CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022383Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 15-MAR-2011

TO: N22383 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: ACCEPTABLE recommendation from the Office of Compliance for application of 14-MAR-2011; Altered CMC recommendation

SUMMARY: Previously on 20-FEB-2011, the Office of Compliance had put forth a WITHHOLD recommendation due to an Official Action Indicated (OAI) alert for the Novartis site at Suffern, NY (CFN 2416082), which is a packaging site for the drug product. After Novartis withdrew the site from the application (10-MAR-2011, amendment), the Office of Compliance re-evaluated the application and altered their recommendation. The Office of Compliance has placed an overall recommendation of ACCEPTABLE into the EES on 14-MAR-2011. The CMC team can now recommend that the application be approved.

RECOMMENDATION: The application is recommended for **approval**.

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
OND/DPARP/CHill
ONDQA/DIV 1/CBertha/15-MAR-2011
ONDQA/DIV 1/PPeri_____
ONDQA/DIV1/ASchroeder
OND/DPARP/TMichele
ONDQA/SPatwardhan

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/s/

CRAIG M BERTHA
03/15/2011

PRASAD PERI
03/15/2011
I concur

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22383/000	**Action Goal:**	
Sta ate:	18-DEC-2008	**District Goal:**	31-JAN-2011
Re y:	01-APR-2011		
Applicant:	NOVARTIS PHARMS 1 HEALTH PLAZA BLDG 405 2006 EAST HANOVER, NJ 079361080	**Brand Name:** **Estab. Name:** **Generic Name:**	Arcapta Neohaler indacaterol maleate
Priority:	1S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	570	001; POWDER, FOR INHALATION; INDACATEROL MALEATE; EQ 150UGM BASE 002; POWDER, FOR INHALATION; INDACATEROL MALEATE; EQ 300UGM BASE 002; CAPSULE, HARD GELATIN; INDACATEROL MALEATE; EQ 300UGM BASE	

Application Comment: THE 28-SEP-2010 AMENDMENT ADDS A NEW 75 MCG STRENGTH FOR THE INHALATION POWDER DRUG PRODUCT. DRUG CONCENTRATION IS LOW IN THIS NEW FORMULATION AT (b) (4) UNIFORMITY DATA APPEAR TO BE GOOD AND THE (b) (4) PROCESS IS ROBUST. ALTHOUGH THE APPLICANT ROUTINELY TESTS FILLED CAPSULES TO BE USED WITH THE INHALER AS PER USP <905>, THEY DO NOT PROPOSE TO TEST (b) (4) UNIFORMITY DURING MANUFACTURING NOR ARE THEY PROPOSING THE (b) (4) APPROACH IN THE AGENCY DRAFT GUIDANCE. (on 01-NOV-2010 by C. BERTHA () 301-796-2410)

THIS IS A NEW NDA FOR AN NEW MOLECULAR ENTITY AND A DRY POWDER INHALER SUBMITTED BY NOVARTIS. THE MAIN CONTACT PERSON FOR ALL OF THE NOVARTIS FACILITIES IS PROVIDED BELOW.
MAIN CONTACT:
MICHAEL BRUCKHEIMER, EXECUTIVE DIRECTOR GLOBAL QUALITY OPERATIONS NOVARTIS PHARMACEUTICALS CORPORATION, ONE HEALTH PLAZA EAST HANOVER, NJ 07936, USA TEL NUMBER: (862) 778-7913 FAX: (973) 781-6052 E-MAIL: MICHAEL.BRUCKHEIMER@PHARMA.NOVARTIS.COM
ALTERNATE CONTACT:
VIVIANNE ARENCIBIA, HEAD GLOBAL COMPLIANCE AND AUDITING NOVARTIS PHARMACEUTICALS CORPORATION, ONE HEALTH PLAZA EAST HANOVER, NJ 07936, USA TEL NUMBER: (862) 778-4970 FAX: (973) 781-8265 E-MAIL: VIVIANNE.ARENCIBIA@NOVARTIS.COM.

(b) (4)

THE ADDRESS OF THE COMPANY IS ONE HEALTH PLAZA, EAST HANOVER, NJ 07936-1080
PH: 973-781-2565. (on 04-FEB-2009 by P. PERI (HFD-820) 301-796-1730)

FDA Contacts:				
	S. PATWARDHAN	Project Manager	(HF-01)	301-796-4085
	C. BERTHA	Review Chemist		301-796-2410
	A. SCHROEDER	Team Leader		301-796-1749

Overall Recommendation:				
	ACCEPTABLE	on 14-MAR-2011	by D. SMITH	()
	WITHHOLD	on 20-FEB-2011	by EES_PROD	
	WITHHOLD	on 20-FEB-2011	by EES_PROD	
	ACCEPTABLE	on 10-NOV-2010	by EES_PROD	
	ACCEPTABLE	on 13-OCT-2009	by EES_PROD	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: THIS IS A SECONDARY PACKAGING SITE OF THE DRUG PRODUCT (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	14-JAN-2009	GMP Inspection			FERGUSONS
DO RECOMMENDATION	25-MAR-2009			ACCEPTABLE	LJARRELL
GMP INSPECTION CONDUCTED (b) (4) NO FDA-483 WAS ISSUED.				INSPECTION	
OC RECOMMENDATION	25-MAR-2009			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-NOV-2010				PATWARDHAN
OC RECOMMENDATION	04-NOV-2010			ACCEPTABLE	INYARDA
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS ONE OF FOUR PRIMARY PACKAGING SITES FOR THE DRUG PRODUCT (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	06-FEB-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	12-AUG-2009		(b) (4)		IRIVERA
INSPECTION PERFORMED	(b) (4)				MARIE.MORIN

The Pre-Approval and cGMP inspection of this finished product and contract finished product packaging firm was conducted per assignment from DFI, International District Office, under FACTS (b) (4) to cover the packaging operations for NDA 22383/000 for Indacaterol (QAB149). The inspection was carried out under CP7346.832, NDA Pre-Approval inspection and CP7356.002, Drug Process Inspections. This was a team inspection by Marie F Morin, Investigator and Luis M. Burgos, Chemist.

previous FDA inspection of this firm was carried out (b) (4). The inspection was a pre-oval for the packaging of Formoterol Fumarate and resulted in a 4 item FDA-483 that cited the s lack of establishing written procedures for some of the key areas of manufacturing, Quality Assurance oversight and lack of training documentation. The current inspection verified that the corrections to the above deficiencies had been implemented.

The current inspection of this API manufacturer was a full GMP inspection covering the Quality System, Facilities and Equipment, Materials Management, Production and Packaging and Labeling. The firm did not contain a Laboratory. There were no objectionable conditions noted. No samples were collected and no refusals were encountered.

DO RECOMMENDATION	13-OCT-2009		ACCEPTABLE	JOHNSONE
NAI			INSPECTION	
OC RECOMMENDATION	13-OCT-2009		ACCEPTABLE	JOHNSONE
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-NOV-2010			PATWARDHAN
OC RECOMMENDATION	04-NOV-2010		ACCEPTABLE	INYARDA
			BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611204 **FEI:** 3002807772

NOVARTIS PHARMA AG

LICHTSTRASSE 35
BASEL, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR MANUFACTURE OF DRUG SUBSTANCE [redacted] (b) (4) (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
DO RECOMMENDATION	23-FEB-2009			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	23-FEB-2009			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-NOV-2010				PATWARDHAN
SUBMITTED TO DO	04-NOV-2010	10-Day Letter			INYARDA
RE-EVALUATION OF COMPLIANCE CHECK - NOTE: NME STATUS					
DO RECOMMENDATION	04-NOV-2010			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	05-NOV-2010			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9612715 **FEI:** 3002807776

NOVARTIS PHARMA AG

CORK
RINGASKIDDY, CORK, , IRELAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR MANUFACTURE OF DRUG SUBSTANCE [redacted] (b) (4) (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
DO RECOMMENDATION	05-FEB-2009			ACCEPTABLE	ADAMSS
AC GMP EI 10/2008				BASED ON FILE REVIEW	
OC RECOMMENDATION	05-FEB-2009			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-NOV-2010				PATWARDHAN
S ED TO DO	04-NOV-2010	10-Day Letter			INYARDA
TE: NME - COMPLIANCE RE-EVALUATION					
DO RECOMMENDATION	04-NOV-2010			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	05-NOV-2010			ACCEPTABLE	INYARDA
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9692042 **FEI:** 3002865753

NOVARTIS PHARMA SCHWEIZERHALLE AG

ROTHAUSWEG
SCHWEIZERHALLE, BASEL-LANDSCHAFT, SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: APPLICANT STATES IN 28-SEP-2010 AMENDMENT THAT THE FEI NUMBER FOR THIS SITE WITH CFN 9692042 IS FEI 3007428657. (on 26-OCT-2010 by C. BERTHA () 301-796-2410)
THIS SITE WITH THIS NUMBER IS LISTED AS NOVARTIS PHARMA SCHWEIZERHALLE, AG, ROTHAUSWEG, CH-4133, PRATTELELN, SITZERLAND BY THE APPLICANT. THE IS SOME CONFUSION ABOUT THE NAME AND SITE NUMBER IN THE DATA BASE IT APPEARS. THIS SITE IS RESPONSIBLE FOR MANUFACTURER OF DRUG SUBSTANCE (b) (4) (b). (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	06-FEB-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	21-APR-2009		03-APR-2009		IRIVERA
DO RECOMMENDATION	15-JUL-2009			ACCEPTABLE	JOHNSONE
				INSPECTION	
OC RECOMMENDATION	15-JUL-2009			ACCEPTABLE	JOHNSONE
				DISTRICT RECOMMENDATION	
INSPECTION PERFORMED	10-SEP-2009		10-SEP-2009		MARIE.MORIN

The Pre-Approval and cGMP inspection of this Active Pharmaceutical Ingredient (API) manufacturer was conducted per assignment from DFI, International District Office, under FACTS 2926739, to cover NDA 22527/000 for Fingolimod, NDA 22383/000 for Indacaterol and NDA 22518/000 for Dulera. The inspection was carried out under CP7346.832, NDA Pre-Approval inspection and CP7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection. This was a team inspection by Marie F Morin, Investigator and Luis M. Burgos, Chemist.

