CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-154

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 22-154

TYZEKA™
(Telbivudine)
Oral solution

Novartis Pharmaceutical Inc.

Andrew Yu
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Chemistry Review Data Sheet

1. NDA 22-154 re-submission

2. REVIEW# 4

3. REVIEW DATE: 4/27/2009

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Presubmission	30/AUG/2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	21/DEC/2007
Amendment (NDA transfer letter)	03/JAN/2008
Amendment [redacted] provided/Response to deficiency – Re-submission)	03/MAR/2009
Amendment*/ [redacted]	24/April/2009

b(4)

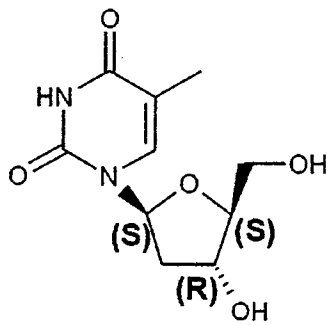
*reported by PM but not officially received

7. NAME & ADDRESS OF APPLICANT:

Name	NavartisPharmaceuticals, Inc.
Address	60 Hampshire Street, Cambridge, MA 02139
Representative	David Hallinan, Ph.D.
Telephone	617-995-9800

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name:
   b) Non-Proprietary Name (USAN): Telbivudine
   c) Code Name/# (ONDC only): LdT
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Antiviral
11. DOSAGE FORM: Oral solution
12. STRENGTH/POTENCY: 600 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:

INN	Telbivudine
Chemical Name	1-((2S,4R,5S)-4-Hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl- 1 H-pyrimidine- 2,4-dione
Other Names	1-(2-Deoxy-ß-L-ribofuranosyl)-5-methyluracil, 1-(2-Deoxy-ß-L-ribofuranosyl)thymine, ß-L-Thymidine , **2'-Deoxy-ß-L-thymidine, L-Thymidine**
Molecular Formula	$C_{10}H_{14}N_2O_5$
Molecular Weight	242.23
Structure Formula	Telbivudine, which presents 3 chiral centers, is the pure isomer with absolute configuration 2S, 4R and 5S .



The Chemistry Review for NDA 22-154

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval. The CDER Office of Compliance has determined that all manufacturing facilities are adequate.

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)

The drug substance, (ß-L-thymidine, LdT) is a synthetic thymidine nucleoside analogue with activity against hepatitis B virus (HBV). Telbivudine is a chiral compound with the 2S, 4R and 5S absolute configuration and is the unmodified ß-L enantiomer of the naturally occurring nucleoside, thymidine.

Telbivudine is [redacted]. The method of synthesis and qualification of supplier(s) have been reviewed and acceptable in a previous NDA for the telbivudine tablet. The commercial batches will be manufactured at Novartis Grimsby Ltd., UK and [redacted] by Novartis Pharma Stein AG, Switzerland. The commercial manufacturing process as well as controls for starting materials, reagents, process intermediate, and the new drug substance are acceptable. b(4) b(4)

The structure of LdT has been established by elemental analysis, UV/VIS, FTIR, ESI/MS, ^{1}H NMR and ^{13}CNMR. Impurities (related substances) introduced during synthesis or degradation products formed during synthesis and /or storage have been studied in a previous NDA and low amount of related substances (<0.05% reporting threshold) and low amounts of residual solvents (1/3 to 1/10 of the ICH Q3C limits). [redacted] Acceptance criteria (AC) of 0.1% for related substances are proposed based on ICH guidance Q3A(R). [redacted] b(4)

[redacted] Stability of the DS was evaluated in the approved NDA for the TYZEKA tablet on 3 registration batches at long-term conditions (25°C/60%RH), intermediate conditions (30°C/70%RH) and accelerated conditions (40°C/75%RH) supporting a retest period of [redacted] b(4)

The drug product, TYZEKA Oral solutions, 100 mg/5 mL is a clear to pale yellow solution. Pharmaceutical development studies were performed. Rationale for formulation, excipient selection and preservation were discussed. Thirty (30) mL provides the standard patient dose of 600 mg per day.

