CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144

CHEMISTRY REVIEW(S)

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21144/000
Org Code : 520
Priority : 1S

Sponsor: AVENTIS PHARMS
10236 MARION PARK DR
KANSAS CITY, MO 641370627

Stamp Date : 01-MAR-2000
PDUFA Date : 17-APR-2004
Action Goal :
District Goal: 17-FEB-2004

Brand Name : KETEK (TELITHROMYCIN) 400MG TABLETS
Estab. Name:
Generic Name: TELITHROMYCIN
Dosage Form: (TABLET)
Strength : 400 MG

FDA Contacts: A. YU Review Chemist (HFD-520) 301-827-2143
ID = 107080 Team Leader

Overall Recommendation: ACCEPTABLE on 01-MAR-2004by J. D AMBROGIO(HFD-322) 301-827-9049

WITHHOLD on 10-DEC-2003by J. D AMBROGIO(HFD-322) 301-827-9049

ACCEPTABLE on 16-DEC-2002by J. D AMBROGIO(HFD-322) 301-827-9049

ACCEPTABLE on 30-AUG-2002by S. FERGUSON(HFD-322) 301-827-9009

ACCEPTABLE on 05-JUN-2000by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : FEI : 1411365

DMF No: AADA:

Responsibilities:

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-MAR-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : 3002806345

DMF No: AADA:

Responsibilities:

Profile	: CSN	OAI Status:	NONE
Last Milestone	: OC RECOMMENDATION		
Milestone Date	: 17-NOV-03		
Decision	: ACCEPTABLE		
Reason	: BASED ON FILE REVIEW		

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

BASED ON PROFILE

Establishment : CFN : 1913298 FEI : 1913298
ADVENTIS PHARMACEUTICALS
10236 MARION PARK DR
KANSAS CITY, MO 64137

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-NOV-03
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

BASED ON PROFILE

Establishment : CFN : FEI : 1421377

DMF No: AADA:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-NOV-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9610672 FEI : 3002807193
AVENTIS PHARMA SA
69583
NEUVILLE-SUR-SAONE, , FR

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
INTERMEDIATE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-NOV-03
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

BASED ON PROFILE

Establishment : CFN : 9610721 FEI : 1463
AVENTIS PHARMA SA
63480
VERTOLAYE, , FR
DMF No: AADA:

Responsibilities: INTERMEDIATE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-NOV-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI : 3002772224

DMF No: AADA:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-NOV-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Chemistry Review Data Sheet

1. NDA 21-144

2. REVIEW #: addendum to Review #3 dated 1/16/03

3. REVIEW DATE: 3/31/04

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 21144 (original)	3/01/00
NDA 21144 BC (amendment)	5/04/00
NDA 21144 BC (amendment)	6/01/00
NDA 21144 BC (amendment)	8/31/00
NDA 21144 BC (Response to deficiency)	12/05/00
NDA 21144 BC (Response to deficiency)	1/22/01
NDA 21144 (Review #1)	10/27/00
NDA 21144 (Review #2)	2/26/01
NDA 21144 (IR Fax)	3/11/02
AE Letter	6/01/01
Response to IR fax of 3/11/02	4/08/02
NDA 21144 RS	7/24/02
NDA 21144 BC (adding packaging site)	12/03/02
NDA 21144 (Review #3)	1/16/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21144 RS (No new CMC are re-submitted, except Package insert and facility). Previous CMC review #3 was adequate. Facilities updates (FUR) was re-submitted to Compliance and found adequate	09/24/03

21144MR (Facility update –no change)	9/24/03
21144AZ (Facility update–no change)	10/17/03
21144BZ (Facility update–no change)	10/27/03
21144BZ (Facility update–no change)	10/31/03
21144BL (Label & carton)	11/18/03
21144BZ (Facility update–no change)	1/13/04
21144BL (Label, carton, & USPI)	2/16/04
21144BC (correction of USAN name)	**3/1/04**