The previous FDA inspection of this firm was carried out 05/30-06/02/2005. The inspection was a pre-approval for (b) (4) and revealed the following 10 FDA-483 Observations: OOS investigations not conducted in accordance with OOS procedure; OOS procedure insufficient because it does not require a sufficient number of retests to overcome the initial failing result; procedure of evaluating stability OOS results is not followed in that the investigation did not determine if the failing result represented a defect which would require an evaluation for possible recall; the annual product review did not include follow-up activities to the conclusions and recommendations of the previous year; manuals for the correct use of equipment were not covered by the document control system; stability failure testing carried out in Ringaskiddy, Ireland were not always reported to Novartis Pharma?s Chemical Operations Compliance Department in a timely manner; OOS procedure is general regarding the practice of resampling; there was no record of the balance used to weigh (b) (4), a critical parameter, used in the (b) (4); the amount of (b) (4) used in the (b) (4) process for Batch #C0014 was incorrectly calculated; there was no weigh ticket or record of the balance used to weigh (b) (4)
That FDA-483 covered all four of the firm?s si

OC RECOMMENDATION	28-APR-2010			ACCEPTABLE	JOHNSONE
				ADMIN CLOSURE-IGNORE RECCOMEND	
SUBMITTED TO OC	04-NOV-2010				PATWARDHAN

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
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SU ED TO DO	04-NOV-2010	10-Day Letter		INYARDA
DO RECOMMENDATION	04-NOV-2010		ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	05-NOV-2010		ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9692043 **FEI:** 3002653483

NOVARTIS PHARMA SCHWEIZERHALLE AG

SCHAFFHAUSERSTRASSE
STEIN, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Estab. Comment: MANUFACTURER OF DRUG PRODUCT, QUALITY CONTROL WITH EXCEPTION OF (b) (4) AND MICROBIOLOGICAL TESTING ONLY ON STABILITY AND IS A PRIMARY PACKAGING SITE. (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

FROM A. INYARD/B. BELZ: THIS PRODUCT IS "POWDER FOR INHALATION", PRESENTED IN A BLISTER-PACK STYLE INHALATION PRODUCT, WHERE THE POWDER IS CONTAINED INS HARD GEL CAPS AND THE INHALER DEVICE PIERCES THE CAPLET ON EACH END SO THE PATIENT CAN INHALE. (on 14-MAR-2011 by E. JOHNSON (HFD-320) 301-796-3334)

THIS SITE IS RESPONSIBLE FOR THE MANUFACTURE OF DRUG SUBSTANCE (b) (4) (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

GIVEN THAT FIRM EFFECTIVELY MANUFACTURES A CAPSULE THAT IS PUT INTO AN AEROSOL DEVICE, THE CAPSULE PROCESSING SHOULD BE OF INTEREST (on 14-MAR-2011 by E. JOHNSON (HFD-320) 301-796-3334)

FIRM PRODUCES THE POWDER THAT GOES INTO INHALER FOR AEROSOL DISPERSION (on 04-NOV-2010 by E. JOHNSON (HFD-320) 301-796-3334)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

NON-STERILE API BY CHEMICAL SYNTHESIS NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
DO RECOMMENDATION	06-FEB-2009			ACCEPTABLE	JOHNSONE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	10-FEB-2009			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-NOV-2010				PATWARDHAN
SUBMITTED TO DO	04-NOV-2010	Product Specific			INYARDA
DO RECOMMENDATION	04-NOV-2010			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	05-NOV-2010			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	14-MAR-2011				PATWARDHAN
SUBMITTED TO DO	14-MAR-2011	10-Day Letter			SMITHDE
DO RECOMMENDATION	14-MAR-2011			ACCEPTABLE	PHILPYE

D ON FIRM'S CHG/TCM PROFILES FOR THIS PRODUCT

			BASED ON FILE REVIEW	
OC RECOMMENDATION	14-MAR-2011		ACCEPTABLE	SMITHDE
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	13-JAN-2009			PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific		ADAMSS
DO RECOMMENDATION	06-FEB-2009		ACCEPTABLE	JOHNSONE
			BASED ON FILE REVIEW	
OC RECOMMENDATION	10-FEB-2009		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-NOV-2010			PATWARDHAN
OC RECOMMENDATION	04-NOV-2010		ACCEPTABLE	INYARDA
			BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9614433 **FEI:** 3002807773

NOVARTIS PHARMANALYTICA SA

VIA SERFINO BLESTRA 31
LOCARNO, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR QUALITY CONTROL OF THE DRUG PRODUCT WITH THE EXCEPTION OF (b) (4) AND MICROBIOLOGICAL TESTING (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
OC RECOMMENDATION	16-JAN-2009			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	04-NOV-2010				PATWARDHAN
SUBMITTED TO DO JUST OVER 3 YEARS	04-NOV-2010	10-Day Letter			INYARDA
DO RECOMMENDATION	04-NOV-2010			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	05-NOV-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	14-MAR-2011				PATWARDHAN
SUBMITTED TO DO	14-MAR-2011	10-Day Letter			SMITHDE
DO RECOMMENDATION	14-MAR-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	14-MAR-2011			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR QUALITY CONTROL OF DRUG SUBSTANCE. (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
OC RECOMMENDATION	16-JAN-2009			ACCEPTABLE	ADAMSS
				BASED ON PROFILE	
SUBMITTED TO OC	04-NOV-2010				PATWARDHAN
OC RECOMMENDATION	04-NOV-2010			ACCEPTABLE	INYARDA
				BASED ON PROFILE	

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 22-FEB-2011

TO: N22383 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: Withhold recommendation from the Office of Compliance for application of 20-FEB-2011; Altered CMC recommendation

SUMMARY: The Office of Compliance had placed an overall recommendation of ACCEPTABLE into the EES on 10-NOV-2010. Based on review of the amended application, the CMC team recommended approval of the application in the 20-DEC-2010, review. However, the Office of Compliance has now provided a WITHHOLD recommendation in the EES for the application on 20-FEB-2011. The Novartis site at Suffern, NY (CFN 2416082), which is a packaging site for the drug product, is listed in the EES with an Official Action Indicated (OAI) alert. All other sites have an acceptable status. Considering that the Office of Compliance now provides a WITHHOLD recommendation, the CMC team no longer can recommend approval of the application.

RECOMMENDATION: The application is **approvable** pending the applicant's resolution of the compliance issues and the issuance of an acceptable recommendation from the Office of Compliance for the application.

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
OND/DPARP/CHill
ONDQA/DIV 1/CBertha/20-FEB-2011
ONDQA/DIV 1/PPeri_____
ONDQA/DIV1/ASchroeder

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

/s/

CRAIG M BERTHA
02/22/2011

PRASAD PERI
02/23/2011
I concur

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 14-JAN-2011

TO: N22383 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: Review of Report PHAD000828A: Drug product capsule and device interchangeability study (28-SEP-2010, Amendment)

BACKGROUND: The clinical team has expressed a concern that patients might unintentionally attempt to use the indacaterol drug product capsules (Arcapta™) in other devices that are similar to the Concept1 or Neohaler™, even though misuse is prohibited by product labeling. Other similar devices that are already approved and marketed are the Aerolizer® device from the Foradil® Aerolizer® product that delivers formoterol fumarate, and the HandiHaler® device from the Spiriva® HandiHaler® drug product that delivers tiotropium bromide. The P.2 section of the 28-SEP-2010, amendment to the application contained a report that addressed this potential interchangeability from the *in vitro* performance testing perspective. Although these studies are not required to be evaluated to support the CMC section of the application, the clinical team has requested that the CMC team review this report to gauge the characteristics and magnitude of any differences in the *in vitro* performance data.

The applicant has studied the effects of potential device interchanges on the pharmaceutical performance through the device-life of 30 days, for the 75 mcg strength Arcapta™ capsules. They assessed the key performance parameters of Aerodynamic particle size distribution (APSD) and delivered dose uniformity (DDU). They chose testing flow rates that lead to a pressure drop across all devices of (b) (4) for Concept1 and Aerolizer®, (b) (4) for HandiHaler®). The total volume of air collected was (b) (4) for all cases for the APSD and (b) (4) for DDU determinations. The applicant accounted for the difference in the aerodynamic cut-offs of the Next Generation Impactor (NGI) with the two different flow rates.