TYZEKA oral solution is manufactured by Novatis Pharma Stein AG via an [redacted] process. In-process controls (with target/range) for the process steps are established. When applying these parameters within the validated ranges, none of the process steps are considered as critical. A representative batch of TYZEKA Oral solution typically consists of approximately [redacted]. Specification of the drug product includes appearance, identity, assay, impurities [redacted], unspecified, and total), content uniformity, and microbial limits [redacted] b(4)

[redacted] An AC of [redacted] for [redacted], is proposed and accepted based on ICH guidance Q3B(R). The DP specification is established based on release and stability data from 3 registration stability batches and release data from 3 process validation batches. Stability of the drug product has been evaluated on 3 stability batches [redacted] oral solutions) at long term conditions (25°C/60%RH, and 30°C/70%RH) for 18-24 months, accelerated conditions (40°C/75%RH) for 6 months, and 50°C/ambient RH and under light irradiation. No significant change was observed for all parameters tested. No degradation products were detected above the acceptance limits. The proposed shelf life of two years is acceptable.

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

TYZEKA (telbivudine) is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.
The recommended dose of TYZEKA is 600 mg once daily, taken orally, with or without food. Telbivudine oral solution may be considered for patients who have difficulty with swallowing tablets. One 600 mg Tyzeka tablet is equivalent to 30 mL (600 mg) Tyzeka oral solution. The oral solution allows dose adjustment for renal impaired patients as described in the package insert.
TYZEKA Oral solutions are packaged in [redacted] bottles. b(4)
Each bottle contains 300 mL oral solution (NDC 0078-0539-85) with child-resistant closure and embossed dosing cup. The bottles are stored at 25°C (77°F), with excursions permitted to15-30°C (59-86°F). Use within two months after opening the bottle. Do not freeze.

C. Basis for Approvability or Not-Approval Recommendation

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval. All manufacturing facilities are adequate and a final EES report is attached.

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Chemistry Review Data Sheet

STATUS OF EER from CDER office of Compliance for 22-154

Hi Andrew,

The application is still acceptable from a compliance standpoint. Therefore, no resubmission is necessary.

Thank you,

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Yu, Andrew B
Sent: Tuesday, March 17, 2009 10:20 AM
To: CDER EESQUESTIONS
Cc: Miller, Stephen
Subject: NDA 22-154 resubmission - Question on facilities

Hi EES:

The NDA was resubmitted due to clinical issues. Approval will be completed in 2-3 months. *Do I have to resubmitted all the facilities* which was
OVERALL ACCEPTABLE as shown on 9/19/09 ?? Thanks.

Andy

* Note there are no new facilities/or change of facilities in resubmission .

****

Attachment of EES Report

07-OCT-2008 FDA CDER EES
Page 1 of 3

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22154/000
Org Code : 530
Priority : 3S

Stamp Date : 21-DEC-2007
PDUFA Date : 21-OCT-2008
Action Goal :
District Goal: 22-AUG-2008

Sponsor: IDENIX PHARMA
60 HAMPSHIRE STREET
CAMBRIDGE, MA 02139

Brand Name :TYZEKA
Estab. Name: TELBIVUDINE
Generic Name: TELBIVUDINE
Dosage Form: (SOLUTION)
Strength : 20 MG/ML

FDA Contacts: A. YU Review Chemist
301-796-1488

Chemistry Review Data Sheet

S. MILLER Team Leader
301-796-1418

Overall Recommendation: ACCEPTABLE on 19-SEP-2008
by S. ADAMS (HFD-325) 301-796-3193

Establishment : CFN : [redacted] FEI : [redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile : [redacted] OAI Status: NONE b(4)
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9612220 FEI : 10656
NOVARTIS GRIMSBY LIMITED
PYEWIPE
GRIMSBY (S. HUMBERSIDE), , UK

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9617227 FEI : 3003157245
NOVARTIS PHARMA INC
SITE INDUSTRIEL DE HUNINGUE
HUNINGUE, , FR

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-SEP-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9692042 FEI : 3002865753
NOVARTIS PHARMA STEIN AG
SCHWEIZERHALLE, BASEL, SZ
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-MAR-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9692043 FEI : 3002653483
NOVARTIS PHARMA STEIN AG
SCHAFFHAUSERSTRASSE
STEIN, , SZ
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE [redacted] b(4)

Profile : CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9611204 FEI : 3002807772
NOVARTIS PHARMACEUTICALS CORP.
LICHSTRASSE 35, ST. JOHANN SITE
BASEL, , SZ
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JAN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9612715 FEI : 3002807776

Chemistry Review Data Sheet

NOVARTIS PHARMACEUTICALS CORP.
CORK

07-OCT-2008 FDA CDER EES
Page 3 of 3

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

RINGASKIDDY, CORK, , EI
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-MAR-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9614433 FEI : 3002807773
NOVARTIS PHARMANALYTICA SA
VIA SERFINO BLESTRA 31
LOCARNO, , SZ
DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

--End of EES report --

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Yu
4/27/2009 10:57:27 AM
CHEMIST

Stephen Paul Miller
4/27/2009 03:15:59 PM
CHEMIST
I concur as acting Branch Chief

NDA 22-154

TYZEKA™
(Telbivudine)
Oral solution

Novartis Pharmaceutical Inc.

