CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-068

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo

NDA 22-068
Tasigna®(nilotinib) Capsules, 200 mg
October 23, 2007

Introduction

Tasigna®(nilotinib) capsules, 200 mg, hard gelatin capsules (Novartis) is indicated to treat CML and (Ph+) [redacted]

Adminstrative

This 505(b)1 NDA was received 26-SEP-2006 and on 12-DEC-2006 was filed as a standard NDA for review after discussions with the applicant. The original PDUFA date was extended three months based on the aggregate of amendments received during the review cycle. The current PDUFA date is 29-OCT-2007.

All CMC related consults including EES (acceptable recommendation 30-NOV-2006) are acceptable.

From the CMC perspective, this NDA is recommended for APPROVAL (AP).

Drug Substance

The drug substance is Nilotinib hydrochloride monohydrate. Nilotinib is 4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide monohydrochloride monohydrate.

Nilotinib is a yellowish to greenish-yellowish powder, and has a molecular formula of $C_{28}H_{22}F_3N_7O \cdot HCl \cdot H_2O$ with a corresponding molecular weight of 583.99 g/mol.

Nilotinib is considered a low solubility/low permeability (Class IV) compound in the BCS. Therefore, dissolution of nilotinib can potentially be the rate-limiting step for *in vivo* absorption. It is soluble in acidic media; being practically insoluble in buffer solutions of pH 4.5 and higher.

There are no outstanding drug substance issues.

Drug Product

Tasigna®(nilotinib) capsules contain the following inactive components (excipients): lactose monohydrate, crospovidone, poloxamer 188, [redacted] colloidal silicon dioxide, and magnesium stearate.

All of the excipients used in the manufacture of the drug product are either USP or NF grade. There are no known excipient incompatibilities among the chosen excipients. The choice of excipients was based on laboratory data demonstrating acceptable performance; especially with respect to dissolution rate.

Several minor changes to the drug product were effected between clinical trials and the final commercial formulation; this ultimately led to a hard capsule formulation [redacted]

The drug product is packaged in blisters [redacted] and is approved [redacted] for a 24 month shelf life at controlled room temperature.

There are no outstanding drug product issues.

Rik Lostritto, Ph.D., Director, ONDQA Division III.

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/s/

Richard Lostritto
10/23/2007 02:44:40 PM
CHEMIST

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	22-068
Applicant:	Novartis Pharmaceutical Corporation
Assigned Date:	02-OCT-2006
Stamp date:	09-AUG-2006(rolling submission)
PDUFA Date:	29-JUL-2007
Proposed Trade Name:	Tasigna®
Established Name:	Nilotinib (AMN107)
Laboratory Code:	G3139
Dosage Form:	Hard Capsules (200 mg)
Route of Administration:	Oral
Indication:	Treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia
CMC Reviewer:	Josephine Jee

	YES	NO
ONDQA Fileability:	√	___
Draft Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 22-068 has been submitted for Tasigna® (nilotinib) 200 mg hard capsules, intended for treatment of chronic phase and accelerated phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML). Tasigna was granted fast track designation for the treatment of CML indication on May 11, 2006, and orphan drug designation on April 27, 2006 under IND 69,764. The trade name Tasigna® was submitted under IND 69,764 (Serial No. 201) on March 23, 2006. The Agency accepted the Applicant's proposal for submission of NDA 22-068 as a rolling submission on August 10, 2006. The current CMC section is the first portion of the rolling submission. This NDA was officially submitted on August 9, 2006.

Nilotinib was submitted under IND 69,764, which has been active at the Agency since 30-APR-2004. A CMC-specific Type B meeting was held on 02-DEC-2005, concerning the stability package proposed to file.

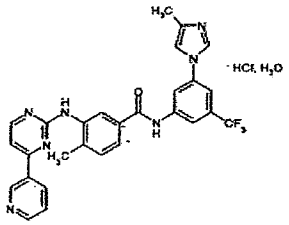
Drug Substance Summary

Nilotinib is a New Molecular Entity. It is a white to slightly yellowish or slightly greenish yellowish powder. The drug substance nilotinib HCl monohydrate does not possess a chiral center. The solubility of Nilotinib hydrochloride monohydrate (AMN107), see Table 1-1, in aqueous solutions at 25 °C strongly decreases with increasing pH, and Nilotinib hydrochloride monohydrate is practically insoluble in buffer solutions of pH 4.5 and higher pH values. Nilotinib hydrochloride monohydrate is very soluble in dimethyl sulfoxide, sparingly soluble in ethanol and methanol, very slightly soluble in acetonitrile and n-octanol.

