Ann Shea
Sr. Associate Director
Drug Regulatory Affairs

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

Tel 862-778-4567
Fax 973-781- 2565
Internet: ann.shea@novartis.com

NOVARTIS

Fax

Attention: Ms. Akilah Green
Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

Fax no.: 301-796-9718
Number of pages: 41 including cover page

Date: March 1, 2006

Concerning: **Foradil® Certihaler® (formoterol fumarate inhalation powder)**
NDA 21-592
General Correspondence – Response to Request for Information

Dear Ms. Green,

Please find attached information being submitted to NDA 21-592 in preparation for our meeting on March 6, 2006.

Should you have any questions, please do not hesitate to call me at 862-778-4567.

Sincerely,

Ann Shea

Ann Shea

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

Ann Shea, Sr. Associate Director
Tel: 862-778-4567
Fax: 973-781-2565
email address: ann.shea@novartis.com

NOVARTIS

March 1, 2006

Badrul Chowdhury, MD, PhD
Division Director
Food and Drug Administration
Division of Pulmonary and Allergy
Drug Products
Office of Drug Evaluation II
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA No. 21-592

Foradil® Certihaler® (formoterol fumarate inhalation powder)

GENERAL CORRESPONDENCE
Response to Request for Information

Dear Dr. Chowdhury:

Reference is made to the telephone conversations with Ms. Akilah Green, Regulatory Project Manager, on February 27 and 28, 2006 and the FDA request for additional information in preparation for our teleconference on March 6, 2006.

As requested, please find attached a table summarizing the interactions between the German Health Authorities (BfArM and the local Federal Government Ansbach) and Novartis Germany regarding the adverse event reports consistent with inadvertent overdose from the Foradil® Certihaler® and the subsequent voluntary recall of Foradil Certihaler in Germany (Appendix 1). Please note that all interactions with the German Health Authorities have either been by telephone, email, or in person.

In addition, please find attached the CIOMS form for a 5th reported case of overdose (Appendix 2), and the Technical Assessment Report (Appendix 3).

If you have any questions or comments, please contact me at (862) 778-4567.

Sincerely,

Ann Shea
Sr. Associate Director

AS
Submitted in triplicate

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	March 1, 2006
TELEPHONE NO. *(Include Area Code)* (862) 778-4567	FACSIMILE (FAX) Number *(Include Area Code)* (973) 781-2565
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* One Health Plaza East Hanover, New Jersey 07936-1080	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **21-592**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
formoterol fumarate inhalation powder	**Foradil® Certihaler®**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
	10 mcg	

(PROPOSED) INDICATION(S) FOR USE:
Asthma

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*

☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER General Corresponden

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
General Correspondence - Response To Request For Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Ann Shea	Ann Shea, Associate Director Drug Regulatory Affairs	03/01/06

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	(862) 778-4567

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Appendix 1

Summary of Interactions between Novartis Pharma (Germany) and German Health Authorities 19th Jan – 1st March 2006

Date	Contact	Details
19-Jan-06	Dr Focker, local federal govt. (Ansbach) Telephone call from Novartis Germany	First contact with local federal Health Authority in Ansbach to report on the issue, the investigations conducted, and immediate (investigation at external expert/lab) and proposed mid-term corrective actions.
20-Jan-06	Dr Focker Local federal govt. (Ansbach) & Dr Thiele BfArM Teleconference with Novartis Germany and Novartis Basel	Local federal government (Ansbach) after consultation with Federal Authority on Food Safety (LGL, Munich) requested: • initiation of a class II, level B (from wholesalers, pharmacies and physicians) recall of all Certihalers from the German market, • issuance of a "Rote Hand" ('Red Hand') warning letter to physicians to inform them of the issue • that Swissmedic be informed HA agreed that the reported over-dosage from the Certihaler is likely due to mishandling and not to a device defect. Direct notification of the public was not requested. Foradil Certihaler will be allowed to be re-packed with a suitably updated patient information leaflet and re-distributed.
22-Jan-06	Dr Thiele BfArM e-mail to Novartis Germany	BfArM agrees with draft wording of 'Rote Hand' letter.
23 – 25 Jan-06		• 'Rote Hand' letter sent to 91,000 doctors • Publication of the recall in 'Pharmazeutische Zeitung' and 'Deutsche Apotheker Zeitung'. online and on homepage of 'Doctors' medicines commission' • All hospital pharmacies that had ordered Certihaler informed of recall • Immediate halt called to sales and distribution • Recall of all sample devices distributed by sales reps
23-Jan-06		*FDA notified of recall.*

Date	Contact	Details
25-Jan-06	Dr Focker (Local federal govt, Ansbach)	Local HA takes 30 samples of Certihaler (3 different batches) for examination at ‚Zentrale Leitstelle für Gesundheit' in Munich. No report of outcome of these investigations to date.
27-Jan-06		Report of fourth case of overdosing received (CIOMS form PHNU2006DE00679) – event took place on 22-Jan-06.
27-Jan-06	Dr Thiele BfArM telephone contact by Novartis Germany, followed up by e-mail to Drs Thiele & Paeschke (BfArM) and Dr Focker (Local federal govt, Ansbach.)	German health authorities informed of fourth case. Health authorities re-affirm that measures so far taken by Novartis are adequate.
09-Feb-06	Dr Thiele BfArM e-mail from Novartis Germany e-mail from Dr Thiele, BfArM to Novartis Germany	Rate of return of Certihaler devices lower than expected. Draft of reminder letter (non-'Rote Hand') to about 20,000 doctors requesting immediate return of sample Certihalers sent to BfArM for approval. N.B. Sample devices (issued in Sept 05) only contain 15 doses i.e. 1 week's therapy, expected that majority of issued devices will have been used up. Wording of reminder letter approved by BfArM.
10-Feb-06	e-mail from Novartis Germany to Dr Focker (Local federal govt. Ansbach) and Dr Thiele (BfArM)	Final version of reminder letter to 19,300 doctors sent to HA and expected date of distribution announced to be 14th & 15th Feb. Thus far, no immediately obvious device defect has been uncovered which would easily explain overdosing.

Date	Contact	Details
15-Feb-06	Meeting between Novartis Germany and local HA (local federal govt. Ansbach (Dr Focker)	Technical assessment report on Certihaler device provided to local federal government. (Ansbach) Copy of information package already sent to all concerned health authorities provided to BfArM and local federal authority. This package based on communication made to FDA on 2nd Feb 06 in response to request by them for further information on events in Germany.
22-Feb-06		Fifth case of patient overdosing with Certihaler reported to Novartis (event occurred on 15-Feb-06, CIOMS form PHNU2006DE01033)
24-Feb-06	e-mail from Novartis Germany to Dr Thiele (BfArM)	Notification of fifth event (patient was dispensed device on 19 Jan). Device is being investigated by QC dept and patient was issued with different formulation of the same medicine. CIOMS form provided.

Appendix 2

***** DRAFT *****

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
-	Germany			1943	Unk	Male	Unk	15	FEB	2006

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

He experienced shaking [Tremor]
A large amount of powder was released/"mouth full of powder" [Device malfunction]

Case Description: This report combines preliminary pharmacist information received on 22 Feb 2006 and a phone call with the patient on 22 Feb 2006. This patient has been treated with Foradil Certihaler (formoterol) twice daily since Dec 2005, he had initially received 3 sample packages, and had started with regular commercial packs, batch K082, on 19 Jan 2006. (continue)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

b(6)

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name)
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Do (continue)

15. DAILY DOSE(S)
#1 large amount of powder

16. ROUTE(S) OF ADMINISTRATION
#1 Inhalation

17. INDICATION(S) FOR USE
#1 Asthma

18. THERAPY DATES (from/to)
#1 15-FEB-2006 00:00 / 15-FEB-2006 00:00

19. THERAPY DURATION
#1 1 day

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1 MIFLONIDE (BUDESONIDE) . ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)
From/To Dates | Type of History / Notes | Description
Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Novartis Pharma AG
Clinical Safety and Epidemiology
Postfach CH-4002
Basel, Switzerland

24b. MFR CONTROL NO.
PHNU2006DE01033

24c. DATE RECEIVED BY MANUFACTURER
22-FEB-2006

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☒ OTHER: Spontaneous Report

DATE OF THIS REPORT
27-FEB-2006

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

26. REMARKS

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

***** DRAFT *****

Mfr. Control Number: PHNU2006DE01033

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

On 15 Feb 2006 in the morning, he inhaled from the Certihaler, dose counter position was at about 20 remaining doses. With this inhalation, a large amount of powder was released, he described that he had his mouth full of powder. He had immediately washed out the powder of his mouth. In the next few hours, he experienced shaking. There were no further symptoms, he did not consult a physician. After a few hours, he recovered. He tried to use the suspected device a few more times, but stated that no powder was released from it any longer. At a dose counter position of 17, he brought the device to his pharmacy. The pharmacist intends to send the device to local Quality Assurance. QA assigned the following numbers to this case: local no.16913 and GCRS no. DENU20060224090956.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Dose Inh (Lot # K082); Regimen #1	large amount of powder; Inhalation	Asthma	15-FEB-2006 00:00 / 15-FEB-2006 00:00; 1 day
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Dose Inh; Regimen #2	UNK, BID; Unknown		DEC-2005 / Unknown; Unknown

APPEARS THIS WAY
ON ORIGINAL

Appendix 3

29 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Ann Shea
Sr. Associate Director
Drug Regulatory Affairs

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

Tel 862-778-4567
Fax 973-781- 2565
Internet: ann.shea@novartis.com

NOVARTIS

Fax

Attention: Ms. Akilah Green
Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

Fax no. ~~796~~ 796
301-~~796~~-9718

Number of pages ~~28~~ 33 including cover page

Date: February 2, 2006

Concerning: **Foradil® Certihaler® (formoterol fumarate inhalation powder)**
NDA 21-592
General Correspondence

Dear Ms. Green,

Please find attached the letter and information package being submitted to NDA 21-592 today. Please note that due to its size (51 pages), Appendix 1 is not included with this fax.