7. NAME & ADDRESS OF APPLICANT:

Name: Aventis Inc

Address: 200 Crossing Blvd.
P.O. Box 6800
Bridgewater, NJ 06320

Representative: Paul Bryers, Ph.D., US Regulatory Liaison

Telephone: 908-231-5875

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ketek® film-coated tablet
b) Non-Proprietary Name (USAN): Telithromycin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

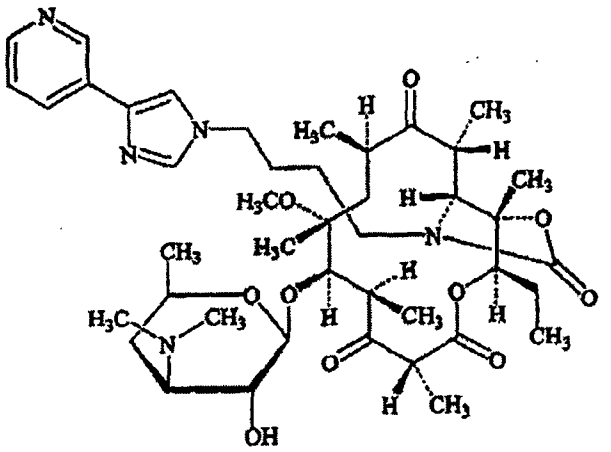
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Oral tablet

12. STRENGTH/POTENCY: 400 mg

13. ROUTE OF ADMINISTRATION: Oral



14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Telithromycin $C_{43}H_{65}N_5O_{10}$
11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl) oxy]6-O-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-erythromycin.
173838-31-8 (Also see attached USAN name on page 19).
M.W. 812.03

Recommend : Ketek was adequate in review #3 and addendum from CMC view point. In the BC amendment dated 3/1/03, minor change to USAN# 2 was submitted and acceptable. The CMC part of the final PI was reviewed on 3/30/04 and found adequate.

/S/

Andrew Yu, Chemistry Reviewer

/S/

James Vidra, Chemistry team Leader

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/s/

Andy Yu
3/31/04 01:45:07 PM
CHEMIST

Jim Vidra
3/31/04 01:50:24 PM
CHEMIST

Chemistry Review Data Sheet

1. NDA 21-144

2. REVIEW #: addendum to Review #3 dated 1/16/03

3. REVIEW DATE: 3/2/04

4. REVIEWER: Andrew Yu

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NDA 21144 (Review #3)	1/16/03

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21144AZ (Facility update–no change)	10/17/03
21144BZ (Facility update–no change)	10/27/03
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21144BL (Label, carton, & USPI)	2/16/04

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Bridgewater, NJ 06320

Representative: Paul Bryers, Ph.D., US Regulatory Liaison

Telephone: 908-231-5875

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ketek® film-coated tablet
b) Non-Proprietary Name (USAN): Telithromycin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

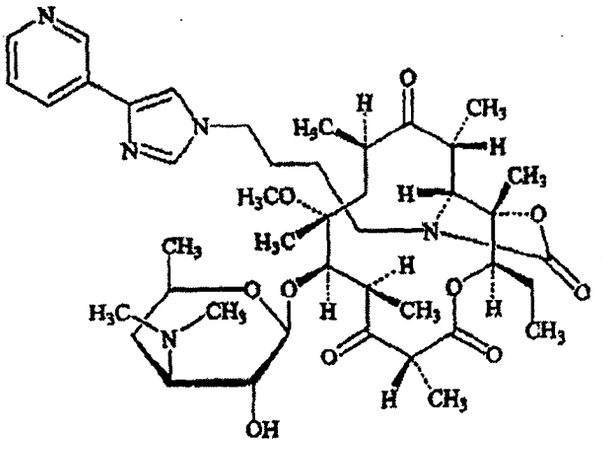
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Oral tablet

12. STRENGTH/POTENCY: 400 mg

13. ROUTE OF ADMINISTRATION: Oral



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173838-31-8 (Also see attached USAN name on page 19).
M.W. 812.03

Recommend : Ketek was reviewed in CMC review #3 and found adequate from CMC view point. No changes are made in the re-submission. The remaining — site which was withheld was approved on 3/1/04. Ketek is recommended for approval for CMC view point. A list of minor changes are recommended for the label and PI, and the list should be sent to the sponsor.