Note that the applicant had provided comparative data earlier, demonstrating the *in vitro* delivery performance (APSD and DDU) for 150 and 300 mcg Arcapta™ capsules with the Concept1 and the Aerolizer® devices (see chemistry review #2 dated 16-JUL-2009). In summary, the *in vitro* data for dose delivery and APSD were considered to be comparable, regardless of whether or not the Arcapta™ capsules were delivered from a Concept1 or an Aerolizer® device.

DATA SUMMARY AND EVALUATION: The applicant has chosen to test the devices with the same pressure drop as opposed to using the same flow rate. A (b) (4) pressure drop can be generated across both the Concept1 (Neohaler™) and Aerolizer® devices, but only at a relatively high flow rate of (b) (4). To generate this same pressure drop across the HandiHaler® device, a much lower flow rate of (b) (4) is needed, thus demonstrating the higher resistance of the HandiHaler® versus the other two devices.[1] As such, it is expected that the greatest *in vitro* performance differences would be observed if Arcapta™ capsules were used with a HandiHaler® device. This would appear to be supported by the *in vitro* performance data in the report.

The study used 75 mcg strength Arcapta™ capsules from production scale batch X296LF and commercially available Aerolizer® and HandiHaler® devices. The cut points for the NGI run at the two flow rates differ and are shown below:

It is noted that a minimum of one (1) hour of rest time was used during the waste shots between the test capsules. This is important as there can be alterations of delivery performance due to electrostatic charge build-up during accelerated wasting scenarios (the applicant is likely aware of this from their development work with the approved Foradil® Certihaler® application). The applicant cleaned the Concept1 device as per the labeling, i.e., every seventh actuation. No cleaning is required nor was any performed when the doses were collected with the Aerolizer® and the HandiHaler® devices.

The specific testing plan is reproduced below from the report.

Start of Sponsor Material

Study arm	Product	Device	Testing regime
1	QAB149	Concept1	Per test point 1 actuation of QAB149 per device
2	QAB149	HandiHaler®	Per test point 1 actuation of QAB149 per device
3	QAB149	Aerolizer®	Per test point 1 actuation of QAB149 per device

[1] Resistance to airflow (R) is a function of the square root of the pressure drop ΔP and the volumetric flow rate Φ as per the equation: $(\Delta P)^{1\backslash 2} = R\ \Phi$. (See Clark, A.R., Hollingworth, A.M., **1993**. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers - implications for in vitro testing. *J. Aerosol. Med.* 6, 99–110.)

Table 2-5 Test plan for Study arms 1 to 3

Actuation (test point)	1	2-3	4-6	7	8	9-13	14	15	16-20	21	22-27	28	29	30
Device cleaning for Concept1 device	-	-	-	c	-	-	c	-	-	c	-	c	-	-
Actuations per test point and device	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Delivered dose per test point	x	x	w	x	x	w	x	x	w	w	w	x	x	x
APSD per test point	x	w	w	w	w	w	x	x	w	w	w	w	w	x

c Device cleaning following the actuation
w Waste shot
- No activity
x Test. Two replicates were generated for each study arm, test point and test parameter. For the determination of a delivered dose one capsule in one device was required. For testing of APSD two capsules in two devices were used, both actuated into one NGI each. This resulted into six devices in total for the two replicates.

End of Sponsor Material

Figures 3-1 to 3-3 (reproduced in attachment 1) show APSD results from the 1st, 14th, 15th, and 30th capsules from each of the devices tested by the NGI. With all three devices, the first capsule displays lower delivery mass of fine particles of indacaterol. This is not unexpected as there is typically more initial hold-up of drug on the virgin surfaces of the parts of the device that form the drug flow path, as compared to hold-up from later doses from the same device. As the surface is coated with drug from subsequent doses, it is observed that for all three devices the APSD is stabilized by the middle of life doses (14th capsule). It can be concluded that regardless of the device used with the Arcapta™ capsules, the pattern of hold-up through device life is similar, at least under the *in vitro* test conditions.

Figures 3-4 to 3-6 (reproduced in attachment 2) provide the mass of drug as a function of aerodynamic size attained at the beginning, middle, and end doses. Note that the middle dose results are the average of the 14th and 15th capsules results for each. From these plots it is observed that the APSD profiles for the delivered indacaterol are similar from the Concept1 and the Aerolizer® devices, and that these profiles differ somewhat from the APSD profile when the HandiHaler® is used. That is, there is a shift in the distribution to larger particle sizes as the HandiHaler® delivers a smaller amount of fine particles below (b) (4) in aerodynamic size and slightly larger amounts of particles above this size. It is generally accepted that particles with an aerodynamic diameter less than approximately 5 mcm can be inhaled into the lungs. In that respect, when using the HandiHaler® device there is (b) (4) fine particles below 5.0 mcm in size when compared to Concept1 delivery. The Aerolizer®, on the other hand, delivers only slightly more mass of drug below 5.0 mcm in size ((b) (4)) than when the Concept1 device is used. The plot reproduced below summarizes these deposition mass differences across the device-life (beginning, middle, and end capsules) for particles less than 5.0 mcm.

Start of Sponsor Material

Figure 3-7 Mean fine particle mass (below 5.0 micrometer)

End of Sponsor Material

Comparing the total amounts of fine particles less than 5.0 mcm in size tends to mask the distribution shift that is also occurring when the HandiHaler® is used. If instead the mass of drug below the NGI stages 2 (for Concept1 and Aerolizer® at (b) (4)) and stage 3 (for HandiHaler® at (b) (4)) are compared,[2] the mean drop in the mass of the finer particles below (b) (4) mcm when using the HandiHaler® as compared to the Concept1 is observed to be even (b) (4) (see plot below).

Also, from this plot it can be seen that the mass of drug [redacted] (b) (4) is similar when the Aerolizer® replaces the Concept1 device for delivery, with the mean delivery only [redacted] (b) (4) higher for the Aerolizer®.

Lastly, the report provides a summary of DDU data when Arcapta™ capsules are used with the three devices. The profiles of dose delivery through-device-life and the overall mean delivery with variability given in terms of %RSD, are reproduced in the plots and table below, respectively.

Start of Sponsor Material

Figure 3-9 **Delivered dose, Study arm 1 (QAB149 / Concept1) and Study arm 3 (QAB149 / Aerolizer)**

[redacted] (b) (4)

(b) (4)

End of Sponsor Material

From the above plots and table, it can be seen that the mean dose delivery of the 75 mcg strength Arcapta™ capsules is similar regardless of which device is used, although there are differences noted in the profiles and levels of variability. The Aerolizer® provides the most variable delivery whereas the HandiHaler® the least, in terms of the %RSD. The through-life dose delivery profiles for the Concept1 and Aerolizer® devices are comparable and both are observed to have lower than target delivery for the first several capsules. This type of drug hold-up is not observed with the HandiHaler® device, which is unexpected, as all three devices were observed to deliver lower than target amounts of fine particles for the initial capsules during the NGI testing to attain APSD data.

CONCLUSIONS: The *in vitro* testing of DDU and APSD has been performed using standard test methods well described in the compendia (e.g., USP <601>). The applicant's choice to match pressure drop as opposed to flow rate for this testing also follows the compendial approach, albeit, the latter proposes (b) (4) as the comparative pressure drop.[3] Whether or not comparisons of *in vitro* device performance should be done at a common pressure drop or a common flow rate is still open for debate. The Office of Generic Drugs currently proposes to compare test and reference DPI devices at several fixed flow rates across a range. But it must be kept in mind that ANDA applicants would likely strive to produce test devices that had a matching flow resistance to the reference device, such that it would not matter which testing approach was taken (i.e., fixed flow rate or fixed pressure drop). As stated above, the HandiHaler® device has a significantly higher resistance than either the Concept1 or the Aerolizer® devices. Considering this, and the differences in the design of the HandiHaler®, it is not unexpected that this results in observed differences in the DDU and APSD data collected with the same Arcapta™ capsules from the HandiHaler® when compared to the other two devices. The Concept1 and Aerolizer® devices have comparable flow resistance (see plot below from the 02-APR-2009, amendment) and similar design.

Start of Sponsor Material

[3] It is unlikely that a (b) (4) pressure drop could be achieved with the relatively low resistance Concept1 and Aerolizer® devices, even at the maximum recommended flow rate of (b) (4) However, the achievement of a (b) (4) kPa pressure drop across the HandiHaler® device would likely be easily achievable below the limiting compendial flow rate of 200 L/min.

End of Sponsor Material

Therefore, it is not surprising that the DDU and APSD data observed for the 75 mcg Arcapta™ capsules with the Concept1 and Aerolizer® devices are comparable. This is consistent with the analogous data that were collected with the two higher strength capsules (150 and 300 mcg). Whereas there are no gross distinctions between the DDU and APSD behavior observed *in vitro* when the Arcapta™ capsules are used with the HandiHaler® versus the Concept1 device, there are some more subtle distinctions. Arcapta™ capsules used with the HandiHaler® delivered similar doses but the initial device drug hold-up that is observed with the Concept1 and Aerolizer devices was not seen. Such differences in drug hold-up are often a result of dissimilarities in surface area and/or materials of construction of the components in the air flow path of the device. However, inconsistent with this was the observation of similar drug hold-up in the beginning of device-life doses collected during NGI testing to characterize APSD. Typically one would expect the device-life dose delivery pattern to be comparable to the device-life total drug recovery pattern observed in APSD testing. The reason that this is not the case for the HandiHaler® device used with Arcapta™ capsules is not clear, nor does the applicant provide an explanation.

