

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020759/020760**

**CHEMISTRY REVIEW(S)**

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

*Katagene*

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-760

CHEM. REVIEW #: 2

REVIEW DATE: 10/15/97

SUBMISSION/TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

AMENDMENT

10/3/97

NAME & ADDRESS OF APPLICANT:

Pfizer Central Research  
Medical Research Laboratory  
Eastern Point Road  
Groton, Connecticut 06340

DRUG PRODUCT NAME

Proprietary:

Trovan I.V.

Nonproprietary/USAN:

Alatrofloxacin Mesylate,  
Alatrofloxacin Injection

Code Names/#'s:

CP-116,517-27

Chemical Type:

1S

Therapeutic Class:

ANDA Suitability Petition/DESI/Patent Status:

N/A [if applicable]

APPROVED BY  
GISHWILL

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: Aqueous Concentrate Injection

STRENGTHS: 5 mg/mL, 100 mg, 200 mg, and 300 mg

ROUTE OF ADMINISTRATION: Intravenous Infusion

DISPENSED:

Rx

OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Structural Formula:

The structural formula of alatrofloxacin mesylate is given below:

APPROVED BY

Molecular Formulae and Weights

Molecular Formula of Alatrofloxacin Mesylate:  $C_{26}H_{25}F_3N_6O_5 \cdot CH_3SO_3H$

Molecular Formula of Alatrofloxacin:  $C_{26}H_{25}F_3N_6O_5$

Molecular Weight of Alatrofloxacin Mesylate: 654.62

Molecular Weight of Alatrofloxacin: 558.52

Nomenclature

Chemical Abstracts Services Name: (1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-L-alanyl-N-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate

APPROPRIATE  
ON SEP 11

Chemical Abstracts Services Number: [157605-25-9]

I.N.N.: alatrofloxacin

Proposed Proprietary or Trade Name: TROVAN® injection

U.S.A.N.: alatrofloxacin mesylate

W.H.O. or B.A.N.: alatrofloxacin mesylate

Laboratory Code

Pfizer Laboratory Code: CP-116,517-27

APPROPRIATE  
ON SEP 11

**8**

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APPEARS THIS WAY  
ON ORIGINAL

**CONCLUSION:**

The NDA may be approved from the chemistry, manufacturing and control point of view. The following items are acceptable.

- NOTE:**
1. EER is acceptable
  2. Trade name approved
  3. EA-FONSI has been issued
  4. All chemistry deficiencies hve been answered satisfactorily
  6. Sterility review has been completed by HFD-805 and found acceptable, 7/3/97.

APPEARS THIS WAY  
ON ORIGINAL

/S/

11/26/97

B. Vithal Shetty, Ph.D.  
Review Chemist

- cc: Orig. NDA 20-760  
HFD-520/Division File  
HFD-520/BVShetty  
HFD-590/MO/Alivisatos  
HFD-590/Pharm/Hastings  
HFD-590/Micro/Lard  
HFD-590/CSO/Fogarty  
HFD-520/DKatague  
R/D Init by: DKatagu

**APPEARS THIS WAY  
ON ORIGINAL**

/S/

11/26/97

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

AUG 28 1997

Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-760

**CHEM. REVIEW #:** 1

**REVIEW DATE:** 7/1/97

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	12/27/96	1/02/97	6/27/97

**NAME & ADDRESS OF APPLICANT:** Pfizer Central Research  
 Medical Research Laboratory  
 Eastern Point Road  
 Groton, Connecticut 06340

**DRUG PRODUCT NAME**

**Proprietary:** Trovan I.V.  
**Nonproprietary/USAN:** Alatrofloxacin Mesylate,  
 Alatrofloxacin Injection  
**Code Names/#'s:** CP-116,517-27  
**Chemical Type:** 1S  
**Therapeutic Class:**

