

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201152Orig1s000

CHEMISTRY REVIEW(S)

NDA 201-152
Nevirapine Extended Release Tablet 400 mg
Boehringer Ingelheim

Shrikant Pagay
Chemistry Reviewer
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA or ANDA 201-152
2. REVIEW #: 1
3. REVIEW DATE: 10/25/2010
4. REVIEWER: Shrikant Pagay
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

6/3/2010

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim
Address: 900 Ridgeway Road
Ridgefield, CT 06877-0368
Representative: Maria Gigliotti
Telephone: (203) 798- 9988

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: XR
b) Non-Proprietary Name (USAN): Nevirapine
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti viral

11. DOSAGE FORM: Extended Release Tablet

12. STRENGTH/POTENCY: 400 mg/Tablet

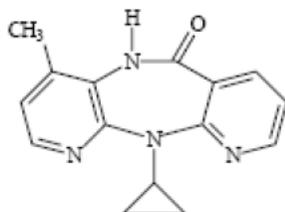
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product Form Completed Not a SPOTS product

Chemistry Review Data Sheet

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

Specification Type	R=Registration
Substance Name	Nevirapine, Anhydrous
Chemical name	5,11-Dihydro-6H-11-cyclopropyl-4-methyl-dipyrido-[3,2-b:2',3'-e][1,4] diazepin-6-one
Relative molecular mass	266.3
Empirical formula	C ₁₅ H ₁₄ N ₄ O
Structural formula	



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			
	III			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")

Chemistry Review Data Sheet

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	74,744	
NDA	20,636	IR Tablet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	7/13/2010	
Pharm/Tox	NA		
Biopharm	NA		Separate review by S. Suarez Sharp
LNC	NA		
Methods Validation	NA		
DMEPA	Comments provided	2/4/2011	Miele
EA	NA		
Microbiology	NA		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

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 201-152

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval from CMC perspective.

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

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Nevirapine was developed as the first non-nucleoside reverse transcriptase inhibitor (NNRTI). The drug substance is white to off-white crystalline material. It is a weak base; the aqueous solubility is dependent upon the pH. Solubility in pH 1.5 is 1.9 mg/mL and in neutral buffer is only 0.078 mg/mL. The octanol/water coefficient is 1.8 indicating the drug is lipophilic. Nevirapine is classified under Biopharmaceutical Classification System (BCS) as a highly permeable drug with low solubility. There are no optical or geometric isomers of nevirapine. Nevirapine has 2 morphic forms – anhydrous form and a hemi hydrate form. The proposed drug is anhydrous. Nevirapine is non-hygroscopic and thus remains stable as the anhydrous form. Nevirapine used in the drug product (b) (4). The drug substance was previously reviewed under Nevirapine 200mg immediate release tablet NDA 20-636. The proposed NDA is for the extended release tablet primarily to improve patient compliance.

Drug Product: The proposed NDA is for nevirapine extended release tablet for once a day dosing. The tablets are yellow, biconvex and oval. The tablet logo embossed on one side as “V04” and the other side as BI tower (Company symbol). The proprietary name is “Viramune XR”. An extended release (b) (4) 400 mg tablet is proposed in the NDA.

(b) (4) Although, no specific explanation was provided in the submission, a 400 mg dose would be difficult to deliver through some type controlled release coating application, e.g. drug coated particles filled in a capsule or compressed as a tablet. (b) (4)

Executive Summary Section

(b) (4) The high solubility of nevirapine in the acidic pH would favor high % drug release under gastric pH. However, this can be controlled through formulation. The manufacturing process is technologically cost effective and can be well controlled.

The proposed drug product is designed to achieve in-vivo-in vitro correlation for the drug delivery. The drug solubility, pH solubility profile, octanol /water partition coefficient, and biopharmaceutical studies to assess the drug absorption were taken into consideration in developing the dosage form. The total tablet weight is 1094 mg; the size of a (b) (4) tablet at this weight is that of a typical multivitamin tablet. The tablet components besides the drug substance are: lactose monohydrate (b) (4), hypromellose (b) (4), iron oxide (b) (4) and magnesium stearate (b) (4). The manufacturing process includes (b) (4).

(b) (4) The finished tablets are stored in plastic bottles (HDPE). All the raw materials, specifically, nevirapine, hypromellose and lactose were extensively characterized during the formulation development and controlled. It is critical that the raw materials including the drug substance meet certain quality attributes for batch reproducibility in terms of tablet hardness and porosity essential to achieve the reproducible dissolution rate. The proposed shelf life is (b) (4) when stored at 25°C with excursion permitted between 15 – 30°C.