Andrew Yu
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Chemistry Review Data Sheet

1. NDA 22-154 re-submission

2. REVIEW# 3

3. REVIEW DATE: 3/19/2009

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Presubmission	30/AUG/2007

6. SUBMISSION(S) BEING REVIEWED:

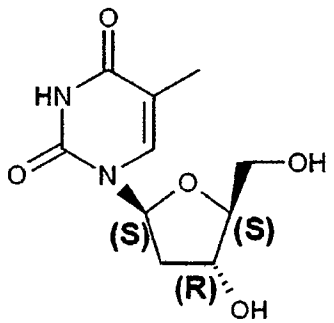
Submission(s) Reviewed	Document Date	
Original	21/DEC/2007	
Amendment (NDA transfer letter)	03/JAN/2008	
Amendment [redacted] provided/Response to deficiency – Re-submission)	03/MAR/2009	b(4)

7. NAME & ADDRESS OF APPLICANT:

Name	NavartisPharmaceuticals, Inc.
Address	60 Hampshire Street, Cambridge, MA 02139
Representative	David Hallinan, Ph.D.
Telephone	617-995-9800

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name:
   b) Non-Proprietary Name (USAN): Telbivudine
   c) Code Name/# (ONDC only): LdT
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Antiviral
11. DOSAGE FORM: Oral solution
12. STRENGTH/POTENCY: 600 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:

INN	Telbivudine
Chemical Name	1-((2S,4R,5S)-4-Hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl- 1 H-pyrimidine- 2,4-dione
Other Names	1-(2-Deoxy-ß-L-ribofuranosyl)-5-methyluracil, 1-(2-Deoxy-ß-L-ribofuranosyl)thymine, ß-L-Thymidine , **2'-Deoxy-ß-L-thymidine, L-Thymidine**
Molecular Formula	$C_{10}H_{14}N_2O_5$
Molecular Weight	242.23
Structure Formula	Telbivudine, which presents 3 chiral centers, is the pure isomer with absolute configuration 2S, 4R and 5S .



The Chemistry Review for NDA 22-154

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval. The CDER Office of Compliance has determined that all manufacturing facilities are adequate. [redacted] b(4)

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)

The drug substance, (ß-L-thymidine, LdT) is a synthetic thymidine nucleoside analogue with activity against hepatitis B virus (HBV). Telbivudine is a chiral compound with the 2S, 4R and 5S absolute configuration and is the unmodified ß-L enantiomer of the naturally occurring nucleoside, thymidine.

Telbivudine is [redacted] b(4)

The method of synthesis and qualification of supplier(s) have been reviewed and acceptable in a previous NDA for the telbivudine tablet. The commercial batches will be manufactured at Novartis Grimsby Ltd., UK and [redacted]by Novartis Pharma Stein AG, Switzerland. The commercial manufacturing process as well as controls for starting materials, reagents, process intermediate, and the new drug substance are acceptable. b(4)

The structure of LdT has been established by elemental analysis, UV/VIS, FTIR, ESI/MS, ^{1}H NMR and ^{13}CNMR. Impurities (related substances) introduced during synthesis or degradation products formed during synthesis and /or storage have been studied in a previous NDA and low amount of related

substances (<0.05% reporting threshold) and low amounts of residual solvents (1/3 to 1/10 of the ICH Q3C limits).

Acceptance criteria (AC) of 0.1% for related substances are proposed based on ICH guidance Q3A(R). b(4)

Stability of the DS was evaluated in the approved NDA for the TYZEKA™ tablet on 3 registration batches at long-term conditions (25°C/60%RH), intermediate conditions (30°C/70%RH) and accelerated conditions (40°C/75%RH) supporting a retest period of b(4)

The drug product, TYZEKA™ Oral solutions, 20 mg/mL is a clear to pale yellow solution. Pharmaceutical development studies were performed. Rationale for formulation, excipient selection and preservation were discussed. Thirty (30) mL
provides the standard patient dose of 600 mg per day.

