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RESEARCH**

APPLICATION NUMBER:

21-797

21-798

CHEMISTRY REVIEW(S)

NDA 21-797

**Entecavir (BMS-200475) 0.5 mg and 1 mg
Film Coated Tablet**

Bristol-Myers Squibb Company

**Lorenzo Rocca, Ph.D.
Division of Anti-Viral Drug Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	12
III. Administrative.....	13
A. Reviewer's Signature.....	13
B. Endorsement Block.....	13
C. CC Block	13
Chemistry Assessment	14
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	14
S DRUG SUBSTANCE [Name, Manufacturer].....	14
P DRUG PRODUCT [Name, Dosage form].....	44
A APPENDICES	79
R REGIONAL INFORMATION	80
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	80
A. Labeling & Package Insert	80
B. Environmental Assessment Or Claim Of Categorical Exclusion	81
III. List Of Deficiencies To Be Communicated.....	82

Chemistry Review Data Sheet

1. NDA 21-797

2. REVIEW #: 1

3. REVIEW DATE: March 28, 2005

4. REVIEWER: Lorenzo Rocca, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>	<u>Document Description</u>
NDA 21-797, Submission	15-March-2005	Sponsor's responses to Clinical Pharmacology, Microbiology and CMC comments in the FDA facsimile of March 3, 2005.
Original NDA	30-September-2004	Original NDA
IND 52,196, Submission No. 262	1-July-2004	Requested consideration of the name Baraclude™
IND 52,196, Submission No. 218	6-January-2004	Requested consideration of the name Baraclude™
CMC End-of-Phase II meeting minutes	19-August-2003	CMC End-of-Phase II meeting (December 13, 2002) minutes
IND 52,196, Submission No. 172	14-April-2003	Proposed starting material and the facsimile received from FDA on June 19, 2003
IND 52,196, Submission No. 148	11-October-2002	Background document for CMC End-of-Phase II meeting
IND 52,196, Submission No. 137	15-August-2002	Information on stability protocols for drug substance and drug product

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	30-September-2004

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Bristol-Myers Squibb Company
5 Research Parkway
Address: P. O. Box 5100
Wallingford, CT 06492-7660
Representative: Michael E. Brady, Ph.D.
Telephone: 203-677-3812

8. DRUG PRODUCT NAME/CODE/TYPE:

- i. Proprietary Name: N/A
- ii. Non-Proprietary Name (USAN): Entecavir
- iii. Code Name/# (ONDC only): BMS-200475-01
- iv. Chem. Type/Submission Priority (ONDC only):
 - i. Chem. Type: 3
 - ii. Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-viral: Anti-Hepatitis B virus

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.5 mg and 1 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

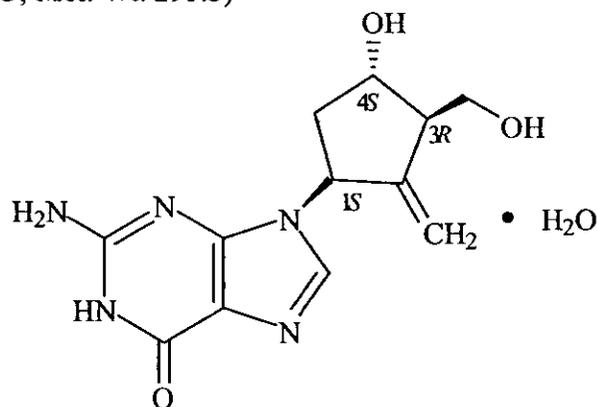
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

2-Amino-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one, monohydrate
(C₁₂H₁₅N₅O₃•H₂O; Mol. Wt. 295.3)



Entecavir

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	3	/	/	4	Adequate	NA	None
/	3	/	/	4	Adequate	NA	None
/	3	/	/	4	Adequate	NA	None
			/				
			/				

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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
Original IND	52,196	Original IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending	N/A	Thomas Hammerstorm, Ph.D.
EES	All Sites Approved	3/22/05	Office of Compliance (Establishment Report Appended)
Clinical Pharmacology	Pending	N/A	Kimberly Bergman, Pharm.D.
Pharm/Tox	Pending	N/A	Peter Verma, Ph.D.
LNC	USAN Available	N/A	N/A
Methods Validation	FDA Method Validation Waved	10/21/04	Lorenzo Rocca, Ph.D.
OPDRA	Completed	3/4/05	N/A
EA	Categorical Exclusion Granted	10/21/04	Lorenzo Rocca, Ph.D.
Microbiology	Pending	N/A	Lisa Naeger, Ph.D.

