CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050762

CHEMISTRY REVIEW(S)

JUN 22 1998

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 50-762

CHEMISTRY REVIEW #: 1 **DATE REVIEWED:** June 9, 1998

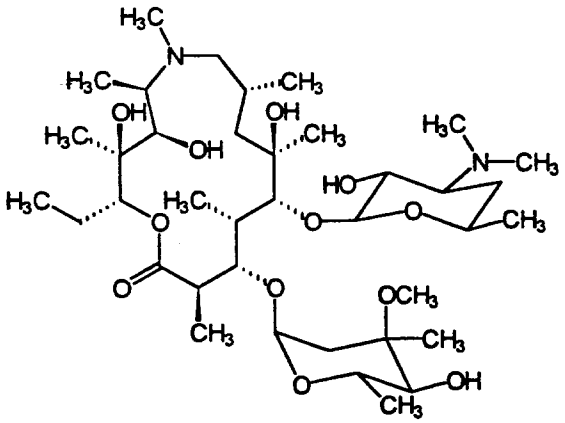
SUBMISSION	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	December 19, 1997	December 22, 1997	January 8, 1998
Amendment	February 27, 1998	March 3, 1998	March 5, 1998

NAME & ADDRESS OF SPONSOR: Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

DRUG PRODUCT NAME
Proprietary: ZITHROMAX®/TROVAN® Compliance Pack
Nonproprietary: azithromycin/trovafloxacin
Code Name/#:

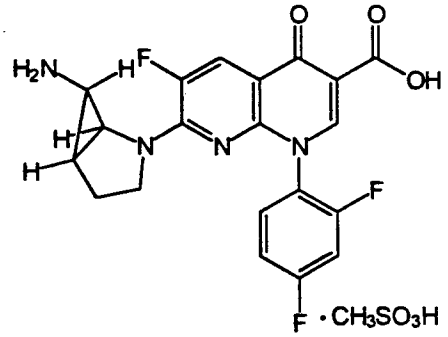
PHARMACOLOGICAL CATEGORY: Antimicrobial
INDICATION: Treatment of sexually transmitted diseases
DOSAGE FORM/STRENGTH: Oral suspension/tablet; 1 gram suspension/100 mg tablet
ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:



Azithromycin

[2*R*-(2*R**,3*S**,4*R**,5*R**,8*R**,10*R**,11*R**,12*S**,13*S**,14*R**)]-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L*-ribo-hexopyranosyl)-oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one



Trovafloxacin

(1α,5α,6α)-7-(6-amono-3-azabicyclo[3.1.0]hex-3-yl)1-(2,4-difluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate

MOLECULAR FORMULA: Azithromycin, $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$
Trovafloxacin, $C_{20}H_{15}F_3N_4O_3 \cdot CH_3SO_3H$

MOLECULAR WEIGHT: Azithromycin, 785.00
Trovafloxacin, 512.46

CAS REGISTRY NUMBERS: Azithromycin, 83905-01-5
Trovafloxacin mesylate 147059-75-4

SUPPORTING DOCUMENTS: NDA 50-693 (Azithromycin)
NDA 20-759 (Trovafloxacin)

RELATED DOCUMENTS:

REMARKS/COMMENTS: This NDA requests approval to market a dual treatment package containing one 1 g single dose of Zithromax® and one 100 mg tablet of Trovan® for treatment of gonorrhea and chlamydia. Both products are currently approved, and CMC information on both products is incorporated by reference to the respective NDA. The sponsor does not request any changes in formulation or primary packaging of either component. Each drug in its current primary packaging will be packaged into the compliance pack.

A claim for categorical exclusion from environmental assessment was submitted in the amendment dated February 27, 1998. Although this application is likely to increase the patient population using these drugs, actual use will is not likely to change significantly since many patients will be switching from single drug therapy. In addition, Pfizer has estimated that the concentration of the drug substances at the point of entry into the aquatic environment will be The request for exclusion is acceptable.

CONCLUSIONS & RECOMMENDATIONS

This NDA may be approved from a chemistry viewpoint.