APPROVED FOR  
 06/27/97

**ANDA Suitability Petition/DESI/Patent Status:**

**PHARMACOLOGICAL CATEGORY/INDICATION:**

APPROVED FOR  
 06/27/97

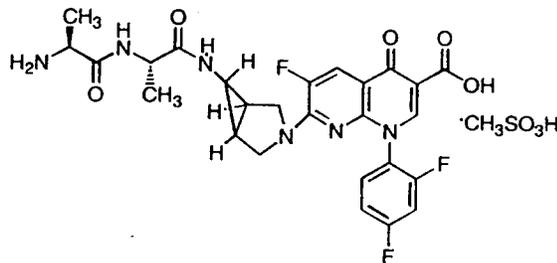
**DOSAGE FORM:** Aqueous Concentrate Injection  
**STRENGTHS:** 5 mg/mL, 100 mg, 200 mg, and 300 mg  
**ROUTE OF ADMINISTRATION:** Intravenous Infusion  
**DISPENSED:**  Rx  OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**

**Structural Formula:**

APPROVED FOR  
 06/27/97

The structural formula of alatrofloxacin mesylate is given below:



APPROVED FOR  
 06/27/97

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Molecular Formulae and Weights

Molecular Formula of Alatrofloxacin Mesylate:  $C_{26}H_{25}F_3N_6O_5 \cdot CH_3SO_3H$   
Molecular Formula of Alatrofloxacin:  $C_{26}H_{25}F_3N_6O_5$   
Molecular Weight of Alatrofloxacin Mesylate: 654.62  
Molecular Weight of Alatrofloxacin: 558.52

Nomenclature

Chemical Abstracts Services Name: (1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-L-alanyl-N-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate  
Chemical Abstracts Services Number: [157605-25-9]  
I.N.N.: alatrofloxacin  
Proposed Proprietary or Trade Name: TROVAN® injection  
U.S.A.N.: alatrofloxacin mesylate  
W.H.O. or B.A.N.: alatrofloxacin mesylate