TYZEKA oral solution is manufactured by Novatis Pharma Stein AG via an b(4)
process. In-process controls (with target/range) for the process steps are established.
When applying these parameters within the validated ranges, none of the process steps are considered as critical. A representative batch of TYZEKA Oral solution typically consists of approximately . Specification of the drug product includes appearance, identity, assay, impurities (, unspecified, and total), content uniformity, and microbial limits b(4)
An AC of or is proposed and accepted based on ICH guidance Q3B(R). The DP specification is established based on release and stability data from 3 registration stability batches and release data from 3 process validation batches. Stability of the drug product has been evaluated on 3 stability batches oral solutions) at long term conditions (25°C/60%RH, and 30°C/70%RH) for 18-24 months, accelerated conditions (40°C/75%RH) for 6 months, and 50°C/ambient RH and under light irradiation. No significant change was observed for all parameters tested. No degradation products were detected above the acceptance limits. The proposed shelf life of two years is acceptable.

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

TYZEKA (telbivudine) is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

The recommended dose of TYZEKA is 600 mg once daily, taken orally, with or without food. For renal impaired patients, dose adjustment is required in patients with creatine

clearance <50 mL /min as indicated in the package insert. The oral solution allows dose adjustment for renal impaired patients [redacted]

b(4)

TYZEKA Oral solutions are packaged in [redacted] bottles as 300 mL per bottle. The bottles are stored at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F). Use within two months after opening the bottle. Do not freeze.

C. Basis for Approvability or Not-Approval Recommendation

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval. All manufacturing facilities are adequate and a final EES report is attached.

18 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Chemistry Review Data Sheet

STATUS OF EER from CDER office of Compliance for 22-154

Hi Andrew,

The application is still acceptable from a compliance standpoint. Therefore, no resubmission is necessary.

Thank you,

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Yu, Andrew B
Sent: Tuesday, March 17, 2009 10:20 AM
To: CDER EESQUESTIONS
Cc: Miller, Stephen
Subject: NDA 22-154 resubmission - Question on facilities

Hi EES:

The NDA was resubmitted due to clinical issues. Approval will be completed in 2-3 months. *Do I have to resubmitted all the facilities* which was
OVERALL ACCEPTABLE as shown on 9/19/09 ?? Thanks.

Andy

* Note there are no new facilities/or change of facilities in resubmission .

****

Attachment of EES Report

07-OCT-2008 FDA CDER EES
Page 1 of 3

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22154/000
Org Code : 530
Priority : 3S

Stamp Date : 21-DEC-2007
PDUFA Date : 21-OCT-2008
Action Goal :
District Goal: 22-AUG-2008

Sponsor: IDENIX PHARMA
60 HAMPSHIRE STREET
CAMBRIDGE, MA 02139

Brand Name :TYZEKA
Estab. Name: TELBIVUDINE
Generic Name: TELBIVUDINE
Dosage Form: (SOLUTION)
Strength : 20 MG/ML

FDA Contacts: A. YU Review Chemist
301-796-1488

Chemistry Review Data Sheet

S. MILLER Team Leader
301-796-1418

Overall Recommendation: ACCEPTABLE on 19-SEP-2008
by S. ADAMS (HFD-325) 301-796-3193

Establishment : CFN [redacted] FEI [redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile : [redacted] OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9612220 FEI : 10656
NOVARTIS GRIMSBY LIMITED
PYEWIPE
GRIMSBY (S. HUMBERSIDE), , UK

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9617227 FEI : 3003157245
NOVARTIS PHARMA INC
SITE INDUSTRIEL DE HUNINGUE
HUNINGUE, , FR

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-SEP-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9692042 FEI : 3002865753
NOVARTIS PHARMA STEIN AG
SCHWEIZERHALLE, BASEL, SZ
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-MAR-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9692043 FEI : 3002653483
NOVARTIS PHARMA STEIN AG
SCHAFFHAUSERSTRASSE
STEIN, , SZ
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE ——————— b(4)

Profile : CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9611204 FEI : 3002807772
NOVARTIS PHARMACEUTICALS CORP.
LICHSTRASSE 35, ST. JOHANN SITE
BASEL, , SZ
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JAN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9612715 FEI : 3002807776

NOVARTIS PHARMACEUTICALS CORP.
CORK

07-OCT-2008 FDA CDER EES
Page 3 of 3

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

RINGASKIDDY, CORK, , EI
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-MAR-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9614433 FEI : 3002807773
NOVARTIS PHARMANALYTICA SA
VIA SERFINO BLESTRA 31
LOCARNO, , SZ
DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

--End of EES report --

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Yu
4/13/2009 08:25:24 AM
CHEMIST

Norman Schmuff
4/16/2009 09:54:01 AM
CHEMIST

Chemistry Review Data Sheet

NDA 22-154

TYZEKA™
(Telbivudine)
Oral solution

Novartis Pharmaceutical Inc.