Should you have any questions, please do not hesitate to call me at 862-778-4567.

Sincerely,

Ann Shea

Ann Shea

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

Ann Shea, Sr. Associate Director
Tel: 862-778-4567
Fax: 973-781-2565
email address: ann.shea@novartis.com

NOVARTIS

February 2, 2006

Badrul Chowdhury, MD, PhD
Division Director
Food and Drug Administration
Division of Pulmonary and Allergy
Drug Products
Office of Drug Evaluation II
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA No. 21-592

Foradil® Certihaler® (formoterol fumarate inhalation powder)

GENERAL CORRESPONDENCE

Dear Dr. Chowdhury:

Reference is made to our telephone conversations with Ms. Carol Hill, Regulatory Project Manager, on January 24, 2006 and January 25, 2006 regarding the adverse event reports from Germany consistent with inadvertent overdose from the Foradil® Certihaler® and the subsequent voluntary recall of Foradil Certihaler in Germany and Switzerland.

As requested, please find attached information summarizing events to date, including the CIOMS forms for the reported cases, the letter announcing the recall in Germany, and patient instructions.

If you have any questions or comments, please contact me at (862) 778-4567.

Sincerely,

Ann Shea
Sr. Associate Director

AS
Submitted in triplicate

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Drug Regulatory Affairs

Foradil® Certihaler®

NDA 21-592

Response to FDA Request

Document type:	Response to FDA Request
Document status:	Final
Release date:	02-Feb-2006
Number of pages:	4

Table of contents

Current situation in Germany and Switzerland

Four reports consistent with inadvertent overdose from the Foradil® Certihaler® were reported from the German market in January 2006. As a precautionary measure in collaboration with the German and Swiss Health Authorities, a voluntary recall was initiated on January 23, 2006 in order to revise the existing instructions to prevent potential accidental mishandling of the device.

As well as recalling Foradil Certihaler stocks from pharmacies, Novartis has contacted healthcare professionals in Germany and Switzerland, the two countries where Foradil Certihaler is currently marketed, and asked that any sample devices (15 doses) be returned to Novartis. Approximately —— devices were distributed to pharmacies in Germany, and —— sample devices were provided to physicians since the launch of Foradil Certihaler in Germany in September 2005. In Switzerland, approximately —— devices were sold to patients and — sample devices were distributed to physicians. b(4)

A case of possible overdose was reported on 28-Jul-2005 from a patient in the Netherlands in Foradil Certihaler Study F2402 (patient 0117/0011). A report of this case was provided in the Complete Response submitted to NDA 21-592 for Foradil Certihaler, dated October 10, 2005 and the case report form (CFR) for this patient is provided in Appendix 1.

A summary of events leading up to the recall, as well as an overview of the investigations into these cases and the current understanding is outlined below.

Summary of events

On January 5, 2006, Novartis received a report (Report 1) of potential overdose from the German market (see CIOMS form Control No. PHNU2006DE00463 - Appendix 2). On January 10, 2006, a second case was received (Report 2) (see CIOMS form Control No. PHNU2006DE00499 - Appendix 3), and on January 11, 2006, a third case was received (Report 3) (see CIOMS form Control No. PHNU2006DE00503 - Appendix 4). On January 27, 2006, a fourth case was received (Report 4) (see CIOMS form Control No. PHNU2006DE00679 - Appendix 5).

The devices that were returned to Novartis are currently under assessment. This assessment includes interviews of the patients, physical inspection of the devices, review of manufacturing records and attempts to simulate the reported events in the laboratory. Please note that the inhalers from Report 1 and Report 4 have not been provided to Novartis by the patients, and a technical assessment of these inhalers has not thus far been performed.

The local Health Authority in Germany was informed of these cases on January 19, 2006.

In collaboration with the German Health Authority (HA), it was decided to initiate a voluntary recall from wholesalers, pharmacies and physicians of all Certihalers from the German market. In the letter to wholesalers, pharmacies and physicians informing them of the recall, Novartis, in agreement with the German HA communicated that the package leaflet will be updated to clearly explain correct use before the product becomes available again.

On January 20, 2006, Swissmedic was informed of the three cases of possible overdosing in Germany.

On January 23, 2006, a "Rote Hand" letter (Appendix 6-1) was published in the "Pharmazeutische Zeitung" and "Deutsche Apotheker Zeitung" to announce the recall. An English translation is also provided (Appendix 6-2). On the same day, Novartis notified FDA of the recall.

On January 25, 2006, the recall was announced in Switzerland.

Patient instructions

A copy of the original language German patient leaflet (Appendix 7-1) and the current pending US patient instructions in their intended layout as submitted to NDA 21-592 for Foradil Certihaler with the Complete Response dated October 10, 2005 (Appendix 7-2) are provided. Please note that the instructions for use in the German patient leaflet are similar to those originally submitted with NDA 21-592 on December 17, 2002 (Appendix 7-3). One possible cause of these potential overdoses is accidental patient mishandling due to the lack of clarity of the German instructions. Investigations are continuing into addressing accidental mishandling caused by lack of clarity in patient instructions.

Appendices

Appendix 1	Case report form for patient 0117/0011 (Study F2402)
Appendix 2	CIOMS form for Report 1 (PHNU2006DE00463)
Appendix 3	CIOMS form for Report 2 (PHNU2006DE00499)
Appendix 4	CIOMS form for Report 3 (PHNU2006DE00503)
Appendix 5	CIOMS form for Report 4 (PHNU2006DE00679)
Appendix 6-1	'Rote Hand' letter (German version)
Appendix 6-2	'Rote Hand' letter (English version)
Appendix 7-1	Patient instructions (Germany)
Appendix 7-2	Patient instructions (US – pending NDA 21-592; submitted 10-Oct-05)
Appendix 7-3	Patient instructions (US – pending NDA 21-592; submitted 17-Dec-02)

Appendix 2

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
[redacted]	Germany		Unk		26 Years	Male	Unk	03	JAN	2006	

b(6)

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Blood pressure was 150/110 mm HG [Blood pressure increased] ([Dizziness], [Headache])
Heart rate at rest 145/min [Heart rate increased]
Patient supected the complete content of powder was released [Overdose]

Case Description: This is a preliminary consumer report received on 05 Jan 2006. A patient has been treated with Foradil Certihaler (formoterol). On 03 Jan 2006, before inhalation, the inhaler's dose-meter showed that there were still 33 puffs available. (continue)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name)
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Do (continue)

15. DAILY DOSE(S)
#1 Unknown

16. ROUTE(S) OF ADMINISTRATION
#1 Inhalation

17. INDICATION(S) FOR USE
#1 Asthma

18. THERAPY DATES(from/to)
#1 03-JAN-2006 00:00 / 03-JAN-2006 00:00

19. THERAPY DURATION
#1 1 day

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)
From/To Dates | Type of History / Notes | Description
Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Novartis Pharma AG
Clinical Safety and Epidemiology
Postfach CH-4002
Basel, Switzerland

26. REMARKS

24b. MFR CONTROL NO.
PHNU2006DE00463

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
11-JAN-2006

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☒ OTHER: Spontaneous Report

DATE OF THIS REPORT
27-JAN-2006

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: PHNU2006DE00463

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

During inhalation, a large and visible amount of white powder was set free. The patient suspected that the complete content of powder was released from the inhaler. The dose-meter showed 32 remaining doses after the inhalation. In the further course, the patient showed a heart rate at rest of 145/min and a blood pressure of 150/110 mmHg, as well as dizziness and headache. This condition lasted for about one day, the patient was in physician surveillance for a few hours. The outcome was reported as recovered. The consumer has planned to send the inhaler to local Quality Assurance.

Follow-up information received from the consumer on 11 Jan 2006. Batch-no. was K082, expiry date Oct 2006. The consumer planned to involve a lawyer and sue Novartis. Local Quality Assurance has assigned GCRS-no. DENU20060112172118 to this case.

Novartis Comment: Serious spontaneous report [medically significant], heart rate increased and overdose suspected assessed as listed and blood pressure increased assessed as unlisted according to the Basic Prescribing Information.
The information provided in this individual case does not warrant a change to the Basic Prescribing Information text. The topic will be monitored closely.
All spontaneous reports are considered suspected for reporting purposes.

