

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-007
21-039

CHEMISTRY REVIEW(S)

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: **21,039**

CHEMISTRY REVIEW #: 1

DATE REVIEWED: 18-Nov-98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	29-Oct-98	30-Oct-98	17-Nov-98
Amendment	7-Dec-98	8-Dec-98	8-Dec-98
Amendment	17-Mar-99		

NAME / ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

DRUG PRODUCT NAME

<u>Proprietary:</u>	AGENERASE™ Oral Solution
<u>Nonproprietary:</u>	amprenavir oral solution
<u>Code Name/#:</u>	141W94

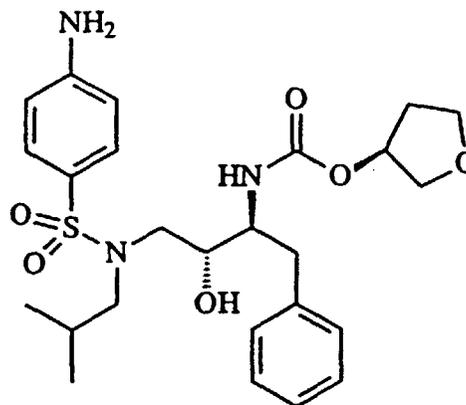
<u>PHARMACOLOGICAL CATEGORY:</u>	Antiviral
<u>INDICATION:</u>	Anti-HIV
<u>DOSAGE FORM/STRENGTH:</u>	Oral solution, 15 mg/mL
<u>ROUTE OF ADMINISTRATION:</u>	Oral

CHEMICAL NAME / STRUCTURAL FORMULA:

(3S)-tetrahydro-3-furyl N-[(1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate

Registry Number [161814-49-9]

C₂₅H₃₅N₃O₆S Formula Weight: 505.64



CONCLUSIONS & RECOMMENDATIONS:

The NDA submission and accompanying amendments provide adequate information on the chemistry, manufacturing and controls for AGENERASE™ (amprenavir) oral solution and the manufacturing facilities have acceptable cGMP status. The NDA, as amended, is therefore recommended for approval from the chemistry perspective.

151

Concurrence:
HFD-530/Smiller

George Lunn, Ph.D.
Review Chemist

cc:

Orig. NDA 21-039
HFD-530/Div. File
HFD-530/GLunn
HFD-530/Smiller

HFD-530/MTruffa
HFD-530/TCvetkovich
HFD-530/OMcMaster
HFD-530/NBattula

HFD-530/Biopharm
HFD-530/Stat
HFD-830/CChen

File: \

**APPEARS THIS WAY
ON ORIGINAL**

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: **21,007**

CHEMISTRY REVIEW #: 1

DATE REVIEWED: 2-Sep-98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	27-Jul-98	28-Jul-98	3-Aug-98
Amendment	1-Oct-98	5-Oct-98	23-Oct-98
Amendment N-008	12-Oct-98	13-Oct-98	23-Oct-98
Amendment	2-Dec-98	4-Dec-98	8-Dec-98
Amendment	9-Dec-98		
Amendment	16-Dec-98		
Amendment	22-Feb-99		
Amendment	17-Mar-99		
Amendment	24-Mar-99		

NAME / ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

DRUG PRODUCT NAME

Proprietary: AGENERASE™ Capsules
Nonproprietary: amprenavir capsules
Code Name/#: 141W94

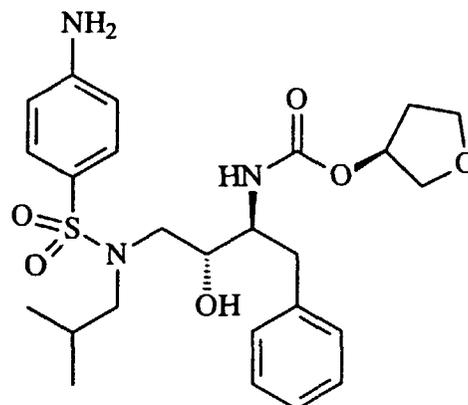
PHARMACOLOGICAL CATEGORY: Antiviral
INDICATION: Anti-HIV
DOSAGE FORM/STRENGTH: Soft Gelatin Capsules, 50 mg and 150 mg
ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME / STRUCTURAL FORMULA:

(3S)-tetrahydro-3-furyl N-[(1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate

Registry Number [161814-49-9]

C₂₅H₃₅N₃O₆S Formula Weight: 505.64



CONCLUSIONS & RECOMMENDATIONS:

The NDA submission and accompanying amendments provide adequate information on the chemistry, manufacturing and controls for AGENERASE™ (amprenavir) capsules and the manufacturing facilities have acceptable cGMP status. The NDA ~~as amended~~ is therefore recommended for **approval** from the chemistry perspective.

1/51

Concurrence:
HFD-530/Smiller

George Lunn, Ph.D.
Review Chemist

cc:

Orig. NDA 21-007
HFD-530/Div. File
HFD-530/GLunn
HFD-530/SMiller

HFD-530/AZeccola
HFD-530/TCvetkovich
HFD-530/OMcMaster
HFD-530/NBattula

HFD-530/Biopharm
HFD-530/Stat
HFD-830/CChen

File:

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

20 pages

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: **21,007**

CHEMISTRY REVIEW #: 1

DATE REVIEWED: 2-Sep-98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	27-Jul-98	28-Jul-98	3-Aug-98
Amendment	1-Oct-98	5-Oct-98	23-Oct-98
Amendment N-008	12-Oct-98	13-Oct-98	23-Oct-98
Amendment	2-Dec-98	4-Dec-98	8-Dec-98
Amendment	9-Dec-98		
Amendment	16-Dec-98		
Amendment	22-Feb-99		
Amendment	17-Mar-99		
Amendment	24-Mar-99		

NAME / ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

DRUG PRODUCT NAME

<u>Proprietary:</u>	AGENERASE™ Capsules
<u>Nonproprietary:</u>	amprenavir capsules
<u>Code Name/#:</u>	141W94

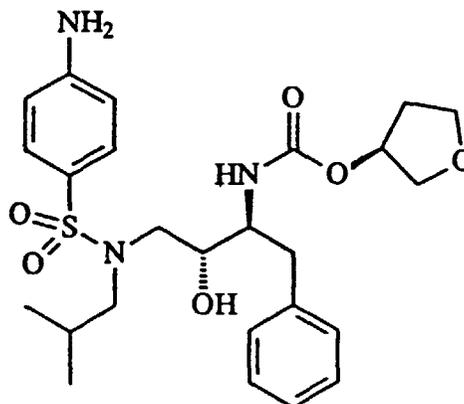
<u>PHARMACOLOGICAL CATEGORY:</u>	Antiviral
<u>INDICATION:</u>	Anti-HIV
<u>DOSAGE FORM/STRENGTH:</u>	Soft Gelatin Capsules, 50 mg and 150 mg
<u>ROUTE OF ADMINISTRATION:</u>	Oral

CHEMICAL NAME / STRUCTURAL FORMULA:

(3S)-tetrahydro-3-furyl N-[(1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate

Registry Number [161814-49-9]

C₂₅H₃₅N₃O₆S Formula Weight: 505.64



CONCLUSIONS & RECOMMENDATIONS:

The NDA submission and accompanying amendments provide adequate information on the chemistry, manufacturing and controls for AGENERASE™ (amprenavir) capsules and the manufacturing facilities have acceptable cGMP status. The NDA, as amended, is therefore recommended for approval from the chemistry perspective.