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

The drug product is intended to be used with other anti-HIV medications, and with nevirapine 200 mg immediate release tablet (for the initial half-dose run-in period). Viramune XR tablets can be taken with or without a meal. Because it is an extended-release tablet, the labeling will warn patients not to break or chew the tablet.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendations.

All labels have the required information.

Executive Summary Section

The separate Biopharmaceutics review (Sandra Suarez Sharp) covers the acceptability of the dissolution method, and assesses the in vivo in vitro correlation (IVIVC).

III. Administrative**A. Reviewer's Signature : ESO**

Shrikaant N. Pagay

B. Endorsement Block

ChemistName/Date: Shrikant Pagay
ChemistryTeamLeader: Stephen Miller
ProjectManagerName/Date

C. CC Block

41 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

SHRIKANT N PAGAY
02/24/2011
CMC Review

STEPHEN P MILLER
02/24/2011
I concur - this NDA is recommended for approval from the CMC perspective

Initial Quality Assessment
Branch V
Division of New Drug Quality Assessment II

OND Division: Division of Anti-Viral Products
NDA: 201-152
Applicant: Boehringer Ingelheim
Stamp Date: June 03, 2010
Proposed Trademark: Viramune® XR™
Established Name: nevirapine extended release tablets
Dosage Form: Tablets
Route of Administration: Oral
Strength: 400 mg
Indication: Treatment of HIV Infection
Reviewer: Suresh Pagay
CMC Lead: Dorota Matecka (Acting)

	YES	NO
Acceptable for filing:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues

Introduction

This NDA has been submitted in the eCTD format and was available in the EDR on the stamp date of June 03, 2010. This NDA provides for a new dosage form of nevirapine, extended release tablet, developed for a once-daily application and will be reviewed on a standard (10 month) timeline.

Nevirapine extended release tablet is indicated for use in the combination with other antiretroviral agents for the treatment of HIV-1 infection. The recommended dose for nevirapine immediate release 200 mg tablet is one tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents. For patients intending to begin treatment with the proposed nevirapine extended release tablets, (b) (4)

The clinical development program of nevirapine extended release tablets for the proposed indication included three Phase I studies and two Phase III studies. The Phase I studies determined the intestinal absorption of nevirapine, the PK profile, and the optimal formulation. Clinical efficacy for the nevirapine extended release tablets program was

established based on two Phase III controlled studies conducted in adult HIV-1 infected patients (Studies 1100.1486 and 1100.1526).

IND Development

The proposed drug product has been developed under IND 74,744.

The discussion and agreements reached during the pre-NDA meeting (October 19, 2009) are available from DARRTS.

The discussion and agreements reached during the IND EOP2 phase (document containing CMC comments in lieu of face-to-face EOP2 meeting dated October 11, 2007) are available from DARRTS.

Some documentation on earlier IND development including the IND safety review is located at: ondcS1 on cdsnas\DPA2\Branch 4\DAVP Applications\74 744 Nevirapine ER Tabs.

Some earlier studies via IND 74,744 (b) (4) only 400 mg strength is currently planned for commercialization.

Other Applications that are relevant to this review

NDA 20-636 for Viramune (nevirapine) Tablets, 200 mg; approved June 1996. A copy of the CMC NDA review is located at: ondcS1 on cdsnas P:\CMC-Reviews-from-Action-Packages\Extracted-CMC-Reviews\ODE-4 Captured\530 Captured.

NDA 20-933 for Viramune (nevirapine) Oral Suspension, approved September 1998.

IND 36,026 for Viramune (nevirapine) Tablets and Oral Suspension.

IND 74,744 for nevirapine extended-release tablets.

Drug Substance

Per agreement at the October 19, 2009 pre-NDA meeting, the applicant cross-referenced the Viramune® NDA (20-636) for all drug substance information. However, per FDA's request, general information (i.e. section 3.2.S.1) and a specification have also been provided in the current NDA. In addition, a report describing the performance of the extended release drug product has been included in the Pharmaceutical Development report in 3.2.P.2, to support the currently approved drug substance specification for the new nevirapine formulation.

Comment: It appears (from DARRTS) that a new manufacturing supplement (CMC supplement # 34) was submitted to NDA 20-636 on June 2, 2010. It would be appropriate to assess if the proposed change has any effect on the currently proposed drug product (e.g. if any EES action is necessary).

