhibitor of topoisomerase II and RNA synthesis/  
Treatment of carcinoma in situ of the urinary bladder

**DOSAGE FORM:**

Sterile solution, Single use vial

**STRENGTHS:**

200mg/5ml/vial(40mg/ml)

**ROUTE OF ADMINISTRATION:**

Intravesical Instillation

**DISPENSED:**

Rx       OTC

**CHEMICAL NAME. STRUCTURAL FORMULA. MOLECULAR FORMULA(M.F.). MOLECULAR WEIGHT(M.W.):**

**CAS Name:** (2S-cis)-2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-[(trifluoroacetyl)amino]-α-L-lyxo-hexapyranosyl]oxy]-2-naphthaceny]-2-oxoethyl ester, Pentanoic acid

**IUPAC Name:** (8s,10s)-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-lyxo-hexapyranosyl]oxy]-5,12-naphthacenedione-8-valerate

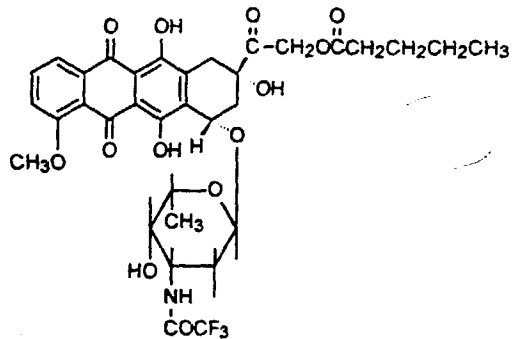
**Common Name:** N-Trifluoroacetyladiamycin-14-valerate

**CAS Number:** 56124-62-0

**Code Number:** AD 32; NSC-246131

**M.F.:** C<sub>34</sub>H<sub>36</sub>F<sub>3</sub>NO<sub>13</sub>

**M.W.:** 723.65



SUPPORTING DOCUMENTS:

INDs: IND

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		6/24/97	manufacture of Valrubicin	Adequate	7/14/98	Reviewed by HFD-150
		5/30/97	Brosilicate tubing vials treated with ammonium sulfate	Adequate	2/20/96	Reviewed by HFD-150
		6/4/97	Rubber stopper	Adequate	5/10/93	Reviewed by HFD-635

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

*EER for sites, submitted on 1/27/98, acceptable recommendation on 4/21/98.*  
*Trademark consultation on 5/5/98, Valstar is accepted (6/11/98)*  
*Micro consultation, initiated on 1/22/98, acceptable on 4/22/98.*  
*Environmental assessment, exemption is requested. Granted.*  
*Stability data consultation on 5/5/98, Eighteen month expiration dating period is recommended (statistical review of 5/28/98)*  
*Method validation will be initiated after satisfactory response to deficiencies regarding method validation.*

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending for satisfactory responses to our comments made in this NDA review # 2 dated 6/15/98 and to labeling comments in this review.

*/S/*

Sung K. Kim, Ph.D.,  
 Review Chemist, HFD-150

cc:

Orig. NDA 20-892  
 HFD-150/Division File  
 HFD-150/S.Kim  
 HFD-150-/A.Staten  
 HFD-150/R.Wood

R/D Init. by: 8-13-98

filename: N20892.org2

JUN 15 1998

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

**NDA #:** 20-892      **CHEMISTRY REVIEW #:** 2      **REVIEW DATE:** June 15, 1998

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	December 30, 1997	December 31, 1997	January 15, 1998
BC	April 21, 1998	April 22, 1998	April 24, 1998
BC	May 22, 1998	May 26, 1998	May 28, 1998

**NAME & ADDRESS OF APPLICANT:**

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

**DRUG PRODUCT NAME:**

Proprietary:  
 Nonproprietary/USAN:

Valstar Sterile Solution for Intravesical Instillation  
 Valrubicin (This name was adopted by the USAN  
 Council, the publication of 11/30/94, see a copy  
 attached)

Code Name/Number:  
 Chem. Type/Ther. Class:

AD 32  
 1P

**PHARMACOL. CATEGORY/INDICATION:**

Inhibitor of topoisomerase II and RNA synthesis/  
 Treatment of carcinoma in situ of the urinary bladder

**DOSAGE FORM:**

Sterile solution, Single use vial

**STRENGTHS:**

200mg/5ml/vial(40mg/ml)

**ROUTE OF ADMINISTRATION:**

Intravesical Instillation

**DISPENSED:**

Rx       OTC

**CHEMICAL NAME. STRUCTURAL FORMULA. MOLECULAR FORMULA(M.F.). MOLECULAR WEIGHT(M.W.):**

CAS Name: Pentanoic acid, (2S-cis)-2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[[2,3,6-trideoxy-3-[(trifluoroacetyl)amino]- $\alpha$ -L-lyxo-hexapyranosyl]oxy]-2-naphthaceny]]-2-oxoethyl ester

IUPAC Name: (8s,10s)-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)- $\alpha$ -L-lyxo-hexapyranosyl]oxy]-5,12-naphthacenedione-8-valerate

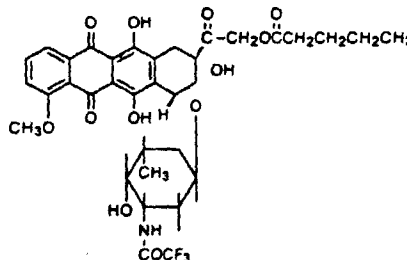
Common Name: N-Trifluoroacetyladrriamycin-14-valerate