151

Concurrence:
HFD-530/Smiller

George Lunn, Ph.D.
Review Chemist

cc:

Orig. NDA 21-007
HFD-530/Div. File
HFD-530/GLunn
HFD-530/SMiller

HFD-530/AZeccola
HFD-530/TCvetkovich
HFD-530/OMcMaster
HFD-530/NBattula

HFD-530/Biopharm
HFD-530/Stat
HFD-830/CChen

File: \

APPEARS THIS WAY
ON ORIGINAL

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

54 pages

Application: NDA 21039/000 Action Goal:
Stamp: 08-DEC-1998 District Goal:
Regulatory Due: 08-JUN-1999 Brand Name: AGENERASE (AMPRENAVIR) 15MG/ML
Applicant: GLAXO WELLCOME ORAL SOLUTI
5 MOORE DR Estab. Name:
RESEARCH TRIANGLE PARK, NC Generic Name: AMPRENAVIR
Priority: 27709 Dosage Form: (LIQUID)
Org Code: 3P* Strength: 15 MG/ML

FDA Contacts: A. ZECCOLA (HFD-550) 301-827-2147, Project Manager
G. LUNN (HFD-530) 301-827-2393, Review Chemist
S. MILLER (HFD-530) 301-827-2392, Team Leader

Overall Recommendation: ACCEPTABLE on 01-APR-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: 1035048

GLAXO INC
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 27709

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: ESTABLISHMENT POC IS DEBRA DRISSEL 919 483 5148 (on 09-NOV-1998 by
G. LUNN (HFD-530) 301-827-2393)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-NOV-1998				LUNNG
OC RECOMMENDATION	09-NOV-1998			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 9611170

GLAXO OPERATIONS UK LTD
SPEKE BOULEVARD
SPEKE, LIVERPOOL, UK

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

Profile: LIQ OAI Status: NONE

Estab. Comment: ESTABLISHMENT POC IS JOHN CLARKE 01144 151 448 5207 (on 09-NOV-
1998 by G. LUNN (HFD-530) 301-827-2393)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-NOV-1998				LUNNG
SUBMITTED TO DO	09-NOV-1998	10D			DAMBROGIOJ
ASSIGNED INSPECTION	10-NOV-1998	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	10-NOV-1998		28-FEB-1999		DAMBROGIOJ
DO RECOMMENDATION	01-APR-1999			ACCEPTABLE BASED ON FILE REVIEW	EGASM
AC BASED ON EI AT BARNARD CASTLE ENDING 2/10/99					
OC RECOMMENDATION	01-APR-1999			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 9610421

GLAXO WELLCOME LTD
HARMIRE RD, DL128DT
BARNARD CASTLE, , UK

DMF No:

AADA:

16-APR-1999

GLAXO WELLCOME

1P

530

Priority:

Org Code:

Application Comment: THIS APPLICATION IS FOR AMPRENAVIR (141W94) A NEW PROTEASE INHIBITOR FOR THE TREATMENT OF HIV-INFECTION IN CHILDREN AND ADULTS. HIV INFECTION IS A SERIOUS AND LIFE-THREATENING ILLNESS. THE DIVISION HAS NOW SET A GOAL DATE OF JANUARY 29, 1999. WE WOULD LIKE TO REQUEST A DECISION BY JANUARY 8, 1999 SO THAT WE CAN PREPARE OUR FINAL REVIEW. THE PRIMARY GLAXO WELLCOME CONTACT FOR SCHEDULING ALL PAI INSPECTIONS IS DR. RON BOBBIE (919) 269 1729 (on 09-NOV-1998 by G. LUNN (HFD-530) 301-827-2393)

WE WOULD LIKE TO REQUEST THAT THE INSPECTION OF THE FRENCH SCHERER SITE TAKE PLACE IN THE FIRST HALF OF JANUARY, IF POSSIBLE. WE UNDERSTAND THAT THIS SITE HAS NOT PREVIOUSLY BEEN INSPECTED, AND WE WOULD LIKE TO HAVE AS MUCH TIME AS POSSIBLE FOR ANY CORRECTIVE ACTIONS THAT MAY BE NEEDED BY THE FIRM. WE NOTE THAT THE PDUFA GOAL IS INCORRECTLY SHOWN IN BOTH COMIS AND EES. THE CORRECT PDUFA GOAL FOR THIS 1P APPLICATION IS 14-APR-99. PLEASE MODIFY THE EES SCREEN ACCORDINGLY (WE WILL HAVE COMIS CHANGED AS WELL).