Andrew Yu
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Chemistry Review Data Sheet

1. NDA 22-154

2. REVIEW# 2

3. REVIEW DATE: 8/1/2008

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

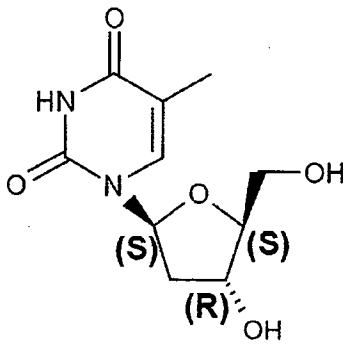
Submission(s) Reviewed	Document Date
Original	21/DEC/2007
Amendment BC (Name transfer)	03/JAN/2008
Amendment BC (Response to CMC/new PI)	19/Sept/2008

7. NAME & ADDRESS OF APPLICANT:

Name	Novartis Pharmaceuticals, Inc.
Address	60 Hampshire Street, Cambridge, MA 02139
Representative	David Hallinan, Ph.D.
Telephone	617-995-9800

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: TYZEKA™
   b) Non-Proprietary Name (USAN): Telbivudine
   c) Code Name/# (ONDC only): LdT
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Antiviral
11. DOSAGE FORM: Oral solution
12. STRENGTH/POTENCY: 20 mg/mL
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:

INN	Telbivudine
Chemical Name	1-((2S, 4R, 5S)-4-Hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl- 1 H-pyrimidine- 2,4-dione
Other Names	1-(2-Deoxy-ß-L-ribofuranosyl)-5-methyluracil, 1-(2-Deoxy-ß-L-ribofuranosyl) thymine, ß-L-Thymidine , 2'-Deoxy-ß-L-thymidine, L-Thymidine
Molecular Formula	$C_{10}H_{14}N_2O_5$
Molecular Weight	242.23
Structure Formula	Telbivudine, which presents 3 chiral centers, is the pure isomer with absolute configuration 2S, 4R and 5S



The Chemistry Review for NDA 22-154

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is NOT recommended for approval due to [redacted] b(4)

All CMC issues other than the [redacted] are adequately addressed.

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)

The drug substance, (ß-L-thymidine, LdT) is a synthetic thymidine nucleoside analogue with activity against hepatitis B virus (HBV). Telbivudine is a chiral compound with the 2S, 4R and 5S absolute configuration and is the unmodified ß-L enantiomer of the naturally occurring nucleoside, thymidine.

Telbivudine is [redacted] b(4)

The method of synthesis and qualification of supplier(s) have been reviewed and acceptable in a previous NDA for the telbivudine tablet. The commercial batches will be manufactured at Novartis Grimsby Ltd., UK and [redacted] by Novartis Pharma Stein AG, Switzerland. The commercial manufacturing process as well as controls for starting materials, reagents, process intermediate, and the new drug substance are acceptable. b(4)

The structure of LdT has been established by elemental analysis, UV/VIS, FTIR, ESI/MS, ^{1}H NMR and $^{13}CNMR$. Impurities (related substances) introduced during synthesis or degradation products formed during synthesis and /or storage have been studied in a previous NDA and low amount of related substances (<0.05% reporting threshold) and low amounts of residual solvents (1/3 to 1/10 of the ICH Q3C limits).

[redacted] b(4)

Acceptance criteria (AC) of 0.1% for related substances are proposed based on ICH guidance Q3A(R). b(4)

Stability of the DS was evaluated in the approved NDA for the TYZEKA™ tablet on 3 registration batches at long-term conditions (25°C/60%RH), intermediate conditions (30°C/70%RH) and accelerated conditions (40°C/75%RH) supporting a retest period of b(4)

The drug product, TYZEKA™ Oral solutions, 20 mg/mL is a clear to pale yellow solution. Pharmaceutical development studies were performed. Rationale for formulation, excipient selection and preservation were discussed. Thirty (30) mL provides the standard patient dose of 600 mg per day.