The Chemistry Review for NDA 21-797

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is approved from a CMC perspective. All sites involved in the manufacturing, packaging and testing of drug substance and drug product have been found acceptable by the Office of Compliance. All other CMC issues are resolved.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Entecavir (BMS 200475-01) is a cyclopentyl guanine analog that has been developed by Bristol-Myers Squibb (BMS) Company for the treatment of Hepatitis B virus. BMS has developed a film coated tablet formulation in two commercial strengths, 0.5 mg and 1 mg, for oral administration. The Entecavir Film Coated Tablet, 0.5 mg and 1 mg is the subject of NDA 21-797. BMS has also developed Entecavir Oral Solution, 0.05 mg/mL. The entecavir oral solution is the subject of NDA 21-798.

Entecavir monohydrate drug substance is a white crystalline powder which is synthesized as a single isomer (1*S*, 3*R*, 4*S*) following the commercial — During development, the early batches of entecavir drug substance used in clinical studies were made by — . Relative to — used different — used the same of — and proceeded through the same — as that of — but there were some minor differences with regard to the — procedures. The FDA previously agreed that — are appropriate starting materials for the synthesis of entecavir monohydrate (IND 52,196, Submission No. 172 dated April 14, 2003 and FDA's facsimile reply to the sponsor, dated June 19, 2003). — are not discussed by the sponsor because no clinical batches were made using them. The drug substance has three chiral centers and is synthesized as a single isomer (1*S*, 3*R*, 4*S*). Two stereocenters (3*R*, 4*S*) are controlled by the — . The sponsor has adequate acceptance specifications and in process controls to assure that the

synthesis. The third chiral center results from a — The sponsor has adequately demonstrated that the parameters (i.e., —

CHEMISTRY REVIEW

Executive Summary Section

The HPLC method developed for the detection of impurities in the drug substance is able to adequately monitor for the possible diastereoisomers of the drug substance. These impurities are detected at less than [redacted]. Likewise, the presence of the enantiomer of the drug substance (i.e., [redacted]), as monitored by [redacted] HPLC, and was found to be present at a level of less than [redacted]. Therefore, it can be concluded that effective stereochemical control of entecavir monohydrate is achieved during synthesis of the drug substance by the commercial [redacted].

The majority of toxicological studies performed in support of NDA 21-797 used drug substance synthesized by [redacted]. The entecavir drug substance batches synthesized by [redacted] had total impurity content values ranging from [redacted] which compares to a total impurity content of approximately [redacted] or less for entecavir drug substance batches synthesized by either [redacted] or the commercial [redacted]. Toxicological studies used to support NDA 21-797 have used drug substance batches which are less pure than the commercial drug substance. The impurity profile for batches of drug substance made by the commercial process are consistently manufactured with individual impurity levels less than [redacted], and [redacted] below the level of detection for all possible [redacted] impurities. In addition, the appropriate in process controls are in place to assure that stereochemical control of the synthesis is achieved. The sponsor has also performed extensive [redacted] studies to confirm that all known drug substance impurities are either removed during [redacted] or are limited to an acceptable level. The results of these studies support the sponsor's proposed specifications for the intermediates involved in the synthesis of entecavir monohydrate. Since all impurities (known and unknown) are seen at levels less than [redacted] the sponsor proposes an Individual Impurities (HPLC) specification of NMT [redacted] and a Total Impurities (HPLC) specification of NMT [redacted] for the drug substance. The impurity discussion and the impurity profiles for drug substance lots synthesized by [redacted] support the sponsor's proposed impurity specifications. [redacted] have not been detected in any of the lots of drug substance synthesized by [redacted] therefore, the sponsor has not proposed [redacted] specifications. However, [redacted] of the synthesis. The FDA recommends that the sponsor include a [redacted] release specification for these [redacted] consistent with the current ICH guidance Q3C. The remaining specifications for entecavir monohydrate drug substance (i.e., [redacted]), are adequate to assure the identity and quality of the drug substance.

CHEMISTRY REVIEW

Executive Summary Section

Entecavir drug substance is manufactured, packaged, tested and released at BMS's facility in Swords, Ireland. The BMS facility in Swords, Ireland has been found acceptable by the Office of Compliance (OC) for manufacture of entecavir monohydrate drug substance. The drug substance is slightly soluble (2.4 mg/mL) in water (USP definition), and the solubility remains virtually unchanged in the pH range — The drug substance BCS solubility classification is highly soluble based on a maximum dose of 1 mg per day. The drug substance is

The drug substance physicochemical characteristics are not expected to influence drug product performance or drug product quality.