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/S/ 6-15-98
Gene W. Holbert, Ph.D., Review Chemist

Concurrence:
HFD-590/Nschmutt /S/ 6/22/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050762

PHARMACOLOGY REVIEW(S)

AUG 1 3 1998

PHARMACOLOGIST'S REVIEW

NDA 50-762
Date Received: 12/19/97
Date Assigned: 1/7/98
Date Report Completed: 5/22/98
HFD-590

Sponsor: Pfizer Pharmaceutical Group
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

Drug: Trovan®/Zithromax® Compliance Pak for STDs
[trovafloxacin mesylate, 100 mg tablet/azithromycin, 1 g for oral suspension]

Related Documents: NDA 20-759
NDA 50-693
NDA 50-670
NDA 20-760

Proposed Use: Treatment of gonococcal and non-gonococcal urethritis and cervicitis.

BACKGROUND

Trovan® (trovafloxacin) and Zithromax® (azithromycin) are approved drug products for a broad-spectrum of infectious indications. In the current submission a single oral administration of 100 mg of trovafloxacin and 1g azithromycin is proposed to treat gonococcal and non-gonococcal urethritis and cervicitis. Trovafloxacin is a fluoronaphthyridone (structurally similar to fluoroquinolones) and is effective against *Neisseria gonorrhoeae*. Azithromycin is an azalide sub-class of macrolides (structurally similar to erythromycin) and is effective against *Chlamydia trachomatis*. The proposed dosing regimen is consistent with approved dose administration protocols for each compound.

No evaluable nonclinical pharmacology and toxicology reports were included in the NDA submission, however, the referenced NDA's for trovafloxacin and azithromycin contained the essential nonclinical studies and were extensively reviewed in the Pharmacologist's Reports on NDA 20-759 and 50-693.

EVALUATION AND CONCLUSION

No regulatory action is required based upon the material provided in this submission.

/S/

Stephen G. Hundley, Ph.D. 5/26/98

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Concurrences:
HFD-590 / R. Albrecht / DDD /S/ 8/13/98
HFD-590 / K. Hastings / TL /S/ 7/26/98

Disk:
HFD-590 / K. Hastings

cc:
HFD-590 / Original NDA
HFD-590 / Division File
HFD-345
HFD-590 / CSO / R. Anderson
HFD-590 / MO / R. Alivisatos
HFD-590 / Pharm / S. Hundley
HFD-590 / Micro / P. Dionne
HFD-590 / Chem / G. Holbert
HFD-590 / Stat / L. Shen
HFD-590 / Biopharm / P. Colangelo

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APPLICATION NUMBER: 050762

STATISTICAL REVIEW(S)

590 Anderson

MAY 18 1998

Statistical Review and Evaluation

NDA:	50-762
Drug Name:	TROVAN/ZITHROMAX (trovafloxacin tablets and azithromycin for oral suspension)
Applicant:	Pfizer
Indications:	Treatment of sexually transmitted disease
Documents Reviewed:	NDA volumes 1.1, 1.9 dated December 22, 1997
Medical Officer:	Regina Alivisatos, M.D., HFD-590

1. Background

NDA 50-762 is submitted for approval of a dual treatment pack consisting of a single 100 mg TROVAN (trovafluxacin) tablet and a 1 gram single dose packet of Zithromax (azithromycin for oral suspension) for sexually transmitted disease. The product as a single dose regimen will treat patients with acute gonococcal urethritis/cervicitis due to *Neisseria gonorrhoeae* and non-gonococcal urethritis/cervivitis due to *Chlamydia trachomatis*.

Trovaflaxcin (tablets) is approved by the FDA (NDA 20-759) for a wide variety of infections including gonorrhea. Zithromax for oral suspension is approved as a 1 gram dose for the treatment of patients with non-gonococcal urethritis/cervivitis due to *Chlamydia trachomatis* (NDA 50-693). Based on the applicant's estimate, approximately of male patients and of female patients diagnosed with urethritis/cervicitis due to *Neisseria gonorrhoeae* also are infected with *Chlamydia trachomatis*. The applicant proposed that the dual therapy with a single dose of 100 mg trovaflocin plus 1 gm azithromycin, administrated simultaneously, would provide single dose treatment for both infections.