The most prominent finding of the study was the drop in mean total mass of fine particles of drug below 5.0 mcm in size when the HandiHaler® device was used instead of the Concept1 device, i.e., a drop of about (b) (4). Examination of particles as a group below this 5.0 mcm size tends to mask the concomitant observed shift in the HandiHaler® APSD distribution to larger particle sizes. Thus, when we instead observe the particles collected below (b) (4) mcm in size, there is about a (b) (4) drop when the HandiHaler® device was used compared to the Concept1 device. Unfortunately, as is most often the case, there is no clear correlation of such *in vitro* differences (mass deposition or distribution shifts) to either patient lung deposition amounts or pattern, or to any clinically measurable quantity. And even in cases where the *in vitro* drug delivery data for two DPI products have been found to be quite comparable, that has not guaranteed comparability in clinically relevant measurements.[4]

---

[4] P.T. Dolovich; C.A. Parkins; M.J. Thomas; B. Gillett; D.W. House; H.G. Ortega, **2009**. Pharmacokinetic,

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
OND/DPAP/CHill
ONDQA/DIV3/CBertha/14-JAN-2011
OND/DPARP/AHarry
OND/DPARP/TMichele
ONDQA/DIV3/PPeri_____
ONDQA/DIV3/ASchroeder

Pharmacodynamic, Efficacy, and Safety Data From Two Randomized, Double-Blind Studies in Patients With Asthma and an In Vitro Study Comparing Two Dry-Powder Inhalers Delivering a Combination of Salmeterol 50 mcg and Fluticasone Propionate 250 mcg: Implications for Establishing Bioequivalence of Inhaled Products. *Clin. Ther.* 31, 370-385.

Start of Sponsor Material

Figure 3-1 APSD by NGI, Study arm 1 (Concept1)

Figure 3-2 APSD by NGI, Study arm 2 (HandiHaler)

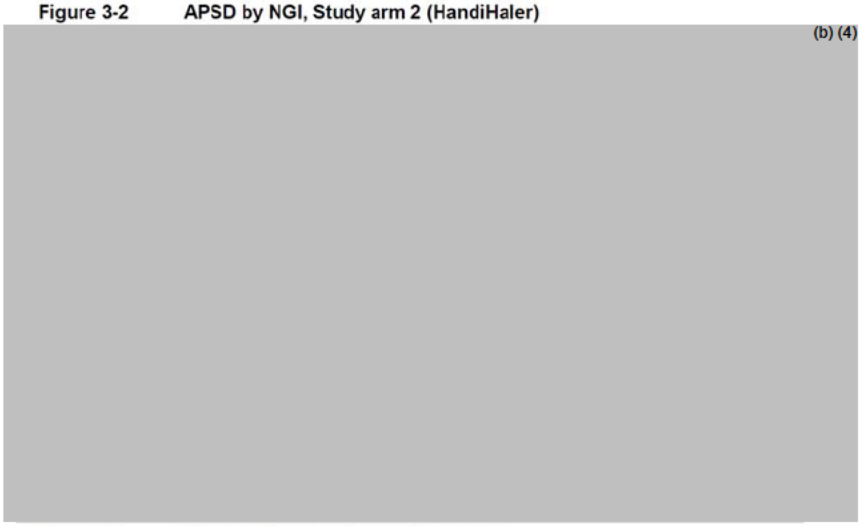

Figure 3-3 APSD by NGI, Study arm 3 (Aerolizer)

End of Sponsor Material

Start of Sponsor Material

Figure 3-4 APSD by NGI, 1st capsule (begin of period of use)

(b) (4)

Figure 3-5 APSD by NGI, average 14th and 15th capsules (middle of period of use)

(b) (4)

Figure 3-6 APSD by NGI, 30th capsule (end of period of use)

(b) (4)

End of Sponsor Material

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/s/

CRAIG M BERTHA
01/14/2011

PRASAD PERI
01/14/2011
I concur

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 16-DEC-2010

TO: N22383 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: Response to Information Request letter of 08-DEC-2010; CMC recommendation

SUMMARY: In the third CMC review dated 18-NOV-2010, the team recommended that the application be approved. Nevertheless, there were a few issues that needed clarification. These issues were identified in the 08-DEC-2010, information request letter in comments 6-9. The applicant's responses to these comments in the 15-DEC-2010, amendment are the subjects of this review.

EVALUATION:

Agency Comment 6
Agree to reassess and revise, as appropriate, the acceptance criteria for lactose impurities, once a sufficient number of batches (e.g., ≥ten) are tested using the new reporting limit of (b) (4). Propose acceptance criteria that are reflective of the data obtained. The limited data for three batches of lactose provided thus far do not support the permissive limit of up to (b) (4) total impurities in lactose, with all having less than (b) (4) totals.

Summary of Applicants Response (15-DEC-2010)
Novartis states that they commit to "reassess and revise, as appropriate, the acceptance criteria for lactose impurities, once fifteen (15) additional batches of lactose monohydrate are evaluated using the new reporting limit of (b) (4) "

Evaluation: Adequate.

Agency Comment 7
Revise the HOW SUPPLIED section of the package insert to more accurately describe the blister cards, e.g., "Box of 30 (5 blister cards with 6 capsules each)."

Summary of Applicants Response (15-DEC-2010)
The HOW SUPPLIED/STORAGE AND HANDLING section of the labeling has been revised with respect to the description of the blister cards. The description now reads:

"Unit Dose (blister pack), Box of 30 (5 blister cards with 6 capsules each) NDC 0078-0619-15

Evaluation: Adequate.

Agency Comment 8
Revise the SPL style sheets for both strengths to list the lactose monohydrate as an inactive ingredient.

Summary of Applicants Response (15-DEC-2010)
The applicant has revised the SPL style sheets to list lactose monohydrate as an inactive ingredient.

Evaluation: Adequate.

Agency Comment 9
Provide an explanation for the [redacted] 75 mcg [redacted] when exposed to the ICH Q1B photostability stress conditions, which is also reflected in the STORAGE AND HANDLING section of the package insert.

Summary of Applicants Response (15-DEC-2010)
Novartis agrees that photostability studies have shown [redacted] the 75 mcg strength of QAB149 [redacted] the 75 mcg dose product as light sensitive.

[redacted]

They also state that capsules are packed in aluminum blisters and are therefore protected from moisture and light during storage. And, the patient instructions [redacted] require the patient to remove the capsules from the blister immediately before use. They state that this should ensure that there is no light exposure of the capsules.

Evaluation: Adequate. It is obvious that the [redacted] concentration of the drug in the lactose matrix [redacted] would lead to an increased contact of the drug with lactose. [redacted]

RECOMMENDATION: The application is **recommended to be approved,** from the CMC perspective.

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
OND/DPAP/CHill
ONDQA/DIV 1/CBertha/16-DEC-2010
ONDQA/DIV 1/PPeri_____
ONDQA/DIV1/ASchroeder

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/s/

CRAIG M BERTHA
12/16/2010

PRASAD PERI
12/20/2010
I concur

NDA 22383

Arcapta™ Neohaler™
(indacaterol inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
ONDQA for DPARP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22383

2. REVIEW #:3

3. REVIEW DATE: 16-NOV-2010

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	17-DEC-2008
Amendment	31-MAR-2009
Amendment	02-APR-2009
Amendment	03-APR-2009
Amendment	30-APR-2009
Amendment	20-MAY-2009
Amendment	18-JUN-2009
Amendment	15-JUL-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	28-SEP-2010 (assigned 06-OCT-2010)

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative:	Ting Chen, MS, Director, Drug Regulatory Affairs
Telephone:	862-778-1530

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Arcapta™ Neohaler™[1]
b) Non-Proprietary Name: indacaterol maleate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: long-acting β_2-adrenergic agonist

11. DOSAGE FORM: inhalation powder

12. STRENGTH/POTENCY: 75 mcg (97 mcg) (b) (4) as free base (as maleate salt)/capsule (once daily)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

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

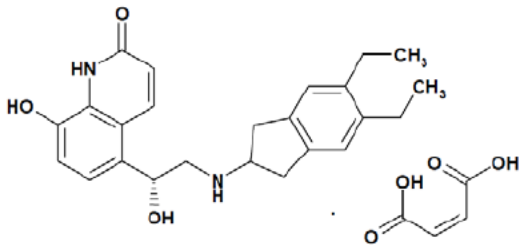
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Indacaterol Maleate is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate

[1] The Division of Pulmonary and Allergy Products sent the applicant a letter dated 19-MAR-2009, stating that the term (b) (4)," is unacceptable as part of the combined drug product trademark. (b) (4) . The 01-MAY-2009, amendment proposed to replace (b) (4) with "Neohaler," however the applicant also questioned the need for a specific proprietary name for the device.