/S/

Andrew Yu, Chemistry Reviewer

/S/

James Vidra, Chemistry team Leader

16 Page(s) Withheld

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/s/

Andy Yu
3/2/04 02:16:00 PM
CHEMIST

Jim Vidra
3/2/04 02:23:32 PM
CHEMIST

NDA 21-144

Ketek® film-coated tablet

Aventis Inc.

Andrew Yu
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS,
HFD-520

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-144

2. REVIEW #:3

3. REVIEW DATE: 1/16/02

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
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NDA 21144 BC (amendment)	5/04/00
NDA 21144 BC (amendment)	6/01/00
NDA 21144 BC (amendment)	8/31/00
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NDA 21144 (Review #2)	2/26/01
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AE Letter	6/01/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Response to IR fax of 3/11/02	4/08/02
NDA 21144 RS	7/24/02
NDA 21144 BC (adding packaging site)	12/03/02

Chemistry Review Data Sheet

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Address:	200 Crossing Blvd. P.O. Box 6800 Bridgewater, NJ 06320
Representative:	Paul Bryers, Ph.D., US Regulatory Liaison
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b) Non-Proprietary Name (USAN): Telithromycin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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11. DOSAGE FORM: Oral tablet

12. STRENGTH/POTENCY: 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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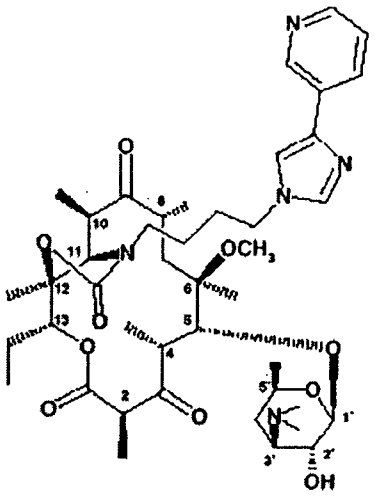
11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl) oxy]6-O-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-erythromycin. 173838-31-8
M.W. 812.03



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1,7	Previously deficient but adequate, with regard to this NDA	12/31/02	Previously reviewed by M. Shih on 10/10/01; DMF holder responded
[redacted]	II	[redacted]	[redacted]	1,7	Adequate	12/31/02	Same [redacted] as that found in the approved
[redacted]	II	[redacted]	[redacted]	1,7	Adequate	12/31/02	Previously reviewed as AADA. Now reviewed as DMF.
[redacted]	III	[redacted]	[redacted]	3	Adequate	3/24/00	No change since the last review
[redacted]	III	[redacted]	[redacted]	3	Adequate	5-2-02	No change since the last review

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION STATUS	DATE	REVIEWER
Biometrics	None		
EES	Acceptable	12/16/02	Janine D Ambrogio
Pharm/Tox	None		
Biopharm	None		
LNC	Acceptable found in review #2.	2/26/01	Dan Boring
Methods Validation	Found acceptable in Rev #2	11/9/00	Method validated by FDA lab in Denver & Laurel. Report issued by James Brower (HFD-920).
OPDRA	Acceptable	2/23/01	D. Diwa, D. Toyer
EA	Categoric exclusion waiver found acceptable in review #2	2/26/01	Andrew Yu
Microbiology	None		

The Chemistry Review for NDA 21-144

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval from CMC view point. The label is pending final revision; all other CMC deficiencies are resolved, and all facility inspections are acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
Telithromycin is a new ketolide

The physico-chemical information for the is covered under a DMF from the two DMF holders.

Under the conditions employed in manufacturing,

. Aventis has developed and validated analytical methods for related impurities The analytical method is capable of monitoring key degradation products, which remain at very low levels during the shelf life.