Drug Product

The proposed drug product, Viramune® XR (nevirapine extended release tablets) 400 mg, are yellow, oval, biconvex tablets. The tablets are debossed with product identification “V04” on one side and the BI tower logo on the other side. The tablets are for oral administration.

The proposed drug product composition is attached below in the Appendix I to this review.

(b) (4) tablet design was developed using hypromellose (b) (4)

Other inactive components include lactose monohydrate (b) (4) iron oxide (b) (4)
(b) (4) magnesium stearate (b) (4)

All of the excipients within the formulation are compendial, non-novel excipients controlled to the requirements of the current monograph in the USP/NF.

Comment: Lactose monohydrate is the only excipient in nevirapine extended-release tablets, (b) (4)

Module 3 contains complete drug product documentation for the to-be-marketed 400 mg dose strength. (b) (4)

The manufacturing process for the drug product involves (b) (4)

The executed batch record has been provided for a production scale primary stability batch (batch no. 089103; (b) (4)) in section 3.2.R.

1. Pharmaceutical Development, Quality Control Strategy including DP Specifications

The pharmaceutical development section includes three documents:

A. Document No.: U10-3066-01

This report summarizes the development of nevirapine extended-release tablets and includes a discussion of formulation development (b) (4)

Nevirapine drug substance is classified as a Biopharmaceutics Classification System (BCS) Class II

compound due to its low solubility and high intestinal permeability. It exists in two polymorphic crystalline forms, an anhydrous form and a less soluble hemihydrate form. The anhydrous form is used for both the currently-marketed immediate-release tablets and the proposed extended-release tablets.

Per EOP2 agreements, a discussion of the effect particle size of hypromellose, lactose, and nevirapine drug substance on the drug product performance (using software package GastroPlus®) has been included in this report. Development of the manufacturing process including discussion of (b) (4), tablet weight and tablet hardness is also described. After making the Phase III clinical trial supplies it was found that the tablets (b) (4)

Comment: The controls proposed in the manufacturing process including hardness as in-process control and their effect on the dissolution of the tablets should be assessed in detail.

B. Document No.: U10-3067-01

This report entitled “Development of Dissolution Method and Establishment of Level A In vitro In vivo correlation for Nevirapine Extended-Release Tablets, 400 mg” will be reviewed by the biopharmaceutics review group in ONDQA.

C. Document No.: U10-3070-01

This report describes the clinical formulations of nevirapine extended-release tablets, which have been used in clinical studies in the dosage strength (b) (4) 400 mg. In addition, information on matching placebos for the nevirapine extended-release tablets and for the commercial nevirapine product, Viramune® (nevirapine) tablets 200 mg, is also included.

The drug product specification table is included in the Appendix I to this IQA.

The proposed drug product specification includes the following tests: description, identification (by HPLC and UV), dissolution, uniformity of dosage units (by weight variation), assay, and degradation products. The proposed testing conditions for a dissolution method are as follows:

Medium ... 0.04 M Phosphate Buffer, pH 6.8, with 2.0% SDS, 900 mL
Temperature ... 37 ± 0.5° C
USP/Ph.Eur Apparatus I ... 75 rpm
Sampling Time ... (b) (4)
400 mg: 2, 8, and 20 hours

(b) (4)

As no degradation products have been observed during the course of development, the proposed test for degradation products includes acceptance criteria only for any unspecified degradation product (b) (4) and total degradation products (b) (4) calculated by summing all individual degradation products observed at a level equal to or greater than the reporting threshold (0.1%).

Tests performed as in-process controls but not included in the specification include: hardness and (b) (4)

Comment: This proposal should be carefully evaluated (per the EOP2 recommendations from the Agency, the results of the (b) (4) have been collected for the tablets on stability).

Tests not proposed for inclusion in the drug product specification include: inorganic impurities, microbiological quality, and (b) (4)

(b) (4)

Comment: The compliance (b) (4) should be evaluated for the drug product (b) (4)

General information and analytical results for the batches used in clinical studies, process transfer, stability studies and process validation are provided in section 3.2.P.5.4. All batches correspond to the to-be-marketed formulation as presented in Section 3.2.P.1, except for batch PD-2705 (b) (4)

2. Packaging Configuration

Tablets (30 count per statement on the container label) are packaged into a plastic bottle (60 cc), with a plastic child resistant cap and an induction foil seal liner. The surfaces which are in direct contact with the product are high density polyethylene (HDPE) and the induction foil seal liner. Additional information including references to applicable food additive regulations has been provided in section 2.3.P.6 and 3.2.P.2 (document U10-3066-01). In addition, letters of authorization to two DMFs for the proposed packaging components have been included in Module 1.