Maleate salt: $C_{24}H_{28}N_2O_3 \bullet C_4H_4O_4$
Free base: $C_{24}H_{28}N_2O_3$
Maleate salt: 392.49 + 116.07 = 508.56
Free base: 392.49
Salt/base ratio: 1.296

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	4		(b) (4)	1	Adequate	02-FEB-2009 07-JUL-2009	
	4			1	Adequate	04-FEB-2009 22-APR-2009	
	3			3	Adequate	28-MAR-2000	Same blister packaging used for Novartis' inhalation powder capsule packaging for N20-831
	3			1	Adequate	26-JAN-2009 21-MAY-2009	

[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 are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	48,649	Novartis	IND for indacaterol maleate inhalation powder (capsules with Concept1 device)
IND	66,337	Novartis	IND for indacaterol maleate inhalation aerosol (HFA)
IND	69,754	Novartis	IND for indacaterol maleate inhalation powder (with multi-dose Certihaler device)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES	cGMP compliance/PAI	13-JAN-2009 04-NOV-2010	Final Final	ACCEPTABLE as of 13-OCT-2009 ACCEPTABLE as of 10-NOV-2010
Pharm/Tox	DS and DP impurities	15-JAN-2009	Final/V. Whitehurst, Ph.D.	NAI
Biopharm		N/A		
LNC		N/A		
Methods Validation		N/A		See p. 66 of review #2.
EA				NAI- see p. 69 of review #2.
Microbiology				N/A

The Chemistry Review for NDA 22383

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval** from a CMC perspective. However, it is requested that the PM send the comments in the attached draft information request letter to the sponsor.

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 product is Arcapta Neohaler (indacaterol) inhalation powder. It is a non-sterile dry powder inhaler drug product indicated for the treatment of chronic obstructive pulmonary disease. The inhalation powder product is pre-metered and the formulation is contained in hard gelatin capsules. Insertion of these capsules into the Neohaler (i.e., the Concept1 device which previously had the trademark (b) (4))[2] device allows the contents to be accessed and inhaled. The patient uses the Neohaler device to pierce the capsule simultaneously once on each end. Inhalation from the mouthpiece causes the capsule to spin and the formulation powder is entrained into the air stream and is emitted from the mouthpiece. There are (b) (4) strengths: 75 (b) (4) of indacaterol (as free base), equivalent to 97 mcg (b) (4) of indacaterol maleate, respectively. The pre-metered amount of formulation in the gelatin capsules is 25 mg (b) (4) with the balance made up by an inhalation-grade lactose monohydrate carrier excipient. No formulation comparability studies were necessary or were included in the application. At 60 L/min for 2 minutes, the *in vitro* dose delivery targets (emitted doses) are 57 (b) (4) mcg as indacaterol for the 75 (b) (4) mcg strengths, respectively.

[2]The Concept1 device (with new proposed trademark "Neohaler") device is very similar to the Aerolizer device that was approved with the applicant's application N20-831, Foradil Aerolizer (formoterol fumarate inhalation powder). The Concept1 device uses a single needle to pierce each end of the capsule whereas the Aerolizer uses four smaller needles for piercing each capsule end. Refer to the response to question 9 of the 74-day letter on p.11 of the second CMC review. In the response, the applicant has provided *in vitro* dose delivery and aerodynamic particle size distribution data demonstrating that Arcapta dosage units incorrectly used with the Aerolizer and Foradil capsules incorrectly used with the Concept1 device, would behave similarly, thereby allaying concerns regarding the consequences of such incorrect usage by patients that have access to both products.

The IUPAC name for the drug substance indacaterol maleate is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate. There is no USAN name for the compound although "indacaterol" is recognized as an INN name for the free base of the salt. The structure of the chiral drug substance is shown on p. 5 above.

The micronized drug substance is a white to very slightly grayish or very slightly yellowish powder. Solubility in water is limited to 0.23 mg/mL but with 0.9% sodium chloride solution the solubility decreases to only 0.06 mg/mL. The compound is slightly soluble in ethanol, methanol, propylene glycol, and polyethylene glycol 400, and freely soluble in *N*-methylpyrrolidone (NMP) and *N,N*-dimethylformamide (DMF). The re-test period of (b) (4) months is supported by stability data provided in the application for the micronized indacaterol maleate.

(b) (4)

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

Both strengths of the drug product are intended for once daily oral inhalation dosing by COPD patients. Each trade version of the drug product will contain a single Neohaler inhaler and 30 capsules of either the 75 (b) (4) mcg strengths. There will be five foil-foil blister cards each containing six capsules individually packaged in six blisters per card. There are also physician samples which would be similar but would only include one of the five blister cards (6 capsules each) with an inhaler. The applicant proposes an expiration dating period of (b) (4) 12 months for the 75 mcg strength, which are supported by the stability data provided. The recommended storage condition is room temperature although the labeling includes warnings about keeping the drug product in a dry place, which is typical for inhalation powder drug products.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/11/16/10
PPeri/ONDQA/DIV III//Branch VIII/Acting Branch Chief_____

C. CC Block

CHill/DPARP/Regulatory PM
ASchroeder/ONDQA/DIV III/Branch VIII/Acting CMC Lead
AHarry/DPARP/Medical Officer
YFan/OBP/Clinical Pharmacologist
VWhitehurst/DPARP/Pharmacologist

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/s/

CRAIG M BERTHA
11/16/2010

PRASAD PERI
11/18/2010
I concur

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 14-OCT-2009

TO: N22-383 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

SUBJECT: Update on Establishment Evaluation Request for N22383 Arcapta Neohaler (indacaterol inhalation powder); CMC recommendation

SUMMARY:

The Office of Compliance issued an overall recommendation of ACCEPTABLE for the application on 13-OCT-2009.

RECOMMENDATION: Considering the recommendation from the Office of Compliance, the application is **recommended to be approved,** from the CMC perspective.

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
OND/DPAP/CHill
ONDQA/DIV 1/CBertha/14-OCT-2009
ONDQA/DIV 1/PPeri
ONDQA/DIV1/ASchroeder

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

CRAIG M BERTHA
10/14/2009

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22383/000	**Sponsor:**	NOVARTIS PHARMS
C de:	570		1 HEALTH PLAZA
P. .y:	1S		EAST HANOVER, NJ 079361080
Stamp Date:	18-DEC-2008	**Brand Name:**	Arcapta Neohaler
PDUFA Date:	18-OCT-2009	**Estab. Name:**	indacaterol maleate
Action Goal:		**Generic Name:**	
District Goal:	19-AUG-2009	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; POWDER, FOR INHALATION; INDACATEROL MALEATE; EQ 150UGM BASE 002; POWDER, FOR INHALATION; INDACATEROL MALEATE; EQ 300UGM BASE 002; CAPSULE, HARD GELATIN; INDACATEROL MALEATE; EQ 300UGM BASE	

FDA Contacts:	C. HILL	Project Manager	(HFD-570)	301-796-1226
	P. PERI	Review Chemist	(HFD-820)	301-796-1730
	A. AL HAKIM	Team Leader		301-796-1323

Overall Recommendation: ACCEPTABLE on 13-OCT-2009 by E. JOHNSON (HFD-320) 301-796-3334

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-MAR-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-JAN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	13-OCT-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9611204	**FEI:** 3002807772	
	NOVARTIS PHARMA AG LICHSTRASSE 35, ST. JOHANN SITE		
	BASEL, , SWITZERLAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE BULK BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
l 'ilestone:	OC RECOMMENDATION		
ı. ,ne Date:	23-FEB-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9612715	**FEI:** 3002807776	
	NOVARTIS PHARMA AG CORK		
	RINGASKIDDY, CORK, , IRELAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
Profile:	NON-STERILE BULK BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-FEB-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9617734 **FEI:** 3000978864		
	NOVARTIS PHARMA PRODUKTIONS GMBH OEFLINGER STRASSE 44		
	WEHR, BADEN, , GERMANY		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-JAN-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 9692042 **FEI:** 3002865753		
	NOVARTIS PHARMA STEIN AG		
	SCHWEIZERHALLE, BASEL, SWITZERLAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE BULK BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
M[illegible]tone Date:	15-JUL-2009		
[illegible]on:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9692043 **FEI:** 3002653483		
	NOVARTIS PHARMA STEIN AG SCHAFFHAUSERSTRASSE		
	STEIN, , SWITZERLAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	10-FEB-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	NON-STERILE BULK BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	10-FEB-2009		
Decision:	ACCEPTABLE		
:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 2416082 **FEI:** 2416082		
	NOVARTIS PHARMACEUTICALS CORP OLD MILL RD		
	SUFFERN, NY 10901		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-JAN-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 9614433 **FEI:** 3002807773

NOVARTIS PHARMANALYTICA SA
VIA SERFINO BLESTRA 31

LOCARNO, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-JAN-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

M[illegible]tone Date: 21-JAN-2009

[illegible]on: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-JAN-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22383/000	**Action Goal:**	
S ate:	18-DEC-2008	**District Goal:**	19-AUG-2009
Regulatory:	18-OCT-2009		
Applicant:	NOVARTIS PHARMS	**Brand Name:**	Arcapta Neohaler
	1 HEALTH PLAZA	**Estab. Name:**	indacaterol maleate
	EAST HANOVER, NJ 079361080	**Generic Name:**	
Priority:	1S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	570	001; POWDER, FOR INHALATION; INDACATEROL MALEATE; EQ 150UGM BASE 002; POWDER, FOR INHALATION; INDACATEROL MALEATE; EQ 300UGM BASE 002; CAPSULE, HARD GELATIN; INDACATEROL MALEATE; EQ 300UGM BASE	