CAS Number: 56124-62-0

Code Number: AD 32; NSC-246131

M.F.:  $C_{34}H_{36}F_3NO_{13}$

M.W.: 723.65





SUPPORTING DOCUMENTS:

INDs: IND  
DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		6/24/97	manufacture of Valrubicin	Pending for review		Reviewed by HFD-150
		5/30/97	Borosilicate tubing vials treated with ammonium sulfate	Adequate	2/20/96	Reviewed by HFD-150
		6/4/97	Rubber stopper	Adequate	5/10/93	Reviewed by HFD-635

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

*EER for* sites, submitted on 1/27/98, acceptable recommendation on 4/21/98.  
*Trademark consultation* on 5/5/98, Pending  
*Micro consultation*, initiated on 1/22/98, acceptable on 4/22/98.  
*Environmental assessment*, exemption is requested. Granted.  
*Stability data consultation* on 5/5/98, Eighteen month expiration dating period is recommended.  
*Method validation* will be initiated after satisfactory response to deficiencies regarding method validation.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

It is noted that non-approval of this NDA was recommended by ODAC members (6/1/98). Regarding CMC, NDA 20-892 is approvable pending satisfactory responses, and satisfactory labeling and referred DMF review. Comments on the last page of this review should be forwarded to the applicant.

*TSI*

Sung K. Kim, Ph.D.,  
Review Chemist, HFD-150

cc:

Orig. NDA 20-892  
HFD-150/Division File  
HFD-150/S.Kim  
HFD-150-/A.Staten  
HFD-150/R.Wood

R/D Init. by: \_\_\_\_\_ -6-15-98  
filename: N20892.org1

A. Staten

APR 29 1998

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

**NDA #:** 20-892      **CHEMISTRY REVIEW #:** 1      **REVIEW DATE:** April 28, 1998

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	December 30, 1997	December 31, 1997	January 15, 1998
BC	February 27, 1998	March 2, 1998	March 5, 1998
BC	March 26, 1998	March 27, 1998	April 1, 1998
BC	April 15, 1998	April 16, 1998	April 21, 1998

**NAME & ADDRESS OF APPLICANT:**

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

**DRUG PRODUCT NAME:**

Proprietary:  
Nonproprietary/USAN:

Valstar Sterile Solution for Intravesical Instillation  
Valrubicin (This name was adopted by the USAN Council, the publication of 11/30/94, see a copy attached)

Code Name/Number:  
Chem. Type/Ther. Class:

AD 32  
1P

**PHARMACOL. CATEGORY/INDICATION:**

Inhibitor of topoisomerase II and RNA synthesis/  
Treatment of carcinoma in situ of the urinary bladder

**DOSAGE FORM:**

Sterile solution, Single use vial

**STRENGTHS:**

200mg/5ml/vial(40mg/ml)

**ROUTE OF ADMINISTRATION:**

Intravesical Instillation

**DISPENSED:**

Rx       OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):**

**CAS Name:** Pentanoic acid, (2S-cis)-2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[[2,3,6-trideoxy-3-[(trifluoroacetyl)amino]-α-L-*hxo*-hexapyranosyl]oxy]-2-naphthacenyl]-2-oxoethyl ester

**IUPAC Name:** (8s,10s)-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-*hxo*-hexapyranosyl]oxy]-5,12-naphthacenedione-8-valerate

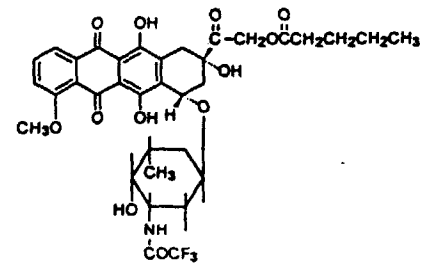
**Common Name:** N-Trifluoroacetyladriamycin-14-valerate

**CAS Number:** 56124-62-0

**Code Number:** AD 32; NSC-246131

**M.F.:** C<sub>24</sub>H<sub>36</sub>F<sub>3</sub>NO<sub>13</sub>

**M.W.:** 723.65



SUPPORTING DOCUMENTS:

INDs: IND

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		6/24/97	manufacture of Valrubicin	Pending for review		Reviewed by HFD-150
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		6/4/97	Rubber stopper	Adequate	5/10/93	Reviewed by HFD-635

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

*EER for sites, submitted on 1/27/98, Pending*  
*Trademark consultation, will be initiated*  
*Micro consultation, initiated on 1/22/98, Pending*  
*Environmental assessment, exemption is requested.*  
*Stability data, will be initiated when the data is submitted*  
*Method validation will be initiated after satisfactory response to deficiencies regarding method validation.*

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

CMC deficiencies were noted in this application. The deficiencies indicated in the draft letter should be forwarded to the applicant.

*/s/*

Sung K. Kim, Ph.D.,  
 Review Chemist, HFD-150

cc:

Orig. NDA 20-892  
 HFD-150/Division File  
 HFD-150/SKim

HFD-150-/AStaten

HFD-150/RWood

R/D Init. by: 4-29-98

filename: N20892.org