13. Relevant Tests

(03 Jan 2006) Heart rate: at rest 145/min

(03 Jan 2006) Blood pressure: 150/110 mmHg

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Dose Inh {Lot # K082; Exp.Dt. OCT-2006}; Regimen #1	Unknown; Inhalation	Asthma	03-JAN-2006 00:00 / 03-JAN-2006 00:00; 1 day

APPEARS THIS WAY
ON ORIGINAL

Appendix 3

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
—	Germany		Unk		Unk	Female	Unk		Unk		

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Nausea [Nausea]
Feeling unwell [Malaise]
State of anxiety [Anxiety]
Palpitations [Palpitations]
Released of increased dosage when inhaling [Overdose]

Case Description: This report combines pharmacist information received on 10 Jan 2006 and a phone call with the patient on 12 Jan 2006. The pharmacist had sent 2 devices of Foradil Certihaler (formoterol) for quality testing, batch-no. K082, expiry date Oct 2006. (continue)

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name)
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Do (continue)

20. DID REACTION ABATE AFTER STOPPING DRUG?
☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1 3-4-fold dose at once

16. ROUTE(S) OF ADMINISTRATION
#1 Inhalation

17. INDICATION(S) FOR USE
#1 Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

18. THERAPY DATES(from/to)
#1 Unknown

19. THERAPY DURATION
#1 Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)
From/To Dates | Type of History / Notes | Description
Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Novartis Pharma AG
Clinical Safety and Epidemiology
Postfach CH-4002
Basel, Switzerland

26. REMARKS

24b. MFR CONTROL NO.
PHNU2006DE00499

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
17-JAN-2006

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☒ OTHER: Spontaneous Report

DATE OF THIS REPORT
27-JAN-2006

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Reason for complaint was release of increased dosage when inhaling. The patient stated that at a position of the dose meter of 20 remaining doses, she tried to inhale and initially there was no substance coming out of the device. She tried further and then inhaled a large amount of powder. The patient estimated that it was a 3 to 4 fold amount. The dose meter position remained at 20 after this inhalation. A few minutes after the inhalation, she felt unwell, including a state of anxiety, palpitations and nausea. This condition lasted for about 1.5 hours. The outcome was reported as recovered. Quality Assurance assigned the number local number 16500 and the GCRS-no. DENU20060111114234 to this case.

This follow-up report was received from Quality Assurance on 17 Jan 2006 and on 20 Jan 2006. Both devices sent from the pharmacy were examined. Both showed misaligned dosing bar and were blocked (jammed). No reset occurred during opening and closing of the devices, they were irreversibly jammed, no powder was dispensed (dosing cavity stayed forward). No further findings (especially no powder in the device or marks/damages to any parts) were observed. In addition to the â€œstandardâ€• determination procedure above, the residual powder weight in the reservoirs was determined. For the device suspected of overdose (dose counter at 20), a powder weight of 39 mg was found in the reservoir, which is about 180 mg less than expected. For the other device (dose counter at 55), a residual powder weight of 488 mg was found, which is within expectations (minimum expected for dose counter 55 is 451 mg). No explanation for the powder loss from complaint device with dose counter at 20 could be found, no residual powder was observed either in the device or in the mouthpiece. No reason was found, why the misaligned device with dose counter at 55 showed no powder loss whereas the one with dose counter at 20 did after both devices being used and misaligned by the same patient. A potential explanation could be that powder loss may be caused by direct mechanical interference of the patient with the dosing mechanism after a device jammed due to misalignment and the patient tried to reset the device and interfered with the dosing bar. However, there was nothing found on the dry powder inhaler to support this. It was further noted that after an endoscopic examination of the interior of the device, a distortion damage was found due to misuse. The damage to the device can result in powder leakage, and could be reproduced by forcibly removing the cap. However, this requires considerable force which the patient would certainly be aware of, and such handling is contrary to the specific instructions given in the leaflet.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Dose Inh {Lot # K082; Exp.Dt. OCT-2006}; Regimen #1	3-4-fold dose at once; Inhalation	Unknown	Unknown; Unknown

APPEARS THIS WAY
ON ORIGINAL

Appendix 4

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH (Day / Month / Year)	2a. AGE	3. SEX	3a. WEIGHT	4-5 REACTION ONSET (Day / Month / Year)	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
—	Germany	—	40 Years	Male	85.00 kg	10 / JAN / 2006	

b(6)

7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Hypertension [Hypertension]
Tachycardia [Tachycardia]
Tremor, also at rest [Tremor]
Sleeplessness [Insomnia] ([Restlessness])
Overdose [Overdose]

Case Description: This report combines information received from a physician and the patient himself, who is — on 11 Jan 2006. (continue)

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name)
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Dose Inh

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1 10 ug, BID

16. ROUTE(S) OF ADMINISTRATION
#1 Inhalation

17. INDICATION(S) FOR USE
#1 Asthma

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☒ NO ☐ NA

18. THERAPY DATES(from/to)
#1 09-JAN-2006 00:00 / 10-JAN-2006 00:00

19. THERAPY DURATION
#1 2 days 0 hrs

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)
From/To Dates | Type of History / Notes | Description
Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Novartis Pharma AG
Clinical Safety and Epidemiology
Postfach CH-4002
Basel, Switzerland

25. REMARKS

24b. MFR CONTROL NO.
PHNU2006DE00503

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
17-JAN-2006

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☒ OTHER: Spontaneous Report

DATE OF THIS REPORT
27-JAN-2006

28a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: PHNU2006DE00503

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The patient had been treated with Foradil Certihaler (formoterol) since 09 Jan 2006, he had used a physician sample of the drug containing 15 single doses. The first 2 applications were normal without any problems. In the evening of 10 Jan 2006, when he inhaled from the Foradil Certihaler, a large amount of dry powder was set free, this "felt like sand" in his mouth. He also inhaled a large portion of the powder. The dose-meter of the device switched regularly from 13 to 12 remaining puffs. After this suspected overdose, he experienced a tachycardia of about 150/min which lasted for about 2 hours. He also showed sleeplessness and restlessness in the following night. His condition had improved at the time of reporting. Causality was reported as suspected. Batch-no. was K001A, expiry date Oct 2006. The case has been forwarded to local Quality Assurance.

This follow-up report combines information received from Quality Assurance on 17 Jan 2006 and a written physician follow-up received on 20 Jan 2006. Quality Assurance assigned the following QA numbers to this case: GCRS number DENU20060112174653 and local number 16542. It was noted that the dose counter showed CD 12. This device was a sample pack that had a dose counter start position of CD 15. The device was visibly inspected and showed no signs of external damage. It was noted that there was powder visible on the outside of the device. The mouthpiece, upon removal, also showed signs of powder within the flow path. The dosing bar and sliding shelter were in proper alignment. The "standard" procedure was used to determine the residual powder weight in the reservoir. The device reservoir was removed and the powder contents weighed. The remaining powder was approximately 27 mg. A calculation was used to determine the theoretical powder loss which was approximately 450 mg. In a further note, QA confirmed that in the interior of the device, there was a distortion damage due to misuse; this damage can result in powder leakage and could be reproduced by forcibly removing the cap. However this required considerable force and was contrary to the instructions given in the leaflet. The physician confirmed that the patient had used Foradil Certihaler from 09 to 10 Jan 2006, at a planned dosage of 10 µg twice daily. On 10 Jan 2006 at about 9.30 pm he had experienced the previously reported overdosing, this resulted in a very high tachycardia and a very high hypertension of more than 200 mmHg. These conditions lasted until the next day. He also showed a tremor, also at rest, this lasted until the next day at about 4 pm. The outcome was reported as recovered. Rechallenge with Foradil P (formoterol) did not show any further problems. Causality was assessed as definite.

Novartis Comment: Serious spontaneous report [medically significant], all events assessed as listed except hypertension according to the Basic Prescribing Information.
However other alternative causes [context of an overdose after a device misuse] provide a possible explanation for the unlisted reported adverse event.
All spontaneous reports are considered suspected for reporting purposes.

13. Relevant Tests

(10 Jan 2006, sometime after 9:30 p.m.) Heart rate: about 150/min for 2 hours

(10 Jan 2006, sometime after 9:30 p.m.) Blood pressure: over 200 mmHg

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (Include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Dose Inh; Regimen #1	10 ug, BID; Inhalation	Asthma	09-JAN-2006 00:00 / 10-JAN-2006 00:00; 2 days 0 hrs
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Dose Inh (Lot # K001A; Exp.Dt. OCT-2006); Regimen #2	Large amount in 1 dose; Inhalation		10-JAN-2006 21:30 / 10-JAN-2006 21:31; 1 min

Appendix 5

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
—	Germany			1939	Unk	Male	Unk	22	JAN	2006	

b(6)

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Restlessness [Restlessness]
Chills [Chills]
Red head [Erythema] ([Feeling hot])
Powder in his mouth and on his hand [Incorrect route of drug administration]
Heart rate increased to 180/min [Heart rate increased]
Irregular pulse [Heart rate irregular]
Shaking [Tremor]
Was about 4 times the normal dosage [Overdose]
(continue)

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name)
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Do (continue)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1 about 4x normal amount

16. ROUTE(S) OF ADMINISTRATION
#1 Inhalation

17. INDICATION(S) FOR USE
#1 Emphysema

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES(from/to)
#1 22-JAN-2006 00:00 / 22-JAN-2006 00:00

19. THERAPY DURATION
#1 1 day

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY, (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	Myocardial infarction

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Novartis Pharma AG
Clinical Safety and Epidemiology
Postfach CH-4002
Basel, Switzerland

26. REMARKS

24b. MFR CONTROL NO.
PHNU2006DE00679

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
27-JAN-2006

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☒ OTHER: Spontaneous Report

DATE OF THIS REPORT
31-JAN-2006

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Description: This is a preliminary consumer report received on 27 Jan 2006. This patient has previously been treated with Foradil P (formoterol dry powder in capsules with aerolizer). He was switched to Foradil Certihaler (formoterol multiple dose dry powder inhaler) about 2 months ago. Following the switch he had used 3 devices of Foradil Certihaler without any problems. In the evening hours of 22 Jan 2006, with the 4th device, at a dose counter position of 43, he opened the device routinely and inhaled. The dose counter position changed to 42. After this inhalation he recognized there was more powder in his mouth and also on his hand. He estimated that the amount inhaled was about 4 times the normal dosage. About 5 to 10 minutes after the inhalation, he started to suffer from shaking of hands and legs, as well as a restlessness and chills. He also experienced a redness of the head and a heat sensation. His heart rate increased to about 180/min, this was measured several times, there was also an irregular pulse. These conditions lasted until late night of the same day; he also contacted his physician that night. The shaking still persisted until 25 Jan 2006. The outcome was reported as recovered. Asked about the handling of the device, the patient stated that he was sure he always handled it correctly and opened the cap of the Certihaler completely before inhaling. Batch number was K082.