Application Comment: THIS IS A NEW NDA FOR AN NEW MOLECULAR ENTITY AND A DRY POWDER INHALER SUBMITTED BY NOVARTIS. THE MAIN CONTACT PERSON FOR ALL OF THE NOVARTIS FACILITIES IS PROVIDED BELOW.
MAIN CONTACT:
MICHAEL BRUCKHEIMER, EXECUTIVE DIRECTOR GLOBAL QUALITY OPERATIONS NOVARTIS PHARMACEUTICALS CORPORATION, ONE HEALTH PLAZA EAST HANOVER, NJ 07936, USA TEL NUMBER: (862) 778-7913 FAX: (973) 781-6052 E-MAIL: MICHAEL.BRUCKHEIMER@PHARMA.NOVARTIS.COM
ALTERNATE CONTACT:
VIVIANNE ARENCIBIA, HEAD GLOBAL COMPLIANCE AND AUDITING NOVARTIS PHARMACEUTICALS CORPORATION, ONE HEALTH PLAZA EAST HANOVER, NJ 07936, USA TEL NUMBER: (862) 778-4970 FAX: (973) 781-8265 E-MAIL: VIVIANNE.ARENCIBIA@NOVARTIS.COM.

(b) (4)

THE ADDRESS OF THE COMPANY IS ONE HEALTH PLAZA, EAST HANOVER, NJ 07936-1080
PH: 973-781-2565. (on 04-FEB-2009 by P. PERI (HFD-820) 301-796-1730)

F tacts:	C. HILL	Project Manager	(HFD-570)	301-796-1226
	P. PERI	Review Chemist	(HFD-820)	301-796-1730
	A. AL HAKIM	Team Leader		301-796-1323

Overall Recommendation:	ACCEPTABLE	on 13-OCT-2009	by E. JOHNSON	(HFD-320)	301-796-3334

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: THIS IS A SECONDARY PACKAGING SITE OF THE DRUG PRODUCT (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	14-JAN-2009	GMP Inspection			FERGUSONS
DO RECOMMENDATION	25-MAR-2009			ACCEPTABLE	LJARRELL
GMP INSPECTION CONDUCTED (b) (4) NO FDA-483 WAS ISSUED.				INSPECTION	
OC RECOMMENDATION	25-MAR-2009			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS A SECONDARY PACKAGING FOR THE DRUG PRODUCT (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	14-JAN-2009	GMP Inspection			FERGUSONS
DO RECOMMENDATION	20-JAN-2009			ACCEPTABLE	VMATUSOV
LAST GMP EI OF (b) (4) IS CLASSIFIED NAI. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION. PROFILE CLASS ADM WILL BE EVALUATED DURING THE NEXT GPM INSPECTION.				BASED ON FILE REVIEW	
OC RECOMMENDATION	21-JAN-2009			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS ONE OF FOUR PRIMARY PACKAGING SITES FOR THE DRUG PRODUCT (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	06-FEB-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	12-AUG-2009		(b) (4)		IRIVERA
DO RECOMMENDATION	13-OCT-2009			ACCEPTABLE	JOHNSONE
NAI				INSPECTION	
OC RECOMMENDATION	13-OCT-2009			ACCEPTABLE	JOHNSONE
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611204 **FEI:** 3002807772

NOVARTIS PHARMA AG

LICHSTRASSE 35, ST. JOHANN SITE
BASEL, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR MANUFACTURE OF DRUG SUBSTANCE [redacted] (b) (4) (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
DO RECOMMENDATION	23-FEB-2009			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	23-FEB-2009			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9612715 **FEI:** 3002807776

NOVARTIS PHARMA AG

CORK
RINGASKIDDY, CORK, , IRELAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR MANUFACTURE OF DRUG SUBSTANCE (b) (4) (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
DO RECOMMENDATION	05-FEB-2009			ACCEPTABLE	ADAMSS
AC GMP EI (b) (4)				BASED ON FILE REVIEW	
OC RECOMMENDATION	05-FEB-2009			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9617734 **FEI:** 3000978864

NOVARTIS PHARMA PRODUKTIONS GMBH

OEFLINGER STRASSE 44
WEHR, BADEN, , GERMANY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS ONE OF FOUR PRIMARY PACKAGING SITES FOR THE DRUG PRODUCT (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
OC RECOMMENDATION	16-JAN-2009			ACCEPTABLE	ADAMSS
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9692042 **FEI:** 3002865753

NOVARTIS PHARMA STEIN AG

SCHWEIZERHALLE, BASEL, SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: THIS SITE WITH THIS NUMBER IS LISTED AS NOVARTIS PHARMA SCHWEIZERHALLE, AG, ROTHAUSWEG, CH-4133, PRATTELELN, SITZERLAND BY THE APPLICANT. THE IS SOME CONFUSION ABOUT THE NAME AND SITE NUMBER IN THE DATA BASE IT APPEARS. THIS SITE IS RESPONSIBLE FOR MANUFACTURER OF DRUG SUBSTANCE (b) (4) . (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
ASSIGNED INSPECTION TO IB	06-FEB-2009	Product Specific			JOHNSONE
INSPECTION SCHEDULED	21-APR-2009		03-APR-2009		IRIVERA
DO RECOMMENDATION	15-JUL-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	15-JUL-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9692043 **FEI:** 3002653483

NOVARTIS PHARMA STEIN AG

SCHAFFHAUSERSTRASSE
STEIN, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Estab. Comment: MANUFACTURER OF DRUG PRODUCT, QUALITY CONTROL WITH EXCEPTION OF [redacted] (b) (4) AND MICROBIOLOGICAL TESTING ONLY ON STABILITY AND IS A PRIMARY PACKAGING SITE. (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)
THIS SITE IS RESPONSIBLE FOR THE MANUFACTURE OF DRUG SUBSTANCE [redacted] (b) (4) (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

NON-STERILE BULK BY CHEMICAL SYNTHESIS NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
D OMMENDATION	06-FEB-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	10-FEB-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	16-JAN-2009	Product Specific			ADAMSS
DO RECOMMENDATION	06-FEB-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	10-FEB-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 2416082 **FEI:** 2416082

NOVARTIS PHARMACEUTICALS CORP

OLD MILL RD
SUFFERN, NY 10901

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS ONE OF THREE PRIMARY PACKAGING SITES FOR THE DRUG PRODUCT (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
OC RECOMMENDATION	14-JAN-2009			ACCEPTABLE	FERGUSONS
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9614433 **FEI:** 3002807773

NOVARTIS PHARMANALYTICA SA

VIA SERFINO BLESTRA 31
LOCARNO, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR QUALITY CONTROL OF THE DRUG PRODUCT WITH THE EXCEPTION OF (b) (4) AND MICROBIOLOGICAL TESTING (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
OC RECOMMENDATION	16-JAN-2009			ACCEPTABLE BASED ON PROFILE	ADAMSS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS A SECONDARY PACKAGING FOR THE DRUG PRODUCT (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
SUBMITTED TO DO	14-JAN-2009	GMP Inspection			FERGUSONS
DO RECOMMENDATION	20-JAN-2009			ACCEPTABLE	VMATUSOV
LAST GMP EI OF (b) (4) IS CLASSIFIED NAI. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION. PROFILE CLASS ADM WILL BE EVALUATED DURING THE NEXT GPM INSPECTION.				BASED ON FILE REVIEW	
OC RECOMMENDATION	21-JAN-2009			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: THIS SITE IS RESPONSIBLE FOR QUALITY CONTROL OF DRUG SUBSTANCE. (on 13-JAN-2009 by P. PERI (HFD-820) 301-796-1730)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-JAN-2009				PERIP
OC RECOMMENDATION	16-JAN-2009			ACCEPTABLE	ADAMSS
				BASED ON PROFILE	

Arcapta™ Neohaler™
(indacaterol inhalation powder)
NDA 22-383

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Indication: Arcapta (indacaterol inhalation powder) Neohaler is for treatment of chronic obstructive pulmonary disease (COPD).

Presentation: The drug product is an inhalation powder contained in hard gelatin capsules with (b) (4) indacaterol maleate). (b) (4) Each trade version of the drug will contain a single Neohaler inhaler and 30 capsules of either the (b) (4) mcg strength. There are five foil-foil blister cards each containing six capsules individually packaged in six blisters per card. The physician sample contains one of the blister cards with an inhaler.

EER Status: Recommendation Pending

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency was not requested
Pharm/toxicology – Acceptable

Original Submission: 17-December-2008

Post-Approval CMC Commitments:

The sponsor agreed to reassess and revise, as appropriate, the acceptance criteria for lactose impurities, once a sufficient number of batches (e.g., ten) are tested using the new reporting limit of (b) (4) and to propose acceptance criteria that are reflective of the data obtained.