KETEK™ tablets are light-orange, oval, film-coated tablets, each containing 400 mg telithromycin, plus the following inactive ingredients: cornstarch, croscarmellose sodium, , lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended for oral administration for the indications of community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), acute sinusitis (AS), and tonsillitis/pharyngitis (T/P). The 400 mg tablet is available in 10-tablet trade blister card (Ketek Pak™) with 2 tablets per blister cavity, and also in bottles of 60 tablets per bottle. The proposed storage condition is 25° C (77° F). The expiry period is 3 years. The expiry is based on → batches of real time long term studies for 3 years. The dosing schedule of the drug is two 400 mg tablets per day with a maximum dose of 800 mg.

C. Basis for Approvability or Not-Approval Recommendation

The basis for approval from a CMC perspective is that telithromycin is documented to be consistently prepared — synthesis. All by products and reactants formed during synthesis were adequately removed, and the purity of the final drug substance is assured (

.. Chemical degradation products are adequately assessed, and the slight light instability is eliminated in the dosage form by a tablet formulation using a film coating. Specification for Ketek for identification and assay and degradation products are well documented. Residual solvents and the process impurities are controlled at an acceptable level. The excipients used in the Ketek 400 mg tablet meet compendial requirements.

The scale of synthesis of telithromycin was increased — (in this resubmission) the original batch size without changing the overall synthetic scheme. The interim specification for the — was modified to allow a slightly higher impurity level (— , but has no overall impact on the purity of the drug substance (the higher impurity reacted during synthesis). The quality of the telithromycin during accelerated stability studies is unchanged. Stability is demonstrated by evaluation of the — batches of drug substance produced with this scale up. New long term stability data from pilot and production batches are presented in this submission. The long term stability data support the extension of the expiry of Ketek tablets from — to 3 years. Stability studies in commercial blister and HDPE bottles were performed according to a — design stability protocol agreed upon with FDA during the early IND phase.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

76 Page(s) Withheld

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/s/

Andy Yu
1/16/03 06:29:41 PM
CHEMIST

Bonnie Dunn
1/16/03 07:01:15 PM
CHEMIST

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-144 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 26-FEB-2000

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	1-MAR-00	2-MAR-00	06-MAR-00
AMENDMENT	04-MAY-00	05-MAY-00	06-MAY-00
AMENDMENT	01-JUN-00	06-JUN -00	12-JUN -00
AMENDMENT	31-AUG-00	01-SEP-00	07-SEP -00
AMENDMENT (Deficiency Response)	05-DEC-00	065-DEC-00	11-DEC-00
AMENDMENT (Deficiency Response)	22-JAN-01	24- JAN -01	24- JAN -01

NAME & ADDRESS OF APPLICANT:
Aventis Pharmaceuticals Inc.
10236 Manon Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

DRUG PRODUCT NAME:

Proprietary:	Ketek film-coated tablets
Nonproprietary/USAN:	Telithromycin film-coated tablets
Code Names/#'s:	
Chemical Type/ Therapeutic Class:	1 S

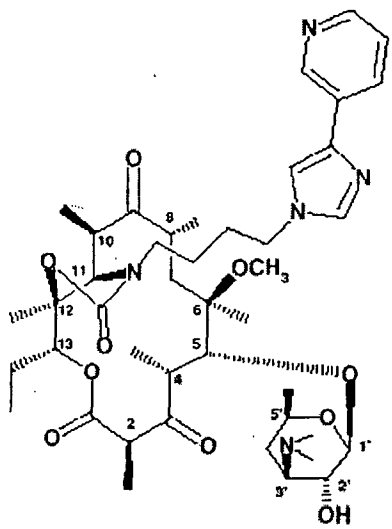
ANDA Suitability Petition/DESI/Patent Status: N/A
[if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Anti-infective

DOSAGE FORM: Film-coated tablets
STRENGTHS: 400 mg

ROUTE OF ADMINISTRATION: oral
DISPENSED: X Rx __ OTC
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Telithromycin $C_{43}H_{65}N_5O_{10}$
11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl) oxy]-6-O-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-erythromycin.
173838-31-8
M.W. 812.03



SUPPORTING DOCUMENTS:
Telithromycin drug substance
IND 55,283 for HMR 3647
NDA 21-144 CMC review #1
RELATED DOCUMENTS (if applicable):

DMFs:

The firm has provided DMF authorization letters.