Novartis Comment: Serious spontaneous report [medically significant], heart rate increased, heart rate irregular, tremor amd overdose assessed as listed and restlessnes, chills, erythema and incorrect route of administration assessed as unlisted according to the Basic Prescribing Information due to greater specificity/severity.

The following term "An overdose of Foradil is likely to lead to effects that are typical of beta2-adrenergic stimulants: nausea, vomiting, headache, tremor, drowsiness, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia" is already included in the Overdose section of the Basic Prescribing Information.
All spontaneous reports are considered 'suspected' for reporting purposes.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1 FORADIL (FORMOTEROL FUMARATE) Dry Powder Multiple Dose Inh {Lot # K082}; Regimen #1	about 4x normal amount; Inhalation	Emphysema	22-JAN-2006 00:00 / 22-JAN-2006 00:00; 1 day

APPEARS THIS WAY
ON ORIGINAL

Appendix 6-2

TRANSLATED FROM THE ORIGINAL GERMAN (REK/1.2006)

NOVARTIS

Dr Thomas Kerscher
Head, Asthma Business Franchise

Novartis Pharma GmbH
Post Office Box
90327 Nuremberg
Tel. 0911/273-0
Fax: 0911/273-12653
www.novartispharma.de

Important announcement concerning a medicinal product

23.01.2006

Foradil® Certihaler™, recall of all batches

Dear Sir / Madam,

Following consultations with the appropriate authorities, and consistent with our responsibility for patient safety, we would like to inform you of the recall of all batches of **Foradil® Certihaler™** (applicable to batches K001, K001A, K082, K082-1, K082-2, L019, L061, L759, L759A, L759A-1).

Due to a potential lack of sufficient clarity in the instructions for use in the package leaflet, there may be rare situations in which the device is used incorrectly. In isolated cases, this may cause malfunctioning of the device and overdosage. In the interest of patient safety, we have therefore decided to take the proactive precaution of recalling all currently available batches of **Foradil® Certihaler™** from the market.

We would like to expressly point out that there are no quality-related risks associated with the active substance, formoterol. The recall applies only to currently marketed batches of the **Foradil® Certihaler™** dosage form.

At present we are planning to replace the package leaflet – in order to clearly explain correct use – before the product becomes available again. In the meantime, we recommend that you switch patients of yours who are currently being treated with **Foradil® Certihaler™** to Foradil® P or CFC-free Foradil® spray, dosage forms that remain available. The latter two dosage forms are not affected by this precautionary measure.

Please return to us your supplies of sample packs of **Foradil® Certihaler™**. Please send these packs – no postage required – to the following address:

PharmLog Pharma Logistik GmbH
c/o Novartis Pharma GmbH
Siemensstr. 1
59199 Bönen

Effective immediately, batches of **Foradil® Certihaler™** that have been available to date may no longer be released to patients.

If you have further questions, please call us at 01802/3672345 (6 cents per minute for calls from the German fixed-line network).

Yours faithfully,
Novartis Pharma GmbH

(*signed*)

Dr Dieter Götte
Medical Director

(*signed*)

Dr Thomas Kerscher
Head, Asthma Business Franchise

APPEARS THIS WAY
ON ORIGINAL

Appendix 7-1

NOVARTIS

Gebrauchsinformation

Lesen Sie die gesamte Gebrauchsinformation sorgfältig durch, bevor Sie mit der Anwendung dieses Arzneimittels beginnen.
- **Heben Sie die Packungsbeilage auf. Vielleicht möchten Sie diese später nochmals lesen.**
- **Wenn Sie weitere Fragen haben, wenden Sie sich bitte an Ihren Arzt oder Apotheker.**
- **Dieses Arzneimittel wurde Ihnen persönlich verschrieben und darf nicht an Dritte weiter gegeben werden. Es kann anderen Menschen schaden, auch wenn diese dasselbe Krankheitsbild haben wie Sie.**

Diese Packungsbeilage beinhaltet:

Foradil® Certihaler™

457675/1 DE

Foradil® Certihaler™

Wirkstoff: Formoterolfumarat $2H_2O$

Der arzneilich wirksame Bestandteil ist:
Formoterolfumarat $2H_2O$
1 Einzeldosis enthält:
10 µg Formoterolfumarat $2H_2O$, entsprechend 8,2 µg Formoterol (dies entspricht einer über das Mundstück abgegebenen Menge von 8,5 µg Formoterolfumarat $2H_2O$).

Die sonstigen Bestandteile sind:
Lactose-Monohydrat (Ph.Eur.) (enthält geringe Mengen an Milchprotein), Magnesiumstearat (Ph.Eur.)

Foradil Certihaler enthält Pulver zur Inhalation für 60 Anwendungen und ist als Einzel- (60 Inhalationen) (N1) und Dreifachpackung (180 Inhalationen) (N3) erhältlich.

Novartis Pharma Arzneimittel GmbH
90327 Nürnberg
Telefon: (09 11) 273-0
Telefax: (09 11) 273-12 653

Novartis Pharma Distributions GmbH
90327 Nürnberg
Telefon: (09 11) 273-0
Telefax: (09 11) 273-12 653

1. Was ist Foradil Certihaler und wofür wird er angewendet?

Der Wirkstoff in Foradil Certihaler erweitert die Bronchien und erleichtert dadurch das Atmen.

Foradil Certihaler ist von:
Novartis Pharma GmbH
90327 Nürnberg
Telefon: (09 11) 273-0
Telefax: (09 11) 273-12 653
Internet/E-Mail:
www.novartispharma.de

Mitvertriebe:
Novartis Pharma Vertriebs GmbH
90327 Nürnberg
Telefon: (09 11) 273-0
Telefax: (09 11) 273-12 653

Novartis Pharma Marketing GmbH
90327 Nürnberg
Telefon: (09 11) 273-0
Telefax: (09 11) 273-12 653

Foradil Certihaler wird angewendet:
- Zur Langzeitbehandlung des mittelschweren bis schweren Asthma bronchiale bei Patienten, die eine regelmäßige bronchalerweiternde Therapie benötigen in Verbindung mit einer entzündungshemmenden Dauertherapie.
  Die Behandlung mit Glukokortikoiden ist regelmäßig weiterzuführen.
- Zur Vorbeugung und Behandlung der vorübergehenden oder dauerhaften Verengung der Atemwege (Bronchokonstriktion) bei Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD).

2. Was müssen Sie vor der Anwendung von Foradil Certihaler beachten?

2.1 Foradil Certihaler darf nicht angewendet werden:
- wenn Sie überempfindlich (allergisch) gegenüber Formoterolfumarat $2H_2O$, Milchprotein oder einem sonstigen Bestandteil von Foradil Certihaler oder anderen β Rezeptor-antagonistischen Wirkstoffen sind;
- wenn Sie an einer Herzerkrankung leiden, die mit einer Herzrhythmusstörung (Beschleunigung des Herzschlages, schwerwiegende Störung der Erregungsleitung des Herzens), Herzklappenfehlern (idiopathische-subvalvuläre Aortenstenose), Herzmuskelverdickung (hypertrophe obstruktive Kardiomyopathie) oder bestimmten EKG-Veränderungen (verlängertes QT-Intervall, $QT_c > 0,44$ sec.) einhergeht;
- wenn Sie an einer schweren Überfunktion der Schilddrüse (Thyreotoxikose) leiden.

2.2 Besondere Vorsicht ist bei der Anwendung von Foradil Certihaler erforderlich:
- wenn Sie an einer schweren Herzerkrankung leiden, insbesondere bei einem frischen Herzinfarkt, koronarer Herzkrankheit, schwerer Herzmuskelschwäche (Herzinsuffizienz);
- wenn Sie an einer Erkrankung mit Einengung der Blutgefäße (okklusive Gefäßerkrankungen), insbesondere Arteriosklerose, Bluthochdruck (Hypertonie) oder einer krankhaften Ausweitung der Gefäßwand (Aneurysmen) leiden;
- wenn Sie an einer Überfunktion der Schilddrüse (Hyperthyreose) leiden;
- wenn Sie an einer schwer kontrollierbaren Zuckerkrankheit (Diabetes mellitus) leiden;
- wenn Sie an einer bestimmten Erkrankung des Nebennierenmarks (Phäochromozytom) leiden.

Dies gilt auch, wenn diese Angaben bei Ihnen früher einmal zutrafen.