The pH value of a 0.02% (m/V) solution of Nilotinib hydrochloride monohydrate (AMN107) in water / ethanol 50:50 (v/v) is 4.3. The pH value of a 0.1% (m/V) suspension of Nilotinib hydrochloride monohydrate in water was determined to be 5.3. pKa1 for Nilotinib hydrochloride monohydrate (AMN107) was found to be 2.1, and pKa2 was determined to be 5.4.
The distribution coefficient (D) for Nilotinib hydrochloride monohydrate (AMN107) in octanol/ 0.1 N HCl buffer at 37.0 ± 0.5 °C was determined to be 0.08, and the corresponding Log D -1.1.
This drug substance has no asymmetric carbon; therefore is not optically active.

Nilotinib has been accepted as a United States Adopted Name (USAN). Additional terminology may reference the Sponsor's research code numbers " AMN107 and AMN107-AAA-001". The CAS number for nilotinib free base is 641571-10-0.

The chemical structure of nilotinib is as follows:



Molecular Formula: Salt form as monohydrate: $C_{28}H_{22}F_3N_7O.HCl.H_2O$
Salt form on anhydrous basis: $C_{28}H_{22}F_3N_7O.HCl$

Relative molecular mass: Salt form as monohydrate: 583.99
Salt form on anhydrous basis: 565.98

4 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		EES have been submitted on 17-OCT-2006
5	Is a statement provided that all facilities are ready for GMP inspection?		√	Email has been sent to Christy Cottrell, PM on 10/13/06, requesting to include this statement
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		Submitted on 29-SEP-2006
12	Has the draft package insert been provided?	√		Submitted on 29-SEP-2006
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √ √ √ √		**Pharm/Tox** Biopharm **Statistics (stability)** LNC DMETS/ODS **EER** **Requested on 13-OCT-2006 thru PM**

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included
[redacted]			Yes
[redacted]			Yes

[redacted]	Yes

Recommendation for Team Review:
This NDA includes a significant portion of drug substance and drug product manufacturing information. The CMC review for the drug product should be straightforward.

The team review approach is not recommended for this NDA. This is a conventional dosage form with typical review issues noted in the Pre-NDA meeting. This review can be easily accomplished by a single CMC reviewer.

Josephine Jee
CMC Reviewer

13-OCT-2006
Date

Ravi Haranpahalli
Branch Chief, Branch V

24-OCT-2006
Date

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/s/

Josephine Jee
10/24/2006 05:45:29 PM
CHEMIST

Ravi Harapanhalli
10/26/2006 03:06:23 PM
CHEMIST

[redacted]

NDA 22-068

TASIGNA® (nilotinib) Capsules

Novartis Pharmaceutical Corporation

William C. Timmer, Ph.D.

Division of Pre-Marketing Assessment III and Manufacturing Science

Office of New Drug Quality Assessment

for the

Division of Oncology Drug Products

Office of Oncology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-068

2. REVIEW #1

3. REVIEW DATE: 15 MAY 2007

4. REVIEWER: William C. Timmer, Ph.D.

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
IND 69, 764	30 April 2004

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-068 RRC (001)	9 August 2006
NDA 22-068 N (000)	26 September 2006
NDA 22-068 N (000) BC	12 January 2007
NDA 22-068 N (000) BL	9 February 2007
NDA 22-068 N (000) BC	2 March 2007

7. NAME & ADDRESS OF APPLICANT:

NAME:	Novartis Pharmaceutical Corporation
ADDRESS:	One Health Plaza, East Hanover, NJ 07936-1080
REPRESENTATIVE:	Robert A. Miranda, Director, Drug Regulatory Affairs
TELEPHONE:	862-778-2282

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	Tasigna
NON-PROPRIETARY NAME (USAN)	Nilotinib
CODE NAME/ NUMBER (ONDC ONLY)	N / A
CHEMISTRY TYPE / SUBMISSION PRIORITY	1 /P