3. Stability

Primary stability studies were conducted on six batches of nevirapine extended-release tablets, 400 mg packaged in HDPE bottles with induction-sealed child resistant closures. The composition of the six batches is identical to the composition of the proposed commercial drug product. All batches were manufactured at the intended commercial manufacturing site, Boehringer Ingelheim Roxane, Inc. (BIRI) using the same processes described for commercial manufacturing.

Three of the batches are designated as primary stability batches (batches 4000179, 4000180 and 4000181) for which stability results through 6 months at the long-term storage condition (25°C/60%RH) and the accelerated storage condition (40°C/75%RH) are available. For three additional full scale batches (089101, 089102 and 089103), (b) (4), results from 18 months at the long-term storage condition and 6 months at the accelerated storage condition have been included.

Stability studies have been conducted for the product packed in white, high density polyethylene (HDPE), 60 cc, wide mouth square (33/400) with two-piece continuous threaded 33/400 plastic child resistant closure with induction foil seal. The description of the container closure system used in the stability studies appears identical to the proposed commercial packaging configuration; however, the type of (b) (4) and suppliers were not provided. *Do we care? Also, the tablet count used was not stated either (or I missed it).*

Intended primary stability batches, 089101, 089102 and 089103 contained (b) (4) was not used for batches 4000179, 4000180, and 4000181 (b) (4)

The statistical analysis (per ICH guideline Q1E "Evaluation for Stability Data") was performed on stability results for assay and dissolution statistical software SAS version 8.02. The results of this analysis have been discussed in the stability section.

At the pre-NDA telecon, an agreement was reached that additional stability data will be submitted within three months of the NDA submission. Batches 4000179, 4000180 and 4000181 were manufactured in August 2009 and put on stability in October 2009, so additional data should be available by now.

Comment: The applicant has not mentioned any plans for the submission of additional stability data that in their NDA submission.

The proposed drug product appears to be quite stable. No degradation products exceeding the reporting threshold of 0.1% have been observed during long-term or accelerated stability testing. Other parameters also seem to be unchanged except for appearance for the tablets manufactured (b) (4)

Comment: Detailed analysis will be needed to confirm these stability trends including dissolution results (this will be done in consultation with the biopharmaceutics reviewer).

Post-approval stability protocol and stability commitments have been submitted in section 3.2.P.8.2. The (b) (4) expiration dating has been proposed for nevirapine extended-release tablets, 400 mg, packaged in 60 cc HDPE bottles, is (b) (4) for climatic zone II. The recommended storage statement is: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

4. Labeling

Color mock-ups of the container labels (trade and sample bottle labels, both 30-count) are provided in Module 1. Both appear to contain the same information; however, the sample bottle label does not include the NDC number.

No carton label has been provided. As described above, no carton use seems to be proposed although there are two secondary manufacturing facilities listed in the list of manufacturing facilities for the drug product. *This will need to be clarified with the applicant.*

The package insert is provided in the PLR format.

Comment: It is not clear if there are any plans to make this product available for a non-US market.

EES Information

Already entered (June 14, 2010 by Jeannie David)

Early action needed

The discussion with the ONDQA biopharmaceutics reviewer regarding the proposed IVIVC and dissolution for the drug product should take place early in the review cycle.

Comments for 74-Day Letter

Biopharmaceutics comments will be included in 74-day letter (for details refer to Biopharmaceutics Filing Review signed off on July 15, 2010 in DARRTS).

Comments and Recommendations

Based on the information assessed for this IQA, this NDA is judged to be complete for filing (refer to Appendix II, below). Issues which may merit discussion are highlighted in *Italics* in this IQA.

Dorota Matecka, Ph.D.
Acting CMC Lead

See DARRTS
Date

Stephen P. Miller, Ph.D.
Acting Branch Chief

See DARRTS
Date

Appendix I

Drug Product Composition

Table 1 Qualitative and quantitative composition of nevirapine extended-release tablets, 400 mg

Name of Ingredient	mg per tablet	Function	Reference to Standards
Nevirapine Anhydrous	400.00 mg	Drug Substance	Company Standard
Lactose Monohydrate			NF/Ph. Eur.
Hypromellose, 			USP/Ph. Eur.
Iron Oxide 			
Magnesium Stearate			NF/Ph. Eur.
			USP/Ph. Eur.
Total Weight	1094 mg*		