Welche Vorsichtsmaßnahmen müssen beachtet werden?
- Wenn Sie eine Vollnarkose unter Verwendung von halogenierten Anästhetika erhalten sollen, sollten Sie Foradil Certihaler innerhalb von mindestens 12 Stunden vor Narkosebeginn nicht mehr anwenden. Sprechen Sie deshalb unbedingt mit Ihrem Arzt darüber.
- Bei der Inhalation von Foradil Certihaler in hohen Dosen kann der Blutzucker-Spiegel ansteigen. Als Diabetiker sollten Sie deshalb engmaschige Blutzucker-Kontrollen durchführen.
- Wenn Sie gleichzeitig mit Glukokortikoiden (Mittel gegen Entzündungen oder Allergien), Theophyllin (Mittel gegen Asthma), harntreibenden Arzneimitteln (Diuretika) und/oder mit Digitalis-haltigen Präparaten (Mittel gegen Herzschwäche) behandelt werden oder Sie einen anderen Risikofaktor für einen niedrigen Kaliumspiegel im Blut haben (siehe Abschnitt 4. „Welche Nebenwirkungen sind möglich?"), wird Ihr Arzt regelmäßige Kaliumspiegel-Kontrollen im Blut vornehmen.
- Wenn Sie unter beschleunigtem und/oder unregelmäßigem Herzschlag leiden, dürfen Sie Foradil Certihaler nur unter besonderen Vorsichtsmaßnahmen (z. B. Überwachung) anwenden.

Spezielle Therapiehinweise
- Die Behandlung von Bronchialasthma sollte dem Schweregrad entsprechend stufenweise erfolgen. Lassen Sie den Erfolg der Therapie durch regelmäßige ärztliche Untersuchungen überprüfen. Erhöhen Sie nicht ohne ärztlichen Rat den Gebrauch von Foradil Certihaler. Es könnte für Sie gefährlich werden! Sprechen Sie mit Ihrem Arzt darüber, wenn Foradil Certihaler nicht mehr ausreichend wirkt.
- Wenn Sie immer mehr Foradil Certihaler brauchen, kann das ein Anzeichen für eine Verschlechterung Ihrer Erkrankung sein. Ihr Arzt wird dann neu über Ihre Behandlung entscheiden.
- Es ist wichtig, dass Sie Ihre Atemfunktion nach ärztlicher Anleitung täglich selbst kontrollieren. Sie können zum Beispiel den mit dem Peak-flow-Meter täglich gemessenen Atemstoß aufschreiben. Das ist wichtig, damit Ihr Arzt den Verlauf der Krankheit und den Therapieerfolg kontrollieren kann.

Warnhinweise
- Kommt es trotz der verordneten Behandlung zu keiner befriedigenden Besserung oder gar zu einer Verschlechterung Ihres Leidens, informieren Sie bitte Ihren Arzt. Er wird dann neu über Ihre Behandlung entscheiden. Möglicherweise wird er Ihnen weitere oder andere Medikamente oder auch mehr von den Medikamenten verschreiben, die Sie bisher bereits erhalten.
- Verwenden Sie Foradil Certihaler nicht öfter als Ihnen dies Ihr Arzt empfohlen hat. Eine erhebliche Überschreitung, insbesondere der vorgegebenen Einzeldosen, aber auch der Tagesdosis kann wegen der Wirkungen auf das Herz (Herzrhythmusstörungen, Blutdruckanstieg) in Verbindung mit Veränderungen der Salzkonzentrationen in Körperflüssigkeiten (Elektrolytverschiebungen) gefährlich sein.
- Bei akuter oder sich rasch verschlimmernder Atemnot nach der Inhalation (paradoxe Bronchospastik) muss die Behandlung sofort abgesetzt und unverzüglich ärztliche Hilfe in Anspruch genommen werden. Ihr Arzt wird dann neu über Ihre Behandlung entscheiden.

Behandlung von Kindern
Foradil Certihaler ist für die Behandlung von Kindern ab 5 Jahren geeignet.
Bis zum Vorliegen ausreichender Erfahrungen soll Foradil Certihaler bei Kindern unter 5 Jahren nicht angewendet werden.

Behandlung von älteren Menschen
Ältere Patienten brauchen im Allgemeinen keine andere Dosis; beachten Sie aber, dass im höheren Lebensalter häufiger weitere Erkrankungen auftreten und Sie zusätzliche Medikamente erhalten (siehe Abschnitt 2. „Was müssen Sie vor der Anwendung von Foradil Certihaler beachten?", Abschnitt 2.3. „Wechselwirkungen mit anderen Mitteln" und Abschnitt 4. „Welche Nebenwirkungen sind möglich?").

Schwangerschaft und Stillzeit
Wenn Sie schwanger sind, sprechen Sie unbedingt mit Ihrem Arzt darüber. Vor allem in den ersten drei Monaten der Schwangerschaft und kurz vor der Entbindung darf Foradil Certihaler nur bei sorgfältiger Ab-

wägung des Nutzen-Risiko-Verhältnisses nach Rücksprache mit dem behandelnden Arzt verwendet werden.
Da nicht bekannt ist, ob der Wirkstoff beim Menschen in die Muttermilch übertritt, sollten Sie vorsichtsf alber nicht stillen.

Verkehrstüchtigkeit und das Bedienen von Maschinen
Foradil Certihaler kann auch bei bestimmungsgemäßem Gebrauch das Reaktionsvermögen so we t verändern, dass die Fähigkeit zur aktiven Teilnahme am Straßenverkehr oder zum Bedienen von Maschinen beeintrachtigt wird. Dies gilt in verstärktem Maße im Zusammenwirken mit Alkohol.

2.3 Wechselwirkungen mit anderen Arzneimitteln

Bitte informieren Sie Ihren Arzt oder Apotheker, wenn Sie andere Arzneimittel einnehmen oder anwenden bzw. vor kurzem eingenommen oder angewendet haben, auch wenn es sich um nicht verschreibungspflichtige Arzneimittel handelt.

- Bei gleichzeitiger Therapie mit einigen Mitteln gegen Herzrhythmusstörungen (Chinidin, Disopyramid, Procainamid), Herzschwäche (Digitalis-haltige Präparate), Malaria (Chinidin), Allergien (Phenothiazine, Antihistaminika), bestimmte geistig-seelische Erkrankungen (Phenothiazine) oder Depressionen (trizyklische Antidepressiva) können Nebenwirkungen in Form von Herzrhythmusstörungen und/ oder spezifischen EKG-Veränderungen (QT-Zeit-Verlängerung) auftreten.
- Die gleichzeitige Einnahme von anderen Mitteln gegen Herzrhythmusstörungen oder Asthma (β-Sympathomimetika, Katecholaminen, Anticholinergika und Kortikoiden) kann die Wirkung von Foradil Certihaler verstärken.
- Die gleichzeitige Gabe von Foradil Certihaler und Theophyllin (Mittel gegen Asthma) kann zu einer wechselseitigen Wirkungsverstärkung und zu einem erhöhten Risiko für Nebenwirkungen an Herz und Kreislauf (kardiovaskuläre Nebenwirkungen) führen.
- Auch Schilddrüsenhormone, wehenfördernde Mittel, bestimmte Mittel gegen Parkinson-Erkrankung (L-Dopa) oder Alkohol können die Herz-Kreislauf-Regulation im Zusammenwirken mit Foradil Certihaler beeinflussen.
- Die gleichzeitige Anwendung von Foradil Certihaler und bestimmten Mitteln gegen Depressionen (Monoaminoxidase-Hemmstoffe oder trizyklische Antidepressiva) soll vermieden werden.
- Die gleichzeitige Verabreichung von harntreibenden Arzneimitteln, Nebennierenrindenhormonen, Abführmitteln (Laxanzien) oder Mitteln gegen Asthma (Xanthin-Derivate, z. B. Theophyllin) kann die Kaliumsenkende Wirkung von Foradil Certihaler verstärken.
- Bei einer Vollnarkose mit bestimmten Narkosemitteln (halogenierte Anästhetika, wie z. B. Halothan, Methoxyfluran oder Enfluran) müssen Sie bei gleichzeitiger Behandlung mit Foradil Certihaler mit einem erhöhten Risiko für schwere Herzrhythmusstörungen und Blutdrucksenkung rechnen.
- β-Rezeptoren-Blocker (Mittel gegen Bluthochdruck, Herzkrankheiten, Schilddrüsenüberfunktion, Migräne oder erhöhten Augeninnendruck) können die Wirkung von Foradil Certihaler abschwächen oder hemmen. Allgemein wirkende (nicht selektive) β-Rezeptoren-Blocker (einschließlich Augentropfen) sollten Sie bei Asthma nicht anwenden. Insbesondere letztere, aber auch besonders am Herzen wirkende (kardioselektive) β-Rezeptoren-Blocker, können einen Asthmaanfall auslösen.

Beachten Sie bitte, dass diese Angaben auch für vor kurzem angewandte Arzneimittel gelten können.

2.4 Anwendung von Foradil Certihaler zusammen mit Nahrungsmitteln und Getränken

Trinken Sie nicht regelmäßig Alkohol während der Behandlung mit Foradil Certihaler. Ansonsten kann ein Teil der Nebenwirkungen verstärkt auftreten, insbesondere Nebenwirkungen, die das Nervensystem betreffen (z. B. Schwindel), so dass die Fähigkeit zur aktiven Teilnahme am Straßenverkehr oder zum Bedienen von Maschinen beeinträchtigt wird.