Laboratory Code

Pfizer Laboratory Code: CP-116,517-27

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**SUPPORTING DOCUMENTS:**

IND  
IND

ADDITIONAL

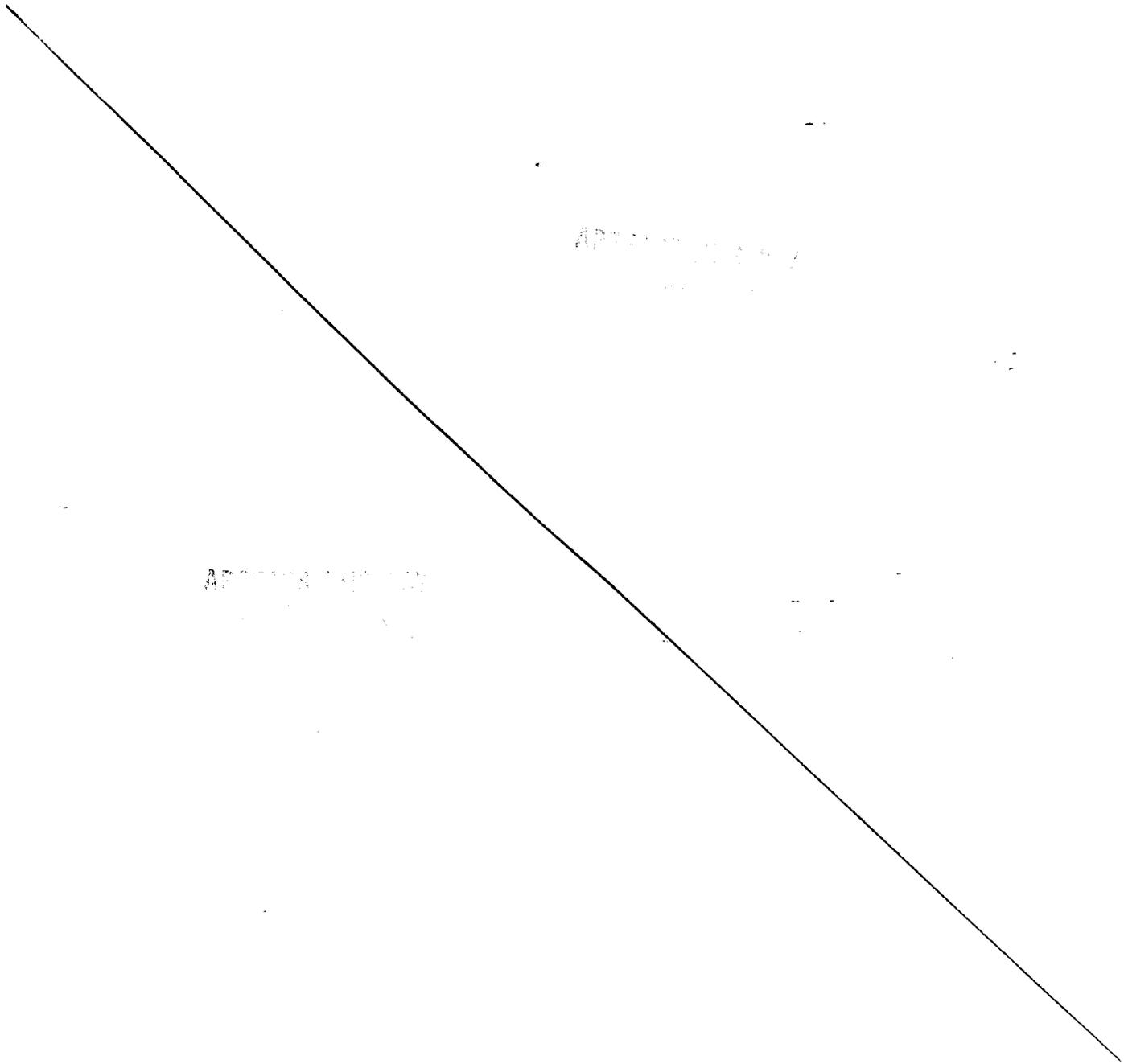
APPROPRIATE  
ON CHEMISTRY

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**RELATED DOCUMENTS (if applicable):**

NDA 20-759 (Trovafloracin Mesylate Tablet)

This NDA was submitted simultaneously with NDA 20-759. It is being reviewed at present.



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CONSULTS:

1. Environmental Assessment
  
3. The trade name, TROVAN I.V., has already been approved.
  
5. EER - The EER dated 6/9/97 was found to be acceptable.

REMARKS/COMMENTS:

Alatrofloxacin is a fluoronaphthyridone derivative, structurally similar to, and with a comparable mechanism of action to the fluoroquinolone class of antibacterial agents.

APPROVED THIS WAY  
BY ORIGINAL

APPROVED THIS WAY  
BY ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505 (or 507 for an antibiotic) of the Act.

131 /S/ 8/27/97

B. Vithal Shetty, Ph.D.  
Review Chemist

cc: Orig. NDA 20-760  
HFD-520/Division File  
HFD-520/BVShetty  
HFD-520/MO/Alivisatos  
HFD-520/Pharm/Hastings  
HFD-520/Micro/Lard  
HFD-520/CSO/Fogarty  
HFD-520/DKatague  
R/D Init by: DKatague/S/ 8/28/97

APPROVED FOR SIGNATURE  
DATE

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

OCT 20 1997

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-759

CHEM. REVIEW #: 2

REVIEW DATE: 9/22/97

SUBMISSION/TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

AMENDMENT/AC

10/09/97

NAME & ADDRESS OF APPLICANT:

Pfizer Central Research  
Eastern Point Road  
Groton, Connecticut 06340

DRUG PRODUCT NAME

Proprietary:

Trovan

Nonproprietary/USAN:

Trovafloxacin Mesylate

Code Names/#'s:

CP-99,219-27

Chemical Type:

1S

Therapeutic Class:

Quinolone, antibacterial

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOLOGICAL CATEGORY/INDICATION:

APPROVED  
ORIGINAL

DOSAGE FORM: Tablets

STRENGTHS: 100 and 200 mg

ROUTE OF ADMINISTRATION: Oral

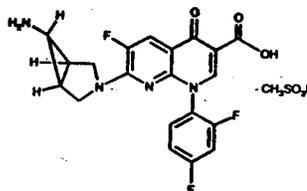
DISPENSED:

Rx  OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Structural Formula:

The structural formula of trovafloxacin mesylate is given below:



Molecular Formulae and Weights

Molecular Formula of Trovafloxacin Mesylate:  $C_{20}H_{15}F_3N_4O_3 \cdot CH_3SO_3H$

Molecular Formula of Trovafloxacin:  $C_{20}H_{15}F_3N_4O_3$

Molecular Weight of Trovafloxacin Mesylate: 512.46

Molecular Weight of Trovafloxacin: 416.36

APPROVED  
ORIGINAL

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APPROVED  
DATE

**CONCLUSION:**

The NDA may be approved from the chemistry, manufacturing and control point of view. The following items are acceptable.

**NOTE:**

1. EER is acceptable
2. FONSI has been issued
3. All chemistry deficiencies have been answered satisfactorily
4. Trade name has been approved.

APPROVED  
DATE

**PENDING:**

APPROVED  
DATE

/S/

10/8/97

B.Vithal Shetty, Ph.D.  
Review Chemist

- cc: Orig. NDA 20-795  
HFD-590/Div. Files  
HFD-520/Shetty  
HFD-590/Albrecht  
HFD-590/Alivisatos  
HFD-590/Hastings  
HFD-590/Schmuff  
HFD-520/Katague  
HFD-590/Lard  
HFD-590/Fogarty  
R/D Init by: DKatague

APPROVED  
DATE

/S/ 10/20/97



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Nomenclature

<u>Chemical Abstracts Services Name:</u>	(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate
<u>Chemical Abstracts Services Number:</u>	[147059-75-4]
<u>I.N.N.:</u>	trovafloxacin
<u>Proposed Proprietary or Trade Name:</u>	TROVAN®
<u>U.S.A.N.:</u>	trovafloxacin mesylate
<u>W.H.O. or B.N.F.:</u>	trovafloxacin mesylate

Laboratory Code

<u>Pfizer Laboratory Code:</u>	CP-99,219-27
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**SUPPORTING DOCUMENTS:**

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**RELATED DOCUMENTS (if applicable):**

NDA 20-760

**CONSULTS:**

3. Trade Name, TROVAN, already approved.
4. EER - Requested on January 29, 1997. It was found to be acceptable.

**REMARKS/COMMENTS:**

Trovafloxacin is a fluoronaphthyridone derivative similar to, and with a comparable mechanism of action to the fluoroquinolone class of antibacterial agents. The tablets are 100 and 200 mg in weight. The firm states that Trovan has demonstrated activity against certain resistant pathogens including penicillin-resistant streptococcus pneumonia and methicillin-resistant staphylococcus aureus. It is stated that this is the only antibacterial agent (trovan) to date that can be administered orally for the treatment of infections caused by these pathogens including serious infections of the respiratory tract, epidemic meningococcal meningitis in children and for the prophylaxis of infection following abdominal or vaginal hysterectomy.

**CONCLUSIONS & RECOMMENDATIONS:**

The application is not approvable for manufacturing and controls under section 505 (or 507 for an antibiotic) of the Act. Specific items which are not approvable are identified under the

following headings: Synthesis, Controls, Drug Product, Stability, Environmental Assessment, Methods Validation, and Labeling.

*IS/*

*7/21/97*

B. Vithal Shetty, Ph.D.  
Review Chemist

cc: Orig. NDA 20-759  
HFD-520/Division File  
HFD-520/BVShetty  
HFD-520/MO/ *Alivisatos*  
HFD-520/Pharm/ *Hastings*  
HFD-520/Micro/ *David*  
HFD-520/CSO/ *Fogarty*  
HFD-520/DKatague  
R/D Init by: DKatague

*IS/ 8/11/97*

APPROVED FOR  
SUBMISSION