The applicant was requested to perform a pharmacokinetic study to assess the effect of azithromycin on the absorption of trovafloxacin. The applicant was also requested to provide safety information in 20 subjects receiving the 1 gram ZITHROMAX Single Dose Packet and a single 100 mg TROVAN tablet concomitantly. To fulfill these requests, the applicant conducted an open, randomized. crossover bioavailability study (Protocol 154-056) in 20 healthy, fasted volunteers. On one occasion, they received the 100 mg trovafloxacin tablet alone and on another occasion they received the 100 mg trovafloxacin coadministered with 1 gram of azithromycin based on a randomization schema. The washout period was at least 14 days between two treatments.

2. Statistical Comments

Based on the information from the background, no clinical efficacy data were submitted for this NDA. Pharmacokinetic analysis will be addressed in the Bio-pharmaceutic review. Safety issues related to this application are addressed in the clinical review. No statistical review was felt to be necessary. For further elucidation, please refer to the appropriate reviews.

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/S/

Liji Shen, Ph.D.
Biostatistician, DBIV

/S/

Concur: _____ 5/18/98
Aloka Chakravarty, Ph.D.
Acting Team Leader, DBIV

cc:
Archival: NDA 50-762
HFD-590
HFD-590/Dr. Goldberger
HFD-590/Ms. Anderson
HFD-590/Dr. Alivisatos
HFD-590/Dr. Leissa
HFD-590 Dr. Albrecht
HFD-725/Dr. Chakravarty
HFD-725/Dr. Shen
HFD-725/Dr. Huque
HFD-725/Chron.

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This review contains 2 pages.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050762

MICROBIOLOGY REVIEW(S)

DEC 2 1998

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA#: 50-762	**REVIEWER:**	Peter A. Dionne
	CORRESPONDENCE DATE:	17-DEC-97
	CDER RECEIPT DATE:	19-DEC-97
	REVIEW ASSIGN DATE:	05-JAN-98
	REVIEW COMPLETE DATE:	22-JAN-98

SPONSOR: Pfizer Pharmaceuticals
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

CONTACT PERSON: Robert B. Clark
Associate Director/Group Leader
Drug Regulatory Affairs
Phone Number: (212) 573-1563

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SUBMISSION REVIEWED: Original NDA submission

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Dual treatment pack for acute gonococcal urethritis/cervicitis due to *Neisseria gonorrhoeae* and non-gonococcal urethritis/cervicitis due to *Chlamydia trachomatis*.

DOSAGE FORM: Trovafloxacin: 100 mg tablets
Azithromycin: 1-gram single dose packet

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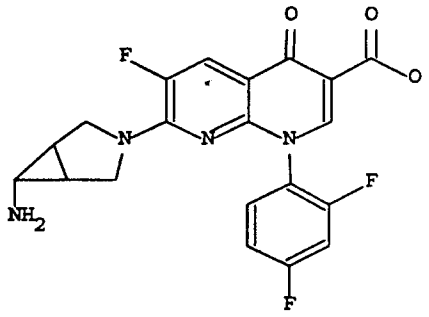
DRUG PRODUCT NAME

PROPRIETARY: TROVAN™ Tablets
NONPROPRIETARY/USAN: Trovafloxacin mesylate tablets
CODE:
CHEMICAL NAME: (1", 5", 6")-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.

STRUCTURAL FORMULA:



$\bullet CH_3SO_3H$

Molecular Formula: $C_{20}H_{15}F_3N_4O_3CCH_3SO_3H$
Molecular Weight: 512.46

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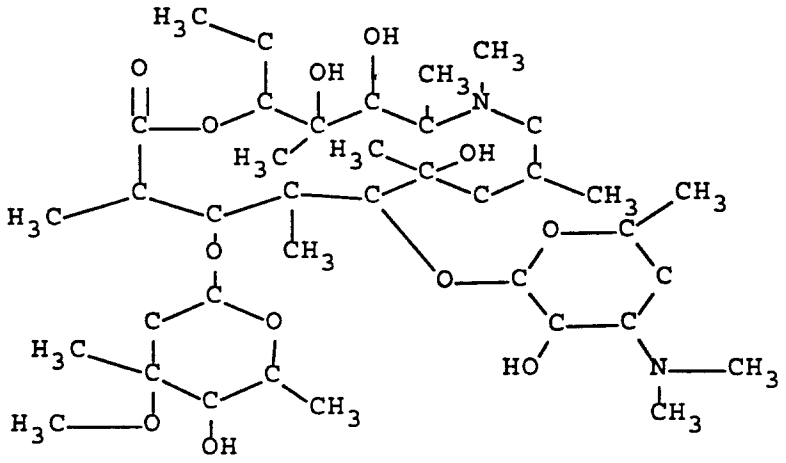
PROPRIETARY: ZITHROMAX[7] for Oral Suspension
NONPROPRIETARY/USAN: Azithromycin for Oral Suspension
CODE:
CHEMICAL NAME: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-((3,4,6-trideoxy- 3-(dimethylamino)-beta-D-Xylo- hexopyranosyl)oxy)-1-oxa-6-azacyclopentadecan- 15-one.
STRUCTURAL FORMULA:



Molecular Formula: $C_{38}H_{72}N_2O_{12}$
Molecule Weight: 749.0

SUPPORTING DOCUMENTS:

NDA 20-759--Trovafloxacin Tablets approved 12/18/97
NDA 50-693- Azithromycin for Oral Suspension approved 9/28/94

BACKGROUND:

This NDA requests approval of a dual treatment pack consisting of a single 100 mg trovafloxacin tablet and a one gram single dose packet of azithromycin for oral suspension. The product is to be used as a single dose regimen in patients with acute gonococcal urethritis/cervicitis due to *Neisseria gonorrhoeae* and non-gonococcal urethritis/cervicitis due to *Chlamydia trachomatis.*

Trovafloxacin is approved for uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in females (single 100 mg oral dose) and for cervicitis due to *Chlamydia trachomatis* (200 mg oral dose for 5 days). Trovafloxacin was somewhat less effective than doxycycline in males with nongonococcal urethritis.

Azithromycin is approved for non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis* (single 1 gram dose).

The dual treatment pack will allow a one dose treatment for patients with urethral and/or cervical coinfections of *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*

No changes are proposed for the microbiology labeling section of either drug product.

The only microbiological aspect of this application was to determine by *in vitro* testing if the presence of one drug affected the MIC value of the other drug when the two drugs were both present. Susceptibility testing of both organisms was performed using both drugs in combination by the checkerboard method.

Chlamydia trachomatis isolates from 20 patients were assayed. Eighty-one combinations of drug concentrations were tested using the checkerboard method. Isolates were grown in McCoy cell monolayers on glass coverslips. The inoculum was adjusted to inclusion forming units (IFU) per high power field. The antibiotics were diluted in Eagle's minimum essential medium, to give azithromycin concentrations ranging Trovafloxacin was tested at concentrations of These concentrations were chosen because they included the MIC range of both drugs for *Chlamydia trachomatis.* Antibiotic concentrations were prepared at 2X the working dilution. The two antibiotics were combined in equal volumes. Inclusions were detected by fixing cultures with methanol followed by fluorescent antibody staining. For chlamydia, the minimum inhibitory concentration (MIC) at which there was a 90% reduction in IFU (MIC_{90}) was determined by comparing the number of IFU in the antibiotic-free well with the number of IFU at each concentration of azithromycin and trovafloxacin. The MIC_{100} was defined as the concentration at which there were no inclusions. The concentrations that met these criteria were plotted for each isolate.

Table 1 shows the concentrations of the two drugs tested against *Chlamydia trachomatis.*

TABLE 1
Concentrations tested against *Chlamydia*
Azithromycin concentration/Trovafloxacin concentration

0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0	0	0	0	0	0	0	0	0
0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004
0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008
0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016
0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0.031	0.031	0.031	0.031	0.031	0.031	0.031	0.031	0.031
0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0.063	0.063	0.063	0.063	0.063	0.063	0.063	0.063	0.063
0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
0	0.016	0.031	0.063	0.125	0.25	0.5	1	2
0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

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Isolates of *Neisseria gonorrhoeae* from 20 patients were also tested. Azithromycin was diluted in methanol to 1 mg/mL. Subsequent dilutions were made in water. All trovafloxacin dilutions were in water. Azithromycin was assayed in a range of and trovafloxacin was tested from . These concentrations were chosen because they included the MIC range of both drugs for *Neisseria gonorrhoeae*.