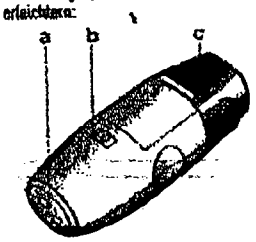
3. Wie ist Foradil Certihaler anzuwenden?

Wenden Sie Foradil Certihaler immer genau nach Anweisung des Arztes an. Bitte fragen Sie bei Ihrem Arzt oder Apotheker nach, wenn Sie sich nicht ganz sicher sind.

3.1 Art der Anwendung

Die korrekte Handhabung von Foradil Certihaler ist für den Therapieerfolg von entscheidender Bedeutung. Die Anwendung bei Kindern darf nur unter Aufsicht von Erwachsenen erfolgen.

Zum Gebrauch Ihres Foradil Certihalers
Ihr Foradil Certihaler hat drei spezielle Vorrichtungen, die den korrekten Gebrauch erleichtern:



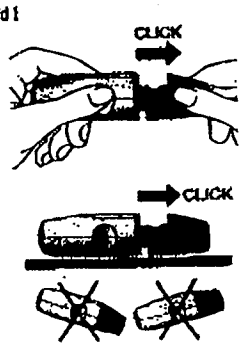
a. Ring aus Luftlöchern: Öffnet sich mit einem Klick, wenn Sie richtig inhalieren.
b. Inhalationszähler: Gibt Ihnen die Anzahl der verbleibenden Inhalationen an. Die Anzeige wird erst verändert, nachdem Sie die Schutzkappe nach einer korrekten Inhalation wieder vollständig geschlossen haben.
c. Schutzkappe: Diese umschließt das Mundstück und kann nur geöffnet werden, wenn Sie Ihren Foradil Certihaler waagerecht halten und der Inhalationszähler nach oben zeigt. Die nachfolgende Anleitung erklärt das Öffnen und Schließen Ihres Foradil Certihalers.

Das klappernde Geräusch beim Bewegen des Certihalers ist normal.

Wichtig: Bitte machen Sie sich mit dem Öffnen und Schließen der Schutzkappe vertraut, bevor Sie beginnen zu inhalieren. Dies hat keinerlei Einfluss auf den Foradil Certihaler und vergeudet keinen Wirkstoff.

Öffnen Ihres Foradil Certihalers

Bild 1

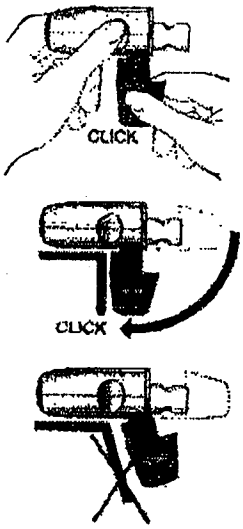


Der Foradil Certihaler wird auf eine besondere Weise geöffnet. Während des Öffnens

müssen Sie Ihren Foradil Certihaler waagerecht halten und der Inhalationszähler muss nach oben zeigen. Zum Öffnen ziehen Sie die Schutzkappe gerade bis zum Anschlag heraus (siehe Bild 1).

Achtung: Falls sich der Foradil Certihaler nicht öffnen lässt, müssen Sie die Kappe vor dem nächsten Versuch erst vollständig schließen. Das Öffnen wird erleichtert, wenn Sie Ihren Foradil Certihaler dabei auf eine flache Oberfläche wie einen Tisch legen.

Bild 2



Als Nächstes drehen Sie die Schutzkappe bis zum Anschlag nach unten wie in Bild 2 dargestellt. Sie müssen dabei einen geringen Widerstand überwinden bis sich die Schutzkappe im rechten Winkel (90 °) zum Gerät befindet. Das Einrasten in der korrekten, vollständig geöffneten Position können Sie spüren.

Schließen Ihres Foradil Certihalers

Zum Schließen Ihres Foradil Certihalers drehen Sie die Schutzkappe nach oben in die waagerechte Position und schieben sie vollständig zurück, so dass sie das Mundstück wieder umschließt.

Wie Sie mit Ihrem Foradil Certihaler eine Inhalation durchführen

1. Schritt: Öffnen der Schutzkappe

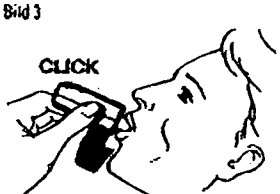
Wichtig: Lesen Sie immer die Nummer des Inhalationszählers, bevor Sie die Schutzkappe öffnen.

Öffnen Sie anschließend den Foradil Certihaler, wie im vorangehenden Abschnitt dargestellt.

2. Schritt: Inhalieren

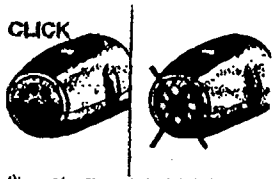
Wichtig: Vergewissern Sie sich, dass sich die Schutzkappe in der korrekten Position befindet, wie in Bild 2 dargestellt.

Bild 3



- Atmen Sie so weit wie möglich aus (aber nicht durch Ihren Foradil Certihaler).
- Nehmen Sie dann das Mundstück in den Mund und schließen Sie die Lippen im Bereich der Vertiefung fest um das Mundstück.
- Halten Sie dabei Ihren Foradil Certihaler an den Griffmulden so, dass der Ring aus Luftlöchern am hinteren Ende nicht verdeckt wird, wie in Bild 3 dargestellt.
- Beugen Sie Ihren Kopf leicht zurück und atmen Sie einmal schnell und tief durch das Mundstück ein. Sie sollten beim Einatmen einen Klick hören, der durch das Öffnen der Lufttöcher entsteht. Dies zeigt Ihnen an, dass Sie schnell und tief genug eingeatmet haben um das Medikament freizugeben.
- Setzen Sie dann den Certihaler ab, halten Sie den Atem möglichst für 5 Sekunden an (ansonsten so lange wie möglich) und atmen Sie anschließend langsam wieder aus (nicht durch Ihren Foradil Certihaler).

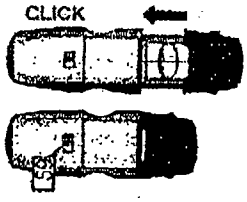
Bild 4a Bild 4b



- Überprüfen Sie nach der Inhalation, ob die Lufttöcher am hinteren Ende des Certihalers geöffnet wurden, wie in Bild 4a dargestellt.
Sind die Lufttöcher jedoch noch geschlossen (wie in Bild 4b), haben Sie kein Medikament erhalten. In diesem Fall müssen Sie die Schutzkappe Ihres Certihalers schließen und mit Schritt 1 wieder beginnen.

3. Schritt: Schließen der Schutzkappe

Bild 5



Nach einer erfolgreichen Inhalation (Lufttöcher waren geöffnet) schließen Sie die Schutzkappe und beobachten, ob sich dabei die Anzeige des Inhalationszählers erwartungsgemäß um eine Einheit verringert (siehe Bild 5).

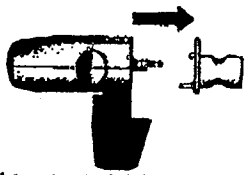
Falls sich die Anzeige nicht um eine Einheit verringert, obwohl die Lufttöcher geöffnet waren, verwenden Sie den Inhaler nicht weiter und wenden Sie sich an Ihren Apotheker.

Falls Ihre Dosis mehr als eine Inhalation beträgt

Falls Ihre Dosis mehr als eine Inhalation beträgt, müssen Sie die Schutzkappe zwischen den Inhalationen jeweils vollständig schließen.

Pflege Ihres Foradil Certihalers

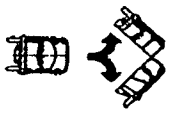
Bild 6a



Reinigen des Mundstücks

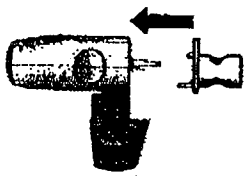
Das Mundstück Ihres Foradil Certihalers sollte einmal pro Woche nach folgender Anleitung gereinigt werden:
- Öffnen Sie die Schutzkappe.
- Ziehen Sie das weiße Mundstück ab wie in Bild 6a dargestellt.
- **Wichtig:** Bitte legen Sie Ihren Foradil Certihaler an einen sicheren und trockenen Ort, wenn das Mundstück entfernt ist; nicht saubern, anblasen oder berühren.

Bild 6b



- Klappen Sie das abgezogene Mundstück auseinander (siehe Bild 6b) und klopfen Sie es vorsichtig auf ein sauberes Tuch, um Pulverreste zu entfernen.
- **Wichtig: Benutzen Sie niemals Wasser** zum Reinigen des Mundstücks oder anderer Teile des Certihalers, da Feuchtigkeit dem Medikament schadet.

Bild 6c



- Nach dem Reinigen klappen Sie das Mundstück zusammen, stecken es wieder auf den Certihaler (siehe Bild 6c) und schließen die Schutzkappe vollständig.

Allgemeine Empfehlungen

Bringen Sie Ihren Foradil Certihaler nicht mit Feuchtigkeit in Berührung, daher:
- Halten Sie die Schutzkappe immer geschlossen, wenn Sie nicht inhalieren.
- Bewahren Sie Ihren Foradil Certihaler nicht an feuchten oder heißen Orten (Badezimmer, Auto) auf.
- Blasen oder atmen Sie nie direkt in Ihren Foradil Certihaler.

Versuchen Sie nie, Ihren Foradil Certihaler auseinander zu bauen oder anderweitig zu manipulieren (abgesehen von der Entfernung des Mundstücks zum Reinigen).