TYZEKA oral solution is manufactured by Novatis Pharma Stein AG via an b(4) process. In-process controls (with target/range) for the process steps are established. When applying these parameters within the validated ranges, none of the process steps are considered as critical. A representative batch of TYZEKA Oral solution typically consists of approximately Specification of the drug product includes appearance, identity, assay, impurities , unspecified, and total), content b(4) uniformity, and microbial limits An AC c for is proposed and accepted based on ICH guidance Q3B(R). The DP specification is established based on release and stability data from 3 registration stability batches and release data from 3 process validation batches. Stability of the drug product has been evaluated on 3 stability batches oral solutions) at long term conditions (25°C/60%RH, and 30°C/70%RH) for 18-24 months, accelerated conditions (40°C/75%RH) for 6 months, and 50°C/ambient RH and under light irradiation. No significant change was observed for all parameters tested. No degradation products were detected above the acceptance limits. The proposed shelf-life of two years is acceptable.

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

TYZEKA (telbivudine) is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

The recommended dose of TYZEKA is 600 mg once daily, taken orally, with or without food. For renal impaired patients, dose adjustment is required in patients with creatine clearance <50 mL /min as indicated in the package insert. The oral solution allows dose adjustment for renal impaired patients. A dosing cup is included.

TYZEKA Oral solutions are packaged in , bottles as b(4) 300 mL per bottle. The bottles are stored at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F). Use within two months after opening the bottle. Do not freeze.

C. Basis for Approvability or Not-Approval Recommendation

From a chemistry, manufacturing, and controls standpoint, the NDA is NOT recommended for approval due to the [redacted] b(4)

The CMC of the NDA was adequate prior to the [redacted]. All manufacturing facilities involved are now adequate and a final EES report is attached.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/ : A. Yu
ChemistryTeamLeaderName/ Steven Miller
ProjectManagerName/ Kenny Shade

C. CC Block

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Attachment of EES Report

07-OCT-2008 FDA CDER EES
Page 1 of 3

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22154/000
Org Code : 530
Priority : 3S

Sponsor: IDENIX PHARMA
60 HAMPSHIRE STREET
CAMBRIDGE, MA 02139

Stamp Date : 21-DEC-2007
PDUFA Date : 21-OCT-2008
Action Goal :
District Goal: 22-AUG-2008

Brand Name :TYZEKA
Estab. Name: TELBIVUDINE
Generic Name: TELBIVUDINE
Dosage Form: (SOLUTION)
Strength : 20 MG/ML

FDA Contacts: A. YU Review Chemist 301-796-1488

S. MILLER Team Leader 301-796-1418

Overall Recommendation: ACCEPTABLE on 19-SEP-2008 by S. ADAMS (HFD-325) 301-796-3193

Establishment : CFN : [redacted] FEI : [redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile : [redacted] OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9612220 FEI : 10656

NOVARTIS GRIMSBY LIMITED

PYEWIPE

GRIMSBY (S. HUMBERSIDE), , UK

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9617227 FEI : 3003157245

NOVARTIS PHARMA INC

SITE INDUSTRIEL DE HUNINGUE

HUNINGUE, , FR

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

07-OCT-2008 FDA CDER EES
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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

Profile : LIQ OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-SEP-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9692042 FEI : 3002865753

NOVARTIS PHARMA STEIN AG

SCHWEIZERHALLE, BASEL, SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAR-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9692043 FEI : 3002653483

NOVARTIS PHARMA STEIN AG

SCHAFFHAUSERSTRASSE

STEIN, , SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE ——— b(4)

Profile : CRU OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9611204 FEI : 3002807772

NOVARTIS PHARMACEUTICALS CORP.

LICHSTRASSE 35, ST. JOHANN SITE

BASEL, , SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-JAN-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9612715 FEI : 3002807776

NOVARTIS PHARMACEUTICALS CORP.

CORK

07-OCT-2008 FDA CDER EES
Page 3 of 3

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

RINGASKIDDY, CORK, , EI

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAR-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9614433 FEI : 3002807773

NOVARTIS PHARMANALYTICA SA

VIA SERFINO BLESTRA 31

LOCARNO, , SZ

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile	:	CTL	OAI Status: NONE
Last Milestone:		OC RECOMMENDATION	
Milestone Date:		30-JAN-08	
Decision	:	ACCEPTABLE	
Reason	:	BASED ON PROFILE	

--End of EES report --

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Yu
10/16/2008 09:37:42 AM
CHEMIST

Norman Schmuff
10/17/2008 10:28:20 AM
CHEMIST

NDA 22-154

TYZEKA™
(Telbivudine)
Oral solution

Novartis Pharmaceutical Inc.