For this study drug dilutions were performed in GC agar with Supplement B at 1%. The desired concentration of azithromycin was added to each liter of agar. To 250 mL of azithromycin-containing agar, the highest concentration of trovafloxacin was added. Subsequent serial two-fold dilutions were prepared by adding 125 mL of agar with the highest concentration of trovafloxacin to 125 mL of agar containing only azithromycin. Agar was then immediately poured into plates. Isolates were plated using a dispenser to place approximately 50 μL of suspension containing *Neisseria gonorrhoeae* on each of the 36 plates containing different drug concentrations. The plate containing no antibiotic was plated last to verify isolate growth. Plates were incubated in 5% CO_2 at 37°C for 48 hours. All growth was recorded as positive. The MIC was the concentration at which there was no visible growth.

The Fractional Inhibitory Concentrations (FIC) were determined for all MICs and were less than 2 in all cases. This indicates that there was no antagonism between the two drugs.

Table 2 shows the concentrations of both drugs used to test *Neisseria gonorrhoeae*.

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TABLE 2
Concentrations assayed against *Neisseria gonorrhoeae*
Azithromycin concentration/Trovafloxacin concentration

0	0.125	0.25	0.5	1	2
0	0	0	0	0	0
0	0.125	0.25	0.5	1	2
0.00125	0.00125	0.00125	0.00125	0.00125	0.00125
0	0.125	0.25	0.5	1	2
0.0025	0.0025	0.0025	0.0025	0.0025	0.0025
0	0.125	0.25	0.5	1	2
0.005	0.005	0.005	0.005	0.005	0.005
0	0.125	0.25	0.5	1	2
0.01	0.01	0.01	0.01	0.01	0.01
0	0.125	0.25	0.5	1	2
0.02	0.02	0.02	0.02	0.02	0.02

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RESULTS:

The addition of trovafloxacin did not raise the MIC of azithromycin for *Chlamydia trachomatis*. Azithromycin is the drug in the combination pack that is approved as a one dose regimen for treatment of *Chlamydia trachomatis*. For all 20 isolates, measurement of the MIC_{100} (concentration at which there were no inclusions) showed a synergistic interaction between azithromycin and trovafloxacin. All isolate plots were represented by one pattern of interaction (shown in Figure 1). Measurement of the MIC_{90} (minimum inhibitory concentration at which there was a 90% reduction in the number of inclusions compared to the number in the antibiotic-free well) showed a synergistic interaction between azithromycin and trovafloxacin for 15 isolates with two patterns (Figures 2 and 3). Measurement of the MIC_{90} of the remaining 5 isolates appeared to show no interaction between the two antibiotics (Figure 4).

The addition of azithromycin did not increase the MIC of trovafloxacin for *Neisseria gonorrhoeae*. Trovafloxacin is the drug in the combination pack that is approved as a one dose regimen for *Neisseria gonorrhoeae*. For 12 isolates, the measurement of MIC showed a synergistic interaction between azithromycin and trovafloxacin with two patterns (Figures 5 and 6). The MIC measurement for the remaining 8 isolates showed no interaction between the two drugs (Figure 7)

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CONCLUSIONS & RECOMMENDATIONS:

For the two organisms involved in the indications for this product, trovafloxacin and azithromycin appear to work *in vitro* with some degree of synergy for many isolates and with indifference for the other isolates tested. No antagonism was seen. *In vitro* testing, however, may not always predict how the drugs will react together in the clinical setting.

From the microbiological viewpoint the product should be approved.

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APPEARS THIS WAY

/S/

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:
HFD-590/Div Dir /S/ Signature 12/2/98 Date
HFD-590/TLMicro /S/ Signature 12/2/98 Date

duplicate — original misplaced (ra)

CC:
HFD-590/Original NDA # 50-762
HFD-590/Division File
HFD-590/TLMicro/SLard-Whiteford
HFD-590/Micro/PDionne
HFD-590/MO/RAlivisatos
HFD-590/Pharm/SHundley
HFD-590/CSO/RAnderson
HFD-590/Chem/GHolbert

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