Drug Substances:

The drug substance, indacaterol maleate, is a chemically synthesized chiral molecule. The USAN modified name is indacaterol maleate and the IUPAC nomenclature is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1- hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate. The micronized drug substance is a white to very slightly grayish or very slightly

yellowish powder. Solubility in water is 0.23 mg/mL but decreases to only 0.06 mg/mL in 0.9% sodium chloride solution. The compound is slightly soluble in ethanol, methanol, propylene glycol, and polyethylene glycol 400, and freely soluble in *N*-methylpyrrolidone (NMP) and *N,N*-dimethylformamide (DMF). The drug substance is non-hygroscopic. Only one crystal form has been identified.

(b) (4)

The proposed release specification for indacaterol maleate includes: appearance, color, clarity of solution, identity by IR and X-ray diffraction, assay by titration and High Performance Liquid Chromatography (HPLC), impurity and enantiomer content by HPLC, heavy metals, residual solvents by Gas Chromatography (GC), particle size by laser light diffraction, moisture content by thermogravimetry, and sulphated ash. Of note, the release specifications also includ (b) (4)

The drug substance is stored in (b) (4). The re-test period of (b) (4) months is supported by stability data provided in the application for the micronized indacaterol maleate.

Conclusion: The drug substance is satisfactory

Drug Product:

The drug product is a non-sterile dry powder inhaler drug product indicated for the treatment of chronic obstructive pulmonary disease. The inhalation powder formulation is contained in hard gelatin capsules. The patient uses the Neohaler device to pierce the capsule simultaneously on each end. Inhalation from the mouthpiece causes the capsule to spin and the formulation powder is entrained into the air stream and is emitted from the mouthpiece.

(b) (4) capsules contained 25 mg of the formulation, consisting of the micronized drug substance with the balance made up by an inhalation-grade lactose monohydrate carrier excipient.

[redacted]

The drug product gelatin capsules are packaged in aluminum foil/foil blisters with a protective backing and perforations. The provided stability data support an expiration dating period for the drug product of [redacted] months at room temperature. The labeling includes a warning to keep the drug product in a dry place.

Conclusion: The drug product is satisfactory.

Additional Items:

A comparability protocol for change in [redacted] for the Neohaler device was reviewed and found to be adequate.

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is approvable pending acceptable cGMP recommendation from the Office of Compliance.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	INDACATEROL

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/s/

CHRISTINE M MOORE
09/03/2009
ONDQA DPA I Director (acting)

CHEMISTRY REVIEW

NDA 22-383

Arcapta™ Neohaler™
(indacaterol inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
ONDQA for DPAP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-383

2. REVIEW #:2

3. REVIEW DATE: 16-JUL-2009

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	17-DEC-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	31-MAR-2009
Amendment	02-APR-2009
Amendment	03-APR-2009
Amendment	30-APR-2009
Amendment	20-MAY-2009
Amendment	18-JUN-2009
Amendment	15-JUL-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative:	Ting Chen, MS, Director, Drug Regulatory Affairs
Telephone:	862-778-1530

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Arcapta™ Neohaler™[1]
b) Non-Proprietary Name: indacaterol maleate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: long-acting β_2-adrenergic agonist

11. DOSAGE FORM: inhalation powder

12. STRENGTH/POTENCY: (b) (4) as free base (as maleate salt)/capsule (once daily)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

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

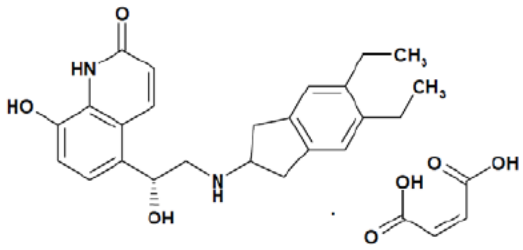
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Indacaterol Maleate is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate

[1] The Division of Pulmonary and Allergy Products sent the applicant a letter dated 19-MAR-2009, stating that the term (b) (4) is unacceptable as part of the combined drug product trademark. (b) (4) The 01-MAY-2009, amendment proposed to replace (b) (4) with "Neohaler," however the applicant also questioned the need for a specific proprietary name for the device.



Maleate salt: $C_{24}H_{28}N_2O_3 \bullet C_4H_4O_4$
Free base: $C_{24}H_{28}N_2O_3$
Maleate salt: 392.49 + 116.07 = 508.56
Free base: 392.49
Salt/base ratio: 1.296

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	4		(b) (4)	1	Adequate	02-FEB-2009 07-JUL-2009	
	4			1	Adequate	04-FEB-2009 22-APR-2009	
	3			3	Adequate	28-MAR-2000	Same blister packaging used for Novartis' inhalation powder capsule packaging for N20-831
	3			1	Adequate	26-JAN-2009 21-MAY-2009	

[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 are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	48,649	Novartis	IND for indacaterol maleate inhalation powder (capsules with Concept1 device)
IND	66,337	Novartis	IND for indacaterol maleate inhalation aerosol (HFA)
IND	69,754	Novartis	IND for indacaterol maleate inhalation powder (with multi-dose Certihaler device)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES	cGMP compliance/PAI	13-JAN-2009	Pending	As of 16-JUL-2009
Pharm/Tox	DS and DP impurities	15-JAN-2009	Final/V. Whitehurst, Ph.D.	NAI
Biopharm		N/A		
LNC		N/A		
Methods Validation		N/A		See p. 66 of this review.
EA				NAI- see p. 69 of current review.
Microbiology				N/A

The Chemistry Review for NDA 22-383

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval** from the CMC perspective, however, a recommendation from the Office of Compliance is pending.

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

The following comment should be sent to the applicant prior to the Agency taking an approval action on the application:

Agree to reassess and revise, as appropriate, the acceptance criteria for lactose impurities, once a sufficient number of batches (e.g., ten) are tested using the new reporting limit of (b) (4). *Propose acceptance criteria that are reflective of the data obtained.*

II. Summary of Chemistry Assessments

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

The drug product is Arcapta Neohaler (indacaterol) inhalation powder. It is a non-sterile dry powder inhaler drug product indicated for the treatment of chronic obstructive pulmonary disease. The inhalation powder product is pre-metered and the formulation is contained in hard gelatin capsules. Insertion of these capsules into the Neohaler (i.e., the Concept1 device which previously had the trademark (b) (4))[2] device allows the contents to be accessed and inhaled. The patient uses the Neohaler device to pierce the capsule simultaneously once on each end. Inhalation from the mouthpiece causes the capsule to spin and the formulation powder is entrained into the air stream and is emitted from the mouthpiece. (b) (4) The pre-metered amount of formulation in the gelatin capsules is 25 mg (b) (4) with the balance

[2]The Concept1 device (with new proposed trademark "Neohaler") device is very similar to the Aerolizer device that was approved with the applicant's application N20-831, Foradil Aerolizer (formoterol fumarate inhalation powder). The Concept1 device uses a single needle to pierce each end of the capsule whereas the Aerolizer uses four smaller needles for piercing each capsule end. Refer to the response to question 9 of the 74-day letter on p. 11. In the response, the applicant has provided *in vitro* dose delivery and aerodynamic particle size distribution data demonstrating that Arcapta dosage units incorrectly used with the Aerolizer and Foradil capsules incorrectly used with the Concept1 device, would behave similarly, thereby allaying concerns regarding the consequences of such incorrect usage by patients that have access to both products.

made up by an inhalation-grade lactose monohydrate carrier excipient. No formulation comparability studies were necessary or were included in the application. (b) (4)

The IUPAC name for the drug substance indacaterol maleate is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate. There is no USAN name for the compound although "indacaterol" is recognized as an INN name for the free base of the salt. The structure of the chiral drug substance is shown on p. 4 above.

The micronized drug substance is a white to very slightly grayish or very slightly yellowish powder. Solubility in water is limited to 0.23 mg/mL but with 0.9% sodium chloride solution the solubility decreases to only 0.06 mg/mL. The compound is slightly soluble in ethanol, methanol, propylene glycol, and polyethylene glycol 400, and freely soluble in *N*-methylpyrrolidone (NMP) and *N,N*-dimethylformamide (DMF). The re-test period of (b) (4) months is supported by stability data provided in the application for the micronized indacaterol maleate.