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

10. PHARMACOL. CATEGORY: Anti-leukemic

11. DOSAGE FORM: Hard Gel Capsules

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

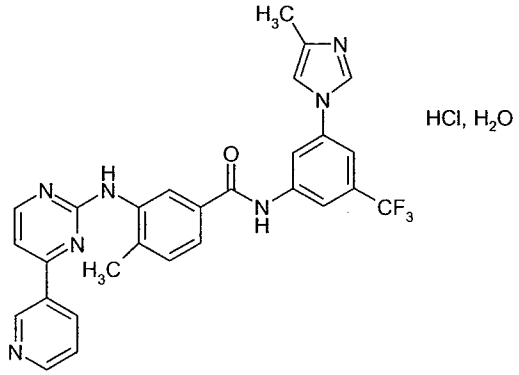
14. R_x/OTC DISPENSED: _x_ R_x ___ OTC

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:



Molecular formula: $C_{28}H_{22}F_3N_7O \cdot HCl \cdot H_2O$
Molecular weight: 583.99 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
	IV			4	----	NA
	III			4	----	NA
	III			4	----	NA
	III			4	----	NA
	III			4	----	NA
	III			4	----	NA
	III			4	----	NA
	III			4	----	NA

[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	69, 764	AMN 107

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	30-NOV-2006	S. Ferguson
Methods Validation	*To be initiated*	----	----
ODS DMETS	Tradename Acceptable	24-JAN-07	T. Bridges, R.Ph.
EA	Acceptable; CE granted	15-MAR-07	W.C. Timmer, Ph.D.

The Chemistry Review for NDA 22-068

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Tasigna®(nilotinib) Tablets, 200 mg is recommended for APPROVAL.

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

There are no Phase IV commitments.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance is Nilotinib hydrochloride monohydrate.

Nilotinib is 4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl) phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide monohydrochloride monohydrate. Nilotinib is a yellowish to greenish-yellowish powder, and has a molecular formula of $C_{28}H_{22}F_3N_7O$•HCl • H_2O with a corresponding molecular weight of 583.99 g/mol.

The solubility of Nilotinib in aqueous solutions decreases with increasing pH, and Nilotinib is practically insoluble in buffer solutions of pH 4.5 and higher. Nilotinib is considered a low solubility/low permeability (Class IV) compound in the BCS. Therefore, dissolution of nilotinib can potentially be the rate-limiting step for *in vivo* absorption.

The structure of Nilotinib is supported by both the synthetic route as well as analytical and spectroscopic analyses. Nilotinib does not have a chiral center and hence no stereochemistry.

The synthesis of Nilotinib involves [redacted]
Starting materials are commercially available or were prepared from commercially available materials. A subsequent agreements with the sponsor defined the starting materials, with the caveat that the starting materials could be appropriately controlled.

[redacted] batches of Nilotinib drug substance have been manufactured by the proposed commercial process.

[redacted]

Accordingly, the pharm-tox reviewer, Shwu-Luan Lee, Ph.D., was apprised of this information.

[redacted]

These by-products/impurities are suitably analyzed by the analytical test methods such that the quality of the drug substance is maintained.

The analytical specifications and tests employed for the release of Nilotinib comply with the requirements of ICH guidelines Q3A(R), Q3C and Q6A.

The sponsor has provided batch analyses for [redacted]

The drug substance is packaged in [redacted]

Stability studies were performed in compliance with the applicable current ICH guidelines. The registration stability reports contain data from long-term and accelerated studies of three pilot batches for storage periods up to 18 months, plus stress and photostability testing. Analysis of the stability data indicate an expiry of 24 months in climatic zones I and II, when stored [redacted] at a temperature no higher than 25°C.

Drug Product

The drug product is Tasigna® (nilotinib) [redacted]

Tasigna® (nilotinib) 200 mg hard capsules are [redacted] for oral administration.

The capsules consists of the following components: lactose monohydrate, crospovidone, poloxamer 188, [redacted] colloidal silicon dioxide and magnesium stearate. All of the excipients used in the manufacture of the drug product are either USP or NF grade. There are no known excipient-excipient incompatibilities among the chosen excipients. The choice of excipients was based on laboratory data demonstrating processibility and performance criteria, especially dissolution rate.