Type	Number	Title/Subject	Holder
DMF			
DMF			

DMF

DMF

DMF

DMF

DMF

CONSULTS:
A consult was sent to OPDRA, and the nomenclature was found to be acceptable.

REMARKS/COMMENTS :
The two method validation reports were received from FDA labs and found to be acceptable.

CONCLUSIONS & RECOMMENDATIONS:
Recommend approval from the manufacturing and controls standpoint. All pending issues have been satisfactory resolved. All manufacturing facilities are currently in acceptable GMP compliance (see EER attachment).

Andrew Yu, Review Chemist

cc: Orig. NDA 21-144
HFD-520
HFD-520/Chem/AYu
HFD-520/MO/EDavidson
HFD-520/MAlbuerne
HFD-520/Pharm/ROsterberg
HFD-520/Micro/SAltaire
HFD-520/CSO/JCintron
R/D Init by: HFD-520/TmLdrChem/ DKatague

34 Page(s) Withheld

/s/

Andy Yu
2/27/01 03:21:12 PM
HEMIST

David Katague
2/27/01 04:12:26 PM
CHEMIST

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-144 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 27-OCT-2000

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	1-MAR-00	2-MAR-00	06-MAR-00
AMENDMENT	04-MAY-00	05-MAY-00	06-MAY-00

NAME & ADDRESS OF APPLICANT:
Aventis Pharmaceuticals Inc.
10236 Manon Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

DRUG PRODUCT NAME:

Proprietary:	Ketek film-coated tablets
Nonproprietary/USAN:	Telithromycin film-coated tablets
Code Names/#'s:	
Chemical Type/	
Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status: N/A
[if applicable]

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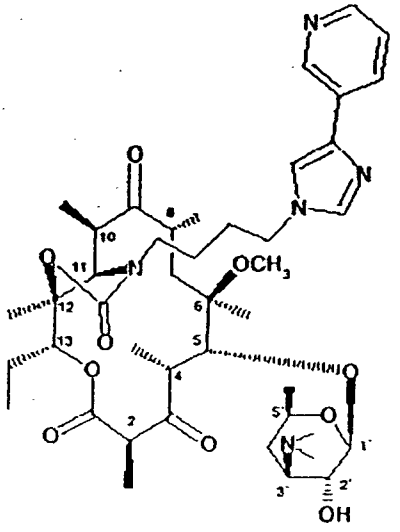
173838-31-8
M.W. 812.03



SUPPORTING DOCUMENTS:
Telithromycin drug substance
IND 55,283 for HMR 3647

RELATED DOCUMENTS (if applicable):

DMFs:

The firm has provided DMF authorization letters.

Type	Number	Title/Subject	Holder
DMF			
DMF			
DMF			
DMF			

DMF

DMF

DMF

CONSULTS:
A consult was sent to OPDRA, and the nomenclature was found to be acceptable.

REMARKS/COMMENTS :

CONCLUSIONS & RECOMMENDATIONS:

The application is **not** approvable for manufacturing and controls under section 505(b) of the Act. Specific items which are not approvable are identified under the following headings: Drug Substance [Description and Characteristics, Synthesis, Specification and Tests, Reference, and Stability], and Drug Products [Manufacturing and Packaging, Specification and Methods, Method Validation and Stability]. All manufacturing facilities are currently in acceptable GMP compliance as of 05-JUN-2000 (see item G., Establishment Inspections).

Andrew Yu, Review Chemist

cc: Orig. NDA 21-144
HFD-520
HFD-520/DivDir/JSoreth
HFD-520/Chem/AYu
HFD-520/MO/EDavidson
HFD-520/MAlbuerne
HFD-520/Pharm/ROsterberg
HFD-520/Micro/FMarsik
HFD-520/CSO/JCintron
R/D Init by: HFD-520/TmLdrChem/ DKatague

84 Page(s) Withheld

/s/

Andy Yu
11/29/00 01:58:47 PM
CHEMIST

Hardcopy previously out on 10/30/00 already, please sign DFS copy as requested by system.

David Katague
11/29/00 02:05:38 PM
CHEMIST