(b) (4)

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

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/7/16/09
AAl-Hakim/ONDQA/DIV I/Branch Chief_____

C. CC Block

CHill/DPAP/Regulatory PM
PPeri/ONDQA/DIV I/Branch II/PAL
LWu/DPAP/Medical Officer
SSuarez/OBP/Clinical Pharmacologist
VWhitehurst/DPAP/Pharmacologist

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/s/

Craig Bertha
7/16/2009 01:14:23 PM
CHEMIST

Ali Al-Hakim
7/17/2009 01:50:41 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-383

Arcapta™ (b) (4) (indacaterol maleate inhalation powder)

Novartis Pharmaceuticals Corporation

Craig M. Bertha, Ph.D.
ONDQA for DPAP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-383

2. REVIEW #:1

3. REVIEW DATE: 06-MAR-2009

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	17-DEC-2008 (assigned 29-DEC-2008)

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative:	Ting Chen, MS, Director, Drug Regulatory Affairs
Telephone:	862-778-1530

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Arcapta™ (b) (4)™
b) Non-Proprietary Name: indacaterol maleate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: long-acting β_2-adrenergic agonist

11. DOSAGE FORM: inhalation powder

12. STRENGTH/POTENCY: [redacted] (b) (4) as free base (as maleate salt)/capsule (once daily)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

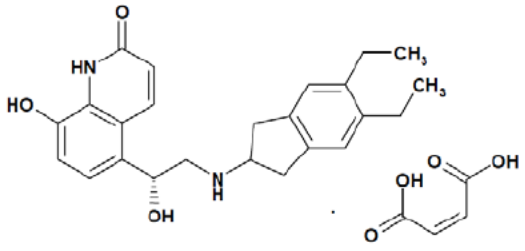
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Indacaterol Maleate is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate



Maleate salt: $C_{24}H_{28}N_2O_3 \bullet C_4H_4O_4$
Free base: $C_{24}H_{28}N_2O_3$
Maleate salt: 392.49 + 116.07 = 508.56

Free base: 392.49
Salt/base ratio: 1.296

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	4		(b) (4)	1	Adequate	02-FEB-2009	IR letter to holder dated 03-FEB-2009
	4			1	**Inadequate**	04-FEB-2009	Deficiency letter dated 05-FEB-2009
	3			3	Adequate	28-MAR-2000	Same blister packaging used for Novartis' inhalation powder capsule packaging for N20-831
	3			1	**Inadequate**	26-JAN-2009	Deficiency letter dated 26-JAN-2009

[1] Action codes for DMF Table:
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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 are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	48,649	Novartis	IND for indacaterol maleate inhalation powder (capsules with Concept1 device)
IND	66,337	Novartis	IND for indacaterol maleate inhalation aerosol (HFA)
IND	69,754	Novartis	IND for indacaterol maleate inhalation powder (with multi-dose Certihaler device)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES	cGMP compliance/PAI	13-JAN-2009	Pending	
Pharm/Tox	DS and DP impurities	15-JAN-2009	Pending	
Biopharm				N/A
LNC				N/A
Methods Validation				Not forwarded until methods are revised.
EA				Requesting EIC calculation information.
Microbiology				N/A

The Chemistry Review for NDA 22-383

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable from the CMC perspective. It is requested that the PM send a discipline review letter to the applicant including the comments contained in the attached draft letter starting on p. 191.

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

None at this time.

II. Summary of Chemistry Assessments

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

The drug product is Arcapta (b) (4) (indacaterol maleate inhalation powder). It is a non-sterile dry powder inhaler drug product indicated for the treatment of chronic obstructive pulmonary disease. The inhalation powder product is pre-metered and the formulation is contained in hard gelatin capsules. Insertion of these capsules into the (b) (4) (a.k.a., Concept1)[1] device allows the contents to be accessed and inhaled. The patient uses the (b) (4) device to pierce the capsule simultaneously once on each end. Inhalation from the mouthpiece causes the capsule to spin and the formulation powder is entrained into the air stream and is emitted from the mouthpiece. (b) (4) The pre-metered amount of formulation in the gelatin capsules is 25 mg for both strengths with the balance made up by an inhalation-grade lactose monohydrate carrier excipient. No formulation comparability studies were necessary or were included in the application. (b) (4)

The IUPAC name for the drug substance indacaterol maleate is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate. There is no USAN name for the compound although "indacaterol" is recognized as an INN name for the free base of the salt. The structure of the chiral drug substance is shown on p. 5 above.

[1]The Concept1 device is very similar to the Aerolizer device that was approved with the applicant's application N20-831, Foradil Aerolizer (formoterol fumarate inhalation powder).

The micronized drug substance is a white to very slightly grayish or very slightly yellowish powder. Solubility in water is limited to 0.23 mg/mL but with 0.9% sodium chloride solution the solubility decreases to only 0.06 mg/mL. The compound is slightly soluble in ethanol, methanol, propylene glycol, and polyethylene glycol 400, and freely soluble in *N*-methylpyrrolidone (NMP) and *N,N*-dimethylformamide (DMF). The re-test period of (b) (4) months is supported by stability data provided in the application for the micronized indacaterol maleate.

(b) (4)

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

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

Refer to the draft deficiency letter starting on p. 191 of the review for details. In summary, the more important issues are:

- clarification is needed regarding some aspects of the drug substance synthesis
- revisions are needed in terms of the drug substance quality control methods, particularly for the system suitability criteria
- the supporting DMFs from the capsule and device manufacturers are inadequate and deficiency letters have been forwarded to the holders of the files
- revisions and clarification of the drug product quality control methods are needed
- revisions to some of the drug product, device, and lactose excipient specification acceptance criteria are necessary

- more specific information regarding the placebo capsules should be provided
- labeling revisions are needed

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/3/06/09
AAl-Hakim/ONDQA/DIV I/Branch Chief_____

C. CC Block

CHill/DPAP/Regulatory PM
PPeri/ONDQA/DIV I/Branch II/PAL
LWu/DPAP/Medical Officer
SSuarez/OBP/Clinical Pharmacologist
VWhitehurst/DPAP/Pharmacologist

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/s/

Craig Bertha
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Ali Al-Hakim
3/8/2009 10:22:36 PM
CHEMIST

OND Division of Pulmonary and Allergy Products

NDA: 22-383
Applicant: Novartis Pharmaceutical Corporation
Stamp Date: 18-Dec-2008
PDUFA Date: 18-Oct-2009
ONDQA 5 month date: 18-Mar-2009
Proposed Proprietary Name: Arcapta® (b) (4)
Established Name: (indacaterol maleate)
Dosage form and strength: Inhalation Powder, (b) (4) per capsule.
Route of Administration: oral inhalation
Indications: Treatment of Chronic Obstructive Pulmonary Disease (COPD)

PAL: Prasad Peri, Ph.D. Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing
Review team recommendation: Single primary reviewer (Craig Bertha, Ph.D)

Time goals:

- **Initial Quality Assessment in DFS: by 06-Feb-2009 (**Filing meeting)
- **Chemistry filing memo in DFS: by 06-Feb-2009**
- Filing decision "Day 45": **06-Feb-2009** (set by Clinical Division)
- Filing review issues "Day 74": 2-Mar-2009 (set by Clinical Division)
- **Chemistry Review (DR/IR) letter: by 18-May-2009**
- Mid-cycle meeting "Month 5": **12-May-2009**
- Wrap Up: 18-Aug-2009
- **Final Chemistry Review "Month 8" in DFS: by 25-Aug-2009**
- **Secondary Review Due**: September 9, 2009
- **L**abeling **T**con: September 14, 2009 (1:30-2:30))
- **CDTL M**emo: September 15, 2009
- Action Package Readiness: September 18, 2009
- Division Director Memo: September 18, 2009
- Division Goal: October 16, 2009
- PDUFA: 18-Oct-2009

Relevant Applications

IND 48,649 (QAB 149 Indacaterol Maleate Inhalation Powder with lactose)

(b) (4)

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be determined by Primary Reviewer
CDRH	*Not Applicable*
EA	Exclusion requested. Certification provided.
EES	EER sent to Office of Compliance on 16-Jan-2009, and 06-Feb-2009. Many foreign sites are pending.
OSE/DMEPA/DDMAC Consult	*Labeling consult request will be sent as part of DPAP's request.*
Methods Validation	*Per decision of reviewer but no critical tests identified.*
Microbiology	*Endotoxins to be evaluated.*
Pharm/Tox	*DS and DP Impurities to be qualified*
Labeling and Nomenclature	*Trade name has been consulted to OSE/DMEPA.*

Summary:

- This is a standard (10 month) electronic NDA in eCTD format with electronic labeling provided in SPL format. There is a Quality Overall Summary (divided into DS and DP sections). This NDA is filed as a 505(b)(2) application. The associated IND is 48649. Several meeting with the sponsor are reported in DARRTS and by the applicant. CMC comments were sent to the sponsor in communications dated 7/3/2007 (CMC SPA), and 5/29/2008 (preNDA)
- Note that this is an **NME** and as per FDAAA requirements, will be taken up for an Advisory Committee meeting and discussion. Additionally this is a single ingredient LABA (long acting beta agonist) which is under a lot of discussion for safety. All LABA's have black box warnings.

Drug Substance

- Indacaterol (QAB149) is a **chiral** molecule. The USAN modified name is indacaterol maleate is and the IUPAC nomenclature is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate. The S-enantiomer is controlled in the drug substance at a limit of NMT (b) (4)
- The drug substance is a white to very slightly grayish or very slightly yellowish powder. It is very slightly soluble in water, and 5% glucose solution and insoluble in most other aq. solutions. It is slightly soluble in methanol, ethanol but freely soluble in organic polar solvents like Dimethylformamide (DMF) or N-Methylpyrrolidone (NMP). NMR spectra are performed in DMSO-D6 for this reason perhaps. The DS has a melting range of 195-202°C with a pKa in water at room temperature 7.3 and 8.0. QAB 149 is the code for indacaterol maleate and the partition coefficient (K_{ow}) is 212 (log D 2.33) and in 0.1N it is 10.0 (Log D 1.00).
- A polymorphism program performed with QAB149 maleate does not show the presence of other crystalline forms other than form A. The crystalline modification A is not hygroscopic.

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/s/

Prasad Peri
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2/17/2009 10:23:11 AM
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