 (b) (4)

Drug Product Specification

Test	Analytical Procedure	Acceptance Criteria								
Description	Visual	Yellow, oval, biconvex tablets debossed with product identification "V04" on one side and the BI tower logo on the other side.								
Identification A (HPLC)	1651-01	The retention time of the nevirapine peak of the sample preparation corresponds (b)(4) to that of the standard preparation.								
Identification B (UV)	1651-01	The UV spectrum of the nevirapine peak of the sample preparation corresponds to that of the standard preparation.								
Dissolution	1651-02	Meets USP requirements (L1, L2, L3): <table border="0" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: left;"><u>Time</u></th> <th style="text-align: left;"><u>% Label Claim Dissolved</u></th> </tr> </thead> <tbody> <tr> <td>2 hours</td> <td>Not more than (b)(4)</td> </tr> <tr> <td>8 hours</td> <td>(b)(4)</td> </tr> <tr> <td>20 hours</td> <td>Not less than (b)(4)</td> </tr> </tbody> </table>	<u>Time</u>	<u>% Label Claim Dissolved</u>	2 hours	Not more than (b)(4)	8 hours	(b)(4)	20 hours	Not less than (b)(4)
<u>Time</u>	<u>% Label Claim Dissolved</u>									
2 hours	Not more than (b)(4)									
8 hours	(b)(4)									
20 hours	Not less than (b)(4)									
Uniformity of Dosage Units	USP <905> by Weight Variation	Meets USP requirements (S1, S2) (b)(4)								
Assay	1651-01	(b)(4) of label claim								
Degradation Products	1651-01	Any Unspecified Degradation Product: Not more than (b)(4) Total Degradation Products: Not more than (b)(4)								

APPENDIX II

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

Filing Checklist

NDA Number: 201-152 Supplement Number and Type: Established/Proper Name:
nevirapine extended-release
tablets

Applicant: Boehringer Letter Date: 03-Jun-2010 Stamp Date: 03-Jun-2010
Ingelheim

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substances manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	✓		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			For all CMC drug substance information cross-reference is provided to NDA 20-636.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See above
14.	Does the section contain information regarding the characterization of the DS?			See above
15.	Does the section contain controls for the DS?			See above
16.	Has stability data and analysis been provided for the drug substance?			See above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			See above
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			See above

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?		✓	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			N/A
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			N/A

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	✓		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	III			03-Apr-2008	
	III			30-Apr-2008	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		There is no proposal to use cartons.

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	✓		

36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	✓		Biopharmaceutics comments*
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* For details regarding biopharmaceutics filing decision (FILABLE) and comments see Biopharmaceutics Filing Review signed off on July 15, 2010 in DARRTS

{See appended electronic signature page}

Dorota Matecka
Acting CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Stephen Miller
Acting Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201152	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	Nevirapine Extended Release Tablets

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/s/

DOROTA M MATECKA
07/27/2010

STEPHEN P MILLER
07/27/2010

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

Filing Checklist

NDA Number: 201-152 Supplement Number and Type: **Established/Proper Name:**
VIRAMUNE® XR
(nevirapine extended-release tablets)

Applicant: Boehringer Ingelheim Letter Date: 03-Jun-2010 Stamp Date: 03-Jun-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

7.	<p>Are drug substances manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	✓		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			For all CMC drug substance information cross-reference is provided to NDA 20-636.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See above
14.	Does the section contain information regarding the characterization of the DS?			See above
15.	Does the section contain controls for the DS?			See above
16.	Has stability data and analysis been provided for the drug substance?			See above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			See above
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			See above

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?		✓	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			N/A
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			N/A

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	✓		

G. MICROBIOLOGY				
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DMF # <small>(b) (4)</small>	TYPE	HOLDER	ITEM REFERENCED <small>(b) (4)</small>	LOA DATE	COMMENTS
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J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓		

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	✓		
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	✓		Biopharmaceutics comments*

* For details regarding biopharmaceutics filing decision (FILABLE) and comments see Biopharmaceutics Filing Review signed off on July 15, 2010 in DARRTS

{See appended electronic signature page}

Dorota Matecka
Acting CMC Lead
Division of New Drug Quality Assessment II
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Date

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Stephen Miller
Acting Branch Chief
Division of New Drug Quality Assessment II
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201152	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	Nevirapine Extended Release Tablets

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/s/

DOROTA M MATECKA
07/19/2010

STEPHEN P MILLER
07/20/2010