The entecavir solid oral dosage form is being developed as a triangular white (0.5 mg) and pink (1 mg) film coated tablet debossed on one side with "BMS", and "1611" or "1612" on the other for 0.5 mg and 1 mg strength, respectively. The entecavir film coated tablet is not scored. Both tablet strengths of entecavir will contain entecavir monohydrate (amount based on a theoretical potency of , as well as lactose monohydrate (NF), microcrystalline cellulose (NF), crospovidone (NF), povidone (USP) and magnesium stearate (NF). The — tablet film coat — , used to manufacture drug product are commercially available from — . The qualitative and quantitative composition of the film coat — have been reviewed and found safe to use in the manufacture of entecavir film coated tablets. No novel excipients are used in the manufacture of entecavir film coated tablets. The lactose monohydrate is certified by the supplier to not contain or is not derived from specified risk materials. The magnesium stearate is certified by BMS to be derived from plant source, and BMS certifies that there are no materials used in the manufacture of Entecavir Film Coated Tablets, 0.5 mg and 1 mg that are derived from cell lines of human origin or from cell lines of animal origin. The sponsor's statements confirm there is low risk from BSE contamination.

Entecavir drug product will be manufactured as 0.5 mg and 1 mg triangular film-coated tablets from — . The sponsor does not describe any — , associated with drug product or drug substance manufacture. However, the —) are adequate to assure the identity and quality of the drug product. This is confirmed by the fact that the sponsor has been able to manufacture — registration batches (—

CHEMISTRY REVIEW

Executive Summary Section

batches of each strength) of Entecavir Film Coated Tablets, 0.1 mg, 0.5 mg and 1 mg at the commercial site which all meet the in-process testing limits. These registration batches have been placed in the sponsor's long term stability study (LTSS). Approval for the 0.1 mg tablet strength is not requested in this submission. However, the 0.1 mg tablet has been included in the sponsor's long term stability study (LTSS).

A capsule formulation was developed for use in Phase I and Phase II entecavir clinical studies. They were available in 0.01 mg, 0.05 mg, 0.1 mg, 0.5 mg, 1 mg, 2 mg, 2.5 mg, 5 mg and 10 mg strengths as capsules manufactured using a

For later clinical studies 0.1 mg, 0.5 mg and 1 mg film coated tablets were developed. The 0.5 mg and 1 mg film coated entecavir tablets were developed as the commercial formulation. The compositions of the proposed commercial film coated tablets are identical to that of the clinical tablets. The difference between the proposed commercial tablets and the clinical tablets is only in the appearance (shape and debossing). The drug product stability samples are identical to the commercial product except for the

. These differences are not expected to alter the physical/chemical stability of the drug product. BMS has manufactured at the proposed commercial manufacturing site a 0.1 mg film coated tablet strength from a

Approval for the 0.1 mg film coated tablet strength is not requested in this submission. However, the 0.1 mg film coated tablet strength has been placed on LTSS to bracket the 0.5 mg tablet.

As per strength of Entecavir Film Coated Tablets, 0.1 mg, 0.5 mg and 1 mg were manufactured at the BMS manufacturing facility in Mount Vernon, IN, and are being monitored in the sponsor's long term stability study (LTSS). BMS has performed pivotal bioequivalence studies on 0.5 mg and 1 mg entecavir film coated tablets that are prepared from a. In the first study the 0.5 mg entecavir film coated tablet was compared to 0.5 mg entecavir clinical capsule. In the second study, the 0.5 mg entecavir film coated tablet was compared to the 1 mg entecavir film coated tablet. The results confirmed the bioequivalence of the earlier clinical capsule formulation to the proposed commercial film coated table, and the bioequivalence of the 0.5 mg and 1 mg film coated table formulation of entecavir. Because the capsule and tablet formulations have been determined to be bioequivalent comparability studies are not required.

The drug product specifications are acceptable, and the sponsor has provided adequate justification for their proposed specifications. The proposed dissolution specification of NLT (Q) dissolved in is supported by the LTSS. The sponsor's dissolution conditions (USP Apparatus 2 (paddles),

, were found acceptable by the FDA's at the End-of-Phase II meeting on December 13, 2002. The LTSS shows that tablet

after storage in bottles at either 5°C, 25°C/60%RH or 30°C/70%RH. The

Based on these results the FDA finds the sponsor's decision not to include a release specification for entecavir film coated tablets acceptable. The

CHEMISTRY REVIEW

Executive Summary Section

impurities specification for the drug product reflect the fact that all individual impurity/degradation values for entecavir film coated tablets were less than _____ except for one value _____, which was seen in a 0.1 mg tablet stored at 25°C/60%RH after _____. This impurity (i.e. _____) has been identified as the _____.