Wenn der Foradil Certihaler leer ist

Bild 7

Sie sollten Ihren Foradil Certihaler nicht mehr benutzen, wenn der Inhalationszähler 00 anzeigt.
In diesem Fall ist nur eine weitere Inhalation möglich, dann springt der Inhalationszähler auf 999 und die Schutzkappe kann nicht mehr geöffnet werden.

3.2 Falls vom Arzt nicht anders verordnet, ist die übliche Dosis:

Für Erwachsene, einschließlich älteren Patienten, sowie Kinder ab 5 Jahren gelten folgende Empfehlungen:

Chronisch-obstruktive Lungenerkrankung
Erwachsene:
Zur Dauertherapie in der Regel zweimal täglich (morgens und abends) 1 Inhalation.

Asthma bronchiale
Erwachsene:
In der Regel morgens und abends je 1 Inhalation.

Kinder ab 5 Jahren:
Morgens und abends je 1 Inhalation.

Eine höhere Dosierung lässt im Allgemeinen keinen zusätzlichen Nutzen erwarten, die Wahrscheinlichkeit des Auftretens auch schwerwiegender Nebenwirkungen kann aber erhöht sein.

Wichtige Hinweise:
Foradil Certihaler kann eine notwendige Basistherapie nicht ersetzen. Die Dauerbehandlung mit Foradil Certihaler sollte von einer entzündungshemmenden Dauertherapie mit Glukokortikoiden zur Inhalation und/oder oralen Glukokortikoiden begleitet werden. Eine zu Beginn der Behandlung mit Foradil Certihaler bereits bestehende Basistherapie mit Glukokortikoiden (oral oder inhalativ) müssen Sie in jedem Fall weiter fortsetzen.

Wie lange sollten Sie Foradil Certihaler anwenden?

Die Dauer der Behandlung richtet sich nach Art, Schwere und Verlauf der Erkrankung und wird von Ihrem Arzt für Sie persönlich festgelegt.
Asthma bronchiale ist eine chronische Erkrankung, die im Allgemeinen einer Dauerbehandlung bedarf.
Bitte lassen Sie den Erfolg der Therapie durch regelmäßige ärztliche Untersuchungen überprüfen.

3.3 Wenn Sie eine größere Menge Foradil Certihaler angewendet haben, als Sie sollten

Die Symptome bzw. Anzeichen einer Überdosierung entsprechen den Nebenwirkungen, die dann sehr schnell und gegebenenfalls in verstärktem Umfang auftreten.
Symptome bzw. Anzeichen einer Überdosierung sind:
Übelkeit, Erbrechen, Kopfschmerzen, Herzklopfen, unregelmäßiger und/oder beschleunigter Herzschlag, heftiges Zittern, insbesondere der Hände, Benommenheit, Ruhelosigkeit, Schlafstörungen und Brustschmerzen.

Treten diese Beschwerden auf, informieren Sie unverzüglich Ihren Arzt. Er wird entscheiden, was zu tun ist.

3.4 Wenn Sie die Anwendung von Foradil Certihaler vergessen haben

Nehmen Sie nicht die doppelte Dosis ein, wenn Sie die vorherige Einnahme vergessen haben.

Eine nachträgliche Anwendung ist nicht erforderlich, im Bedarfsfall aber möglich. Der zeitliche Abstand bis zur nächsten regulären Einnahme sollte mindestens 6 Stunden betragen.

3.5 Auswirkungen, wenn die Behandlung mit Foradil Certihaler abgebrochen wird

Informieren Sie auf jeden Fall Ihren behandelnden Arzt über die Unterbrechung oder Beendigung der Behandlung und nennen Sie ihm bitte die Gründe (z. B. Nebenwirkungen etc.).

4. Welche Nebenwirkungen sind möglich?

Wie alle Arzneimittel kann Foradil Certihaler Nebenwirkungen haben.

Für die Bewertung der Nebenwirkungen werden folgende Häufigkeitsangaben zu Grunde gelegt:

Sehr häufig:	Mehr als 1 von 10 Behandelten
Häufig:	Weniger als 1 von 10, aber mehr als 1 von 100 Behandelten
Gelegentlich:	Weniger als 1 von 100, aber mehr als 1 von 1000 Behandelten
Selten:	Weniger als 1 von 1000, aber mehr als 1 von 10 000 Behandelten
Sehr selten:	Weniger als 1 von 10 000 Behandelten, einschließlich Einzelfälle

4.1 Abhängig von der Dosierung und der individuellen Empfindlichkeit können folgende Nebenwirkungen auftreten:

Zentralnervensystem und Sinnesorgane

Häufig:	Zittern der Finger oder Hände (feinschlagiger Tremor), Kopfschmerzen, Übelkeit
Gelegentlich:	Schwitzen, Unruhe, Schwindel, Störungen des Geschmacksempfindens, Missempfindungen im Mund- und Rachenbereich

Vereinzelt ist über zentralnervös stimulierende (anregende) Wirkungen nach Inhalation von β_2-Sympathomimetika berichtet worden, die sich in Übererregbarkeit, Verhaltensstörungen mit krankhaft vermehrter Aktivität (hyperaktiven Verhaltensauffälligkeiten), Schlafstörungen sowie Sinnestäuschungen (Halluzinationen) äußerten. Diese Beobachtungen wurden überwiegend bei Kindern im Alter bis zu 12 Jahren gemacht.

Herz-Kreislauf-System

Häufig:	Herzklopfen (Palpitationen)
Gelegentlich:	Beschleunigter Herzschlag (Tachykardie), Herzrhythmusstörungen mit erhöhter Herzschlagfrequenz (Tachyarrhythmie)
Selten:	Herzrhythmusstörungen mit Extraschlägen des Herzmuskels (ventrikuläre Extrasystolen), anfallsweiser Brustschmerz infolge Verengung der Herzkranzgefäße (Angina pectoris), Beeinflussung des Blutdrucks (Senkung oder Steigerung)

Muskulatur

Häufig:	Muskelkrämpfe

Atemwege

Häufig:	Husten
Selten:	Akute und sich rasch verschlimmernde Atemnot nach der Inhalation (paradoxer Bronchospasmus)

Sonstiges

Gelegentlich:	Beeinflussung des Stoffwechsels (metabolische Veränderungen), wie Senkung des Blutkalium-Spiegels (Hypokaliämie), Erhöhung des Blutzucker-Spiegels (Hyperglykämie), Anstieg des Blutspiegels von Insulin, freien Fettsäuren, Glycerol und Ketonkörpern
Selten:	Überempfindlichkeitsreaktionen wie z. B. Juckreiz, Hautausschlag (Exanthem), starker Blutdruckabfall, Verminderung der Blutplättchen (Thrombopenie), Gewebeschwellung (Angioödem), Nesselsucht (Urtikaria) und Entzündung der Nieren (Nephritis)
Sehr selten:	Schwellungen der Gliedmaßen (periphere Ödeme)

Feinschlägiger Tremor, Übelkeit, Störungen des Geschmacksempfindens, Missempfindungen im Mund- und Rachenbereich, Schwitzen, Unruhe, Kopfschmerzen, Schwindel sowie Muskelkrämpfe können sich bei Fortführung der Behandlung im Verlauf von 1 bis 2 Wochen zurückbilden.

Laktose enthält geringe Mengen Milchprotein und kann deshalb allergische Reaktionen hervorrufen.

4.2 Welche Gegenmaßnahmen sind bei Nebenwirkungen zu ergreifen?

Informieren Sie Ihren Arzt über die bei Ihnen aufgetretenen Nebenwirkungen. Gegebenenfalls muss eine Dosisanpassung durch Ihren Arzt vorgenommen werden. Ändern Sie nicht ohne Rücksprache mit Ihrem Arzt die Dosierung.
Bei schwerwiegenden Nebenwirkungen ist Foradil Certihaler sofort abzusetzen und umgehend ein Arzt zu benachrichtigen.

Informieren Sie Ihren Arzt oder Apotheker, wenn Sie Nebenwirkungen bemerken, die nicht in dieser Packungsbeilage aufgeführt sind.

5. Wie ist Foradil Certihaler aufzubewahren?

Arzneimittel für Kinder unzugänglich aufbewahren.

Sie dürfen Foradil Certihaler nach dem auf der Faltschachtel und der inneren Verpackung angegebenen Verfallsdatum nicht mehr verwenden.

Für Foradil Certihaler sind keine besonderen Lagerungsbedingungen erforderlich.

Stand der Information
Mai 2005

Novartis Pharma GmbH, 90327 Nürnberg

417615/1 DE 4/2
01705

Appendix 7-2

9 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Office of Drug Safety

MEMO

To: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Products, HFD-570

Through: Alina Mahmud, R.Ph., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

From: Kimberly Pedersen, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

CC: Akilah Green
Project Manager, Division of Pulmonary and Allergy Products, HFD-570

Date: December 15, 2005

Re: ODS Consult 03-0011-4, Foradil Certihaler Patient Instructions for Use and Educational Campaign, NDA 21-592

This memorandum is in response to a December 7, 2005 request from your Division for a review of the Patients Instructions for Use and Educational materials for the drug product, Foradil Certihaler.

In the review of the Patients Instructions for Use and Educational materials, DMETS has attempted to focus on safety issues relating to possible medication errors and have identified the following areas of possible improvement, which might minimize potential user error.