Andrew Yu
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-154

2. REVIEW# 1

3. REVIEW DATE: 8/1/2008

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

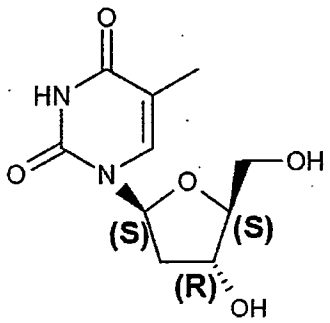
Submission(s) Reviewed	Document Date
Original	21/DEC/2007
Amendment BC (Name transfer)	03/JAN/2008
Amendment BC (Response to IR)	12/JSept/2008

7. NAME & ADDRESS OF APPLICANT:

Name	Novartis Pharmaceuticals, Inc.
Address	60 Hampshire Street, Cambridge, MA 02139
Representative	David Hallinan, Ph.D.
Telephone	617-995-9800

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: TYZEKA™
   b) Non-Proprietary Name (USAN): Telbivudine
   c) Code Name/# (ONDC only): LdT
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Antiviral
11. DOSAGE FORM: Oral solution
12. STRENGTH/POTENCY: 20 mg/mL
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:

INN	Telbivudine
Chemical Name	1-((2S, 4R, 5S)-4-Hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl- 1 H-pyrimidine- 2,4-dione
Other Names	1-(2-Deoxy-ß-L-ribofuranosyl)-5-methyluracil, 1-(2-Deoxy-ß-L-ribofuranosyl) thymine, ß-L-Thymidine , 2'-Deoxy-ß-L-thymidine, L-Thymidine
Molecular Formula	$C_{10}H_{14}N_2O_5$
Molecular Weight	242.23
Structure Formula	Telbivudine, which presents 3 chiral centers, is the pure isomer with absolute configuration 2S, 4R and 5S



17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]					Adequate	7/31/08, A. Yu	acceptable
					Adequate	5/03/01 Previously reviewed by D. Christodoulou	Additional information in NDA
					Adequate	A. Yu	Information in NDA

b(4)

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,459	Telbivudine Oral solutions and [redacted]

b(4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
Pharm/Tox			
Biopharm			
LNC			

Methods Validation	Not needed		
OPDRA			
EA	Exclusion Acceptable	7/28/08	Andy Yu
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-154

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval pending inspection of the manufacturing site (not completed as of 9/9/08). Several CMC clarification issues (page 66) were faxed to Novartis on 7/21/08 and have been adequately responded to on 9/12/08.

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)

The drug substance, (ß-L-thymidine, LdT) is a synthetic thymidine nucleoside analogue with activity against hepatitis B virus (HBV). Telbivudine is a chiral compound with the 2S, 4R and 5S absolute configuration and is the unmodified ß-L enantiomer of the naturally occurring nucleoside, thymidine.

Telbivudine is [redacted] The method of synthesis and qualification of supplier(s) have been reviewed and acceptable in a previous NDA for the telbivudine tablet. The commercial batches will be manufactured at Novartis Grimsby Ltd., UK and [redacted] by Novartis Pharma Stein AG, Switzerland. The commercial manufacturing process as well as controls for starting materials, reagents, process intermediate, and the new drug substance are acceptable. b(4) b(4)

The structure of LdT has been established by elemental analysis, UV/VIS, FTIR, ESI/MS, ^{1}H NMR and ^{13}CNMR. Impurities (related substances) introduced during synthesis or degradation products formed during synthesis and /or storage have been studied in a previous NDA and low amount of related substances (<0.05% reporting threshold) and low amounts of residual solvents (1/3 to 1/10 of the ICH Q3C limits). [redacted] b(4)

Acceptance criteria (AC) of 0.1% for related substances are proposed based on ICH guidance Q3A(R) [redacted] b(4)

[redacted]. Stability of the DS was evaluated in the approved NDA for the TYZEKA™ tablet on 3 registration batches at long-term conditions (25°C/60%RH), intermediate conditions (30°C/70%RH) and accelerated conditions (40°C/75%RH) supporting a retest period of [redacted] b(4)

The drug product, TYZEKA™ Oral solutions, 20 mg/mL is a clear to pale yellow solution. Pharmaceutical development studies were performed. Rationale for formulation, excipient selection and preservation were discussed. Thirty (30) mL provides the standard patient dose of 600 mg per day.