The ICH (Q3B(R)) identification threshold for individual impurity/degradants in a drug product with a maximum daily dose of 1 mg to 10 mg is 0.5%. The maximum daily dose for entecavir film coated tablets is 1 mg. The impurity is seen at a level in excess of 0.5% in only one lot of the 0.1 mg strength tablet, and is inconsistent with all other values for _____ seen in lots of 0.1 mg tablets in 30-count bottles stored at 25°C/60%RH or 30°C/70%RH for up to _____. In addition, the impurity _____ is expected to be _____.

Based on the stability data, the proposed release specifications for impurities/degradants in entecavir film coated tablets of NMT _____ individual and NMT _____ Total Impurities are acceptable.

Categorical exclusion from the requirement to file an Environment Assessment is requested by the sponsor based on their claim being in accordance with 21 CFR 25.31(b). BMS states that to their knowledge no extraordinary circumstances exist (21 CFR 25.15(d)). The sponsor's proposed container label is in accordance with the CFR drug labeling requirements (21 CFR 201.10 (g)(2)).

The Quality Overall Summary in NDA 21-797 Module 2 is an 82 page summary of CMC. The summary highlights the key points covered in greater detail in Module 3 including pharmaceutical development, description of the composition of the drug product, control of excipients and drug product, justification of drug product specifications, drug product container closure system and drug product stability. The material presented in the Quality Overall Summary is sufficient, in this reviewer's opinion, to allow for an accurate preliminary evaluation of the CMC portion of NDA 21-797.

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

The usual recommended oral dose of entecavir film coated tablets in adults and adolescents older than 16 years is 0.5 mg once daily, administered on an empty stomach (at least 2 hours before and at least 2 hours after a meal). For lamivudine-refractory patients [patients with evidence of viremia while on therapy with lamivudine or the presence of LVD^R (YMDD) mutations], the recommended dose is 1 mg once daily. Dosage adjustment is recommended for patients with creatine clearance <50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). The recommended dosage adjustment is described in the proposed entecavir package insert. The entecavir film coated tablets will be distributed in 30-count and 90-count _____ bottles with a _____.

BMS has incorporated the 0.1 mg strength entecavir tablet into their drug product LTSS in order to bracket the 0.5 mg strength commercial product. The FDA agreed to the stability study design at the End-of-Phase _____.

Executive Summary Section

II meeting on December 13, 2002. Approval for the 0.1 mg tablet strength is not requested in this submission. For the LTSS entecavir tablets were also packaged into

Approval for the [redacted] are not requested in this NDA. Tablets stored in the [redacted] were stable from initial after storage for [redacted] at 30°C/60%RH. Drug product [redacted] showed only a slight increase in total impurities. Bulk storage of entecavir tablets in the [redacted] and the proposed commercial container closure system is suitable for the storage of entecavir film coated tablets. BMS is proposing a 24-month expiry for entecavir film coated tablets. The LTSS test results for Entecavir Film Coated Tablet, 0.1 mg, 0.5 mg and 1 mg support a 24-month expiry at 25°C (77°F) when drug product is stored in the commercial container closure system. Further more,

C. Basis for Approvability or Not-Approval Recommendation
 NDA 21-797 is approved for CMC.

The CMC for entecavir drug substance are adequately described in NDA 21-797. All sites involved in the manufacture, packaging and testing of entecavir drug substance and drug product have been found acceptable by the Office of Compliance, and the Establishment Evaluation Request Detail Report is appended to this review. The composition, manufacturing process and specifications for Entecavir Film Coated Tablet, 0.5 mg and 1 mg are adequate to assure the identity and quality of the drug product. The container/closure system is adequate to assure the drug product will be stable and protected. The sponsor's proposed 24 month expiration dating period is acceptable, and is supported by the available drug product stability data. The drug product package insert and patient information has been reviewed for CMC and found adequate. On March 3, 2005 the FDA sent by facsimile comments on clinical pharmacology, microbiology and CMC review of NDA 21-797 (entecavir tablet) as well as NDA 21-798 (entecavir oral solution). The sponsor provided their responses in their letter to the FDA dated March 15, 2005. The sponsor has adequately responded to the CMC comments. The CMC comments and the BMS's responses are described in the *Chemistry Assessment* portion of this review.

III. Administrative

A. Reviewer's Signature

Lorenzo Rocca, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Stephen P. Miller, Ph.D. {Signed Electronically in DFS}/Date

C. CC Block

Norman Schmuff, Ph.D.
Marsha Holloman, BS Pharm, JD

71 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

/s/

Lorenzo Rocca
3/28/05 01:20:40 PM
CHEMIST

Stephen Paul Miller
3/28/05 02:18:02 PM
CHEMIST
NDA 21-797 is recommended for approval from the CMC
perspective