(on 25-NOV-1998 by S. MILLER (HFD-530) 301-827-2392)

Establishment: 9610421

GLAXO WELLCOME LTD
HARMIRE RD, DL128DT
BARNARD CASTLE, , UK

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTL

OAI Status: OAI ALERT

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-SEP-1998				LUNNG
SUBMITTED TO DO	18-SEP-1998	10D			FERGUSONS
ASSIGNED INSPECTION	'22-SEP-1998	GMP			DAMBROGIOJ
OC RECOMMENDATION	19-OCT-1998			WITHHOLD	DAMBROGIOJ
				FACILITY (FIRM) WITHDRAWN	

PER AMENDMENT DATED 10/12/98.

Establishment: 9610414

GLAXO WELLCOME OPERATIONS UK
WELLCOME FNDTN TEMPLE HILL
DARTFORD, KENT, UK DA1 5AH

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE STABILITY TESTER

Profile: CSN

OAI Status: NONE

Estab. Comment:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-SEP-1998				LUNNG
OC RECOMMENDATION	18-SEP-1998			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 9615710

RP SCHERER SA,
74 RUE PRINCIPALE 67930
BEINHEIM, , FR

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile:

CSG

OAI Status: NONE

Estab. Comment: THE SPONSOR TELLS US THAT THIS FACILITY HAS NOT PREVIOUSLY BEEN INSPECTED BY THE FDA. THERE IS NO CFN NUMBER. A FORM 2656 (SITE REGISTRATION) WILL BE SUBMITTED TO FDA IN SEPTEMBER. ALSO 2 DMFS ALREADY ON FILE WILL BE UPDATED. THESE ARE
(on 08-SEP-1998 by G. LUNN (HFD-530) 301-827-2393)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-SEP-1998				LUNNG
SUBMITTED TO DO	18-SEP-1998	GMP			FERGUSONS
ASSIGNED INSPECTION	22-SEP-1998	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	19-JAN-1999		14-JAN-1999		DAMBROGIOJ
INSPECTION PERFORMED	19-JAN-1999		14-JAN-1999		DAMBROGIOJ
DO RECOMMENDATION	03-MAR-1999			ACCEPTABLE	EGASM
				INSPECTION	
OC RECOMMENDATION	03-MAR-1999			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

**APPEARS THIS WAY
ON ORIGINAL**

08-JUN-1999

GLAXO WELLCOME

3P*

530

Priority:

Org Code:

Application Comment: THIS APPLICATION IS FOR A PEDIATRIC FORMULATION FOR THE TREATMENT OF HIV INFECTION, A SERIOUS AND LIFE-THREATENING ILLNESS. THE DIVISION HAS SET APPROVAL FOR THE PERIOD APRIL-JUNE, 1999. THE SPONSOR TELLS US THAT ALL SITES WILL BE PAI-READY BY DECEMBER 15, 1998. THE PRIMARY GLAXO WELLCOME CONTACT FOR ACHEDULING ALL PAI INSPECTIONS IS DR. RON BOBBIE (919 269 1729). (on 23-NOV-1998 by G. LUNN (HFD-530) 301-827-2393)

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: ESTABLISHMENT POC IS RICHARD PACKER 011 44 183 369 2304 (on 09-NOV-1998 by G. LUNN (HFD-530) 301-827-2393)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-NOV-1998				LUNNG
SUBMITTED TO DO	09-NOV-1998	10D			DAMBROGIOJ
ASSIGNED INSPECTION	10-NOV-1998	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	10-NOV-1998		28-FEB-1999		DAMBROGIOJ
DO RECOMMENDATION	01-APR-1999			ACCEPTABLE	EGASM
OC RECOMMENDATION	01-APR-1999			INSPECTION ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: 9610414

GLAXO WELLCOME OPERATIONS UK
 WELLCOME FNDTN TEMPLE HILL
 DARTFORD, KENT, UK DA1 5AH

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-NOV-1998				LUNNG
SUBMITTED TO DO	09-NOV-1998	10D			DAMBROGIOJ
DO RECOMMENDATION	10-NOV-1998			ACCEPTABLE	DAMBROGIOJ
OC RECOMMENDATION	10-NOV-1998			BASED ON FILE REVIEW ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	