Manufacturing formulation development aimed to develop an [redacted] oral dosage form with the following prerequisites:

- high dose; maximum daily dose = [redacted] mg of drug substance
- acceptable size for swallowing to ensure patient compliance
- drug substance: slightly soluble at pH 1 but insoluble at pH 6.8
- tendency of drug substance for agglomeration

Several minor changes were effected between clinical trial and the final commercial formulation; this ultimately led to a hard capsule formulation

[redacted] Although the drug substance exhibited several [redacted] was selected since it [redacted] *No transformation of this form was observed after storage, even after several months at room temperature.*

The manufacturing process can be divided into the following functions:

[redacted]

A representative batch size consists of approximately [redacted]

The analytical specifications and tests employed for the release of Tasigna (nilotinib) comply with the requirements of ICH guidelines Q3A(R), Q3C and Q6A. The sponsor has provided batch analyses for all drug product batches.

As to be expected, dissolution testing proceeded through several iterations before a final test method was developed. The method was validated for selectivity, accuracy, precision and linearity. The acceptance criteria for release and stability

control (Q = [redacted] in 30 minutes) represents a standard requirements for [redacted] solid oral dosage forms.

The drug product will be marketed in [redacted] blister packs [redacted]

Stability studies were performed in compliance with the applicable current ICH guidelines. The registration stability reports contain data from long-term and accelerated studies of three pilot and three production batches for storage up to 18 months, plus stress and photostability testing. Analysis of the stability data indicate an expiry of 24 months [redacted] at a temperature no higher than 25°C.

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

Tasigna® (nilotinib) tablets are indicated for chronic myelogenous leukemia (CML) and Philadelphia chromosome positive (Ph+) [redacted]

CML arises from the excessive production of abnormal stem cells in the bone marrow which eventually suppress the production of normal white blood cells. CML usually has three identifiable phases: the chronic phase, which is typically benign and lasts for an average three to five years, the accelerated phase and the blast-crisis phase.

CML and Ph+ ALL are caused by the *bcr-abl* oncogene. The chimeric *bcr-abl* gene, which results from a translocations between the long arms of chromosome 9 and 22, encodes the fusion protein BCR-ABL. The BCR-ABL protein is a tyrosine kinase that influences cell growth, differentiation and survival; because this protein is almost never seen outside leukemia cells, it presents an attractive therapeutic target.

At present there are several treatment options for patients with CML; they include conventional cytotoxic chemotherapy, interferon-α, allogeneic stem-cell transplant (the only potentially curative therapy) and the current gold standard, Gleevec® (imatinib mesylate).

Although most patients with CML initially respond to treatment with imatinib, cases of imatinib resistance, due to the emergence of imatinib-resistant point mutations within the *BCR-ABL* tyrosine kinase domain, and are increasingly being reported. Thus there is a need for a drug that can override imatinib resistance in CML, especially in those who progress to the accelerated and blast-

Tasigna® (nilotinib) is a new, orally active, amino pyrimidine-derivative tyrosine kinase inhibitor that is considerably more potent clinically. Nilotinib functions through competitive inhibition at the ATP-binding site of BCR-ABL, leading to the inhibition of tyrosine phosphorylation of proteins that are involved in the intracellular signal transduction that *BCR-ABL* mediates. Nilotinib has a higher binding affinity and selectivity for the ABL kinase than does imatinib. In clinical trials, nilotinib has a relatively favorably safety profile and is active in imatinib resistant CML.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, the NDA sponsor, Novartis Pharmaceutical Corporation, has submitted sufficient and appropriate information to support the approval of the drug product. The physical and chemical characteristics, impurity profile, and stability for nilotinib drug substance and Tasigna (nilotinib) capsules has been adequately demonstrated in this submission. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of both the drug substance and the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations.

Based on analysis of the stability data, the approved shelf life for Tasigna® (nilotinib) Capsules, 200 mg, is 24 months at room temperature.

III. Administrative

A. Reviewer's Signature /s/ William C. Timmer, Ph.D.

B. Endorsement Block

Chemist Name:	W.C. Timmer, Ph.D.
Chemistry TL:	R. Harapanhalli, Ph.D.
Project Manager:	J. Jamison

87 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 3

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/s/

William Timmer
8/30/2007 05:09:45 PM
CHEMIST

Sarah Pope
8/30/2007 05:15:00 PM
CHEMIST

Ravi Harapanhalli
10/4/2007 06:57:21 PM
CHEMIST
CMC responses to the questions in this review have been received and are reviewed in BC memo.