A. General Comments

1. DMETS recommends the sponsor develop web-based instructions for use (as they have done for the Foradil Aerolizer). This will give the patient or provider another venue for details of proper Foradil Certihaler utilization.

2. DMETS remains concerned that patients will inadvertently occlude or partially occlude the rings of airholes for unit activation in order to hold the inhaler. DMETS suggests the sponsor develop a method to warn patients of the potential for a lack of effect due to the chosen method of holding the device (i.e. improved warnings in the pamphlets and product information referring to the necessity to not cover the airholes or the placing of a warning note/sticker on the device to draw attention to the airholes, "Do not cover"). Furthermore, the sponsor could suggest multiple methods of holding the device to alleviate the potential for covering the airholes in the back of the device during use (i.e. under #5 of the educational materials and patient instructions for use, TIP: you may achieve a better grip on the device without covering the airholes by holding the indentations on the dark blue cap or wrapping two/three fingers around the dark blue cap).

3. DMETS is unclear as to problems that may occur with delivery if the device is used in any position, other than level? As only the first step for inhaler describes holding the device level in order to open, will tilting or inverting the device affect medication drop-down or delivery after this? If so, please note in the appropriate steps for use.

4. Data from the clinical trials suggest patients had difficulty triggering a completed actuation and had subsequent counter issues. Per the sponsor's analysis, there were no technical problems; therefore suggesting human error. These problems may be prevented with more detailed explanations on device use. Also, device redesign may be needed if post-marketing data shows confusion.

B. Patient Instructions for Use

1.

b(

2.

3. General Recommendations

a.

b(4)

b.

c.

C. Educational Campaign

1. See Comment B3 a through c.

2. DMETS also recommends DSRCS and/or DDMAC be consulted on these materials.

D. Package Insert

1

b(4)

2.

In summary, DMETS recommends implementation of the label and labeling revisions outlined in this memo, which may lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

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

/s/

Kimberly Culley-Pedersen
1/31/2006 07:50:30 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
1/31/2006 08:22:16 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
1/31/2006 09:28:01 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/31/2006 10:09:53 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: January 30, 2006

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products

VIA: Akilah Green, Regulatory Project Manager
Division of Pulmonary and Allergy Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Medication Guide for Foradil Certihaler (fomoterol fumarate inhalation powder), NDA 21-592

Background and Summary

The sponsor submitted revised labeling (PI and PPI) on October 10, 2005, in response to an Approvable Action take December 14, 2004. On November 18, 2005, the manufacturers of the Long-Acting beta$_2$ Agonists (including Foradil Aerolizer) were asked to revised their labeling and include a Medication Guide for patients.

We have revised the submitted patient information into a Medication Guide that mirrors the Medication Guide language requested of all LABA manufacturers on November 18, 2005, and have revised and appended the *Instructions for Use* at the end of the MG. Our revisions to the *Instructions for Use* were done to increase patient comprehension.

We can provide a Word copy of the document and tracked changes of the revisions to the *Instructions for Use,* if requested by the review division.

10 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Jeanine Best
1/30/2006 09:11:34 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/30/2006 05:49:04 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Ann Shea
Senior Associate Director
Drug Regulatory Affairs

Dear Ms. Shea:

We acknowledge receipt on October 11, 2005, of your October 10, 2005, resubmission to your new drug application for Foradil Certihaler (formoterol fumarate inhalation powder).

We consider this a complete, class 2 response to our December 14, 2004, action letter. Therefore, the user fee goal date is April 11, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver granted on February 16, 2001, for the pediatric study requirement for this application for the maintenance and treatment of asthma for children up to 5 months of age and for exercise-induced bronchospasm for children up to 3 years of age. In addition, we reference the deferral granted on December 31, 2001, for the pediatric study requirement for this application the maintenance and treatment of asthma for children 6 months to 5 years of age.

If you have any question, call Ms. Akilah Green, Regulatory Project Manager, at (301) 796-1219.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Akilah Green
11/17/2005 01:57:00 PM
Signed for Sandy Barnes

NOVARTIS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Ann Shea, Sr. Associate Director
Tel: 862-778-4567
Fax: 973-781-2565
Internet:ann.shea@novartis.com

October 10, 2005

Badrul Chowdhury, MD, PhD
Director
Division of Pulmonary and Allergy
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

NDA No. 21-592

Foradil® Certihaler® (formoterol fumarate inhalation powder)

Complete Response to Approvable Letter dated 14-Dec-04

Dear Dr. Chowdhury:

Reference is made to NDA 21-592 for Foradil® Certihaler® (formoterol fumarate inhalation powder) for long-term, twice-daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older and the Approvable Letter dated December 14, 2004. Please find enclosed a complete response to the items outlined in the Approvable Letter.

Format and Content of the Complete Response

This complete response is presented in a Question and Answer format in the main document, "Complete Response to the Approvable Letter dated December 14, 2004", followed by attachments.

One clinical study report (Study F2309) is included as Attachment 6, and a safety update is included as Attachment 7.

Electronic Sections

This submission is being provided in accordance with the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). The relevant technical details of the electronic portions of this submission are as follows:

• **Submission size:**	approximately 35 MB
• **Electronic media:**	one compact disc
• **Virus scan:**	Network Associates Incorporated VirusScan© version 7.1.0 (formerly known as the McAfee VirusScan). The submission is virus free.

This submission includes the following components in electronic form only, and is contained on one CD-ROM that is located in Volume E1.

- Proposed Labeling Text
- Case Report Forms (Studies F2309 and F2402)
- Case Report Tabulations (Study F2309)

Follow-up to April 25, 2005 teleconference

Novartis would like to follow-up on a question raised by the Division at the April 25, 2005 teleconference with regard to Study F2306 and the classification of patients discontinuing the study due to device failure. In this study, seven patients discontinued due to administrative reasons described as device failure or malfunction. None of these patients were able to successfully take a dose from the device at the center when they attended their final visit and the investigator therefore classified these patients as having discontinued due to a device failure or malfunction. Two of these devices could not be tested *in vitro* because one had been destroyed by a dog and the other by a patient who used a screwdriver to open the device. One additional patient in the study missed 9 doses due to device issues, and although she was able to successfully take a dose from the device at her final visit, she was discontinued from the study because she had withdrawn consent. This patient is not counted in the seven patients who discontinued due to device failure or malfunction because the patient was able to take a dose at the final visit when assisted by the study staff, which indicated that the device itself was working. Since the objective of this study was to investigate technical device function and since this device was working, it was not counted as a device failure according to the study objective. However, of the six devices that could be tested *in vitro*, all were functioning normally, and it can therefore be concluded that these patients discontinued due to their inability to use the device.

If you have any questions concerning this submission, please do not hesitate to contact me at 862-778-4567.

Sincerely,

Ann Shea

Ann Shea
Senior Associate Director
Drug Regulatory Affairs

Attachments:
3 volumes
E1 volume (1 CD-ROM)

Memorandum of Meeting Minutes Facsimile Correspondence

Date: June 21, 2005

To: Ann Shea
Senior Associate Director, Regulatory Affairs

Fax: 973-781-3966

From: Akilah Green
Regulatory Project Manager

Subject: IND 60,254/Foradil Certihaler (formoterol fumarate) Inhalation Powder
June 14, 2005, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on June 14, 2005. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-5585.

MEMORANDUM OF TELECON

DATE: June 14, 2005

APPLICATION NUMBER: IND 60,254 Foradil Certihaler (formoterol fumarate inhalation powder)

BETWEEN:

Name: Eric Floyd, Ph.D., Drug Regulatory Affairs
Ann Shea, Drug Regulatory Affairs
Ian Hassan, Ph.D., Project Management
Andre Van As, M.D., Ph.D., Clinical Research
Chad Orevillo, Clinical Research
Michael Belman, Drug Regulatory Affairs, Schering-Plough

Phone: 1-877-331-6867

Representing: Novartis

AND

Name: Eugene Sullivan, M.D., Deputy Director
Richard Nicklas, M.D., Clinical Reviewer
Akilah Green, Senior Regulatory Management Officer
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Patient Use Study for NDA 21-592 Foradil Certihaler

BACKGROUND: This teleconference is in response to Novartis' submission dated May 17, 2005, regarding a protocol amendment for a new protocol entitled "A 3-week multicenter study evaluating patient use and functionality of the Foradil Certihaler device in patients with asthma." The submission was in response to the April 25, 2005, teleconference with the Division and the approval letter for NDA 21-592 dated December 14, 2004.

DISCUSSION: The Division commented that Novartis' study is generally acceptable and is consistent with what we requested. The Division noted that the final decision on whether this study will support NDA approval will depend on the data. In making that decision, the Division will review all of the data from the study. Treatment failure, as specifically defined in the protocol, is only one index that will be considered. The Division will also consider other findings, including unscheduled visits, inability to take a dose, the number of steps the patient has to go through to get the dose, i.e., re-try, website, video, study center visit, call center, etc. as possible indicators of utilization failure.

The Division noted that it was not clear in the protocol that Novartis plans to submit data on the number of patients who are unable to use the device despite the initial instructions, and therefore must utilize the various support resources. The Division requested that Novartis amend the protocol so that it is clear that the support mechanisms utilized by patients (e.g. use of video, use of web site, etc) will be tracked and reported. Novartis stated that it intends to capture and report

all such data. The Division suggested that the patient diary be modified so that it captures this type of data. Currently, the only available options are: Regarding your dose did you: a) take it; b) forget to take it or did not use the device at all; or c) tried to take the dose, but could