TYZEKA oral solution is manufactured by Novatis Pharma Stein AG via ar [redacted] b(4) process. In-process controls (with target/range) for the process steps are established. When applying these parameters within the validated ranges, none of the process steps are considered as critical. A representative batch of TYZEKA Oral solution typically consists of approximately [redacted] Specification of the drug product includes appearance, identity, assay, impurities [redacted], unspecified, and total), content uniformity, and microbial limits. [redacted] b(4) [redacted] An AC of [redacted] for [redacted] is proposed and accepted based on ICH guidance Q3B(R). The DP specification is established based on release and stability data from 3 registration stability batches and release data from 3 process validation batches. Stability of the drug product has been evaluated on 3 stability batches [redacted] oral solutions) at long term conditions (25°C/60%RH, and 30°C/70%RH) for 18-24 months, accelerated conditions (40°C/75%RH) for 6 months, and 50°C/ambient RH and under light irradiation. No significant change was observed for all parameters tested. No degradation products were detected above the acceptance limits. The proposed shelf-life of two years is acceptable.

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

TYZEKA (telbivudine) is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

The recommended dose of TYZEKA is 600 mg once daily, taken orally, with or without food. For renal impaired patients, dose adjustment is required in patients with creatine clearance <50 mL /min as indicated in the package insert. The oral solution allows dose adjustment for renal impaired patients.

TYZEKA Oral solutions are packaged in [redacted] bottles as 300 mL per bottle. The bottles are stored at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F). Use within two months after opening the bottle. Do not freeze. b(4)

C. Basis for Approvability or Not-Approval Recommendation

One manufacturing site is pending pre-approval inspection as of 9/9/08, and all other manufacturing and testing facilities were found acceptable. The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for the product of TYZEKA™ Oral solutions, 20 mg/mL.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/ : A. Yu
ChemistryTeamLeaderName/ Steven Miller
ProjectManagerName/ Kenny Shade

C. CC Block

58 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

05-MAY-2008 FDA CDER EES
Page 1 of 3

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22154/000 Sponsor: IDENIX PHARMA

Org Code : 530 60 HAMPSHIRE STREET

Priority : S CAMBRIDGE, MA 02139

Stamp Date : 21-DEC-2007 Brand Name : TYZEKA (TELBIVUDINE) ORAL

PDUFA Date : 21-OCT-2008 Estab. Name:

Action Goal : Generic Name: TELBIVUDINE

District Goal: 22-AUG-2008 Dosage Form: (SOLUTION)

Strength : 20 MG/ML

FDA Contacts: A. YU Review Chemist 301-796-1488

S. MILLER Team Leader 301-796-1418

--Overall Recommendation: ----------

Establishment : CFN : [redacted] FEI : [redacted] b(4)

[redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile : [redacted] OAI Status:
NONE b(4)

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9612220 FEI : 10656

NOVARTIS GRIMSBY LIMITED

PYEWIPE

GRIMSBY (S. HUMBERSIDE), , UK

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status:
NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9617227 FEI : 3003157245

NOVARTIS PHARMA INC

SITE INDUSTRIEL DE HUNINGUE

HUNINGUE, , FR

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

Profile : LIQ OAI Status: NONE

Last Milestone: ASSIGNED INSPECTION TO IB

Milestone Date: 05-MAR-08

:

:

Establishment : CFN : 9692042 FEI : 3002865753

NOVARTIS PHARMA STEIN AG

SCHWEIZERHALLE, BASEL, SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAR-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9692043 FEI : 3002653483

NOVARTIS PHARMA STEIN AG

SCHAFFHAUSERSTRASSE

STEIN, , SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE ——— b(4)

Profile : CRU OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9611204 FEI : 3002807772

NOVARTIS PHARMACEUTICALS CORP.

LICHSTRASSE 35, ST. JOHANN SITE

BASEL, , SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-JAN-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9612715 FEI : 3002807776

NOVARTIS PHARMACEUTICALS CORP.

CORK

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

RINGASKIDDY, CORK, , EI

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAR-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9614433 FEI : 3002807773

NOVARTIS PHARMANALYTICA SA

VIA SERFINO BLESTRA 31

LOCARNO, , SZ

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

This facility is pending inspection. Other sites are acceptable.

Establishment : CFN : 9617227 FEI : 3003157245

NOVARTIS PHARMA INC

****

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Yu
9/17/2008 12:16:10 PM
CHEMIST

Norman Schmuff
9/18/2008 08:42:12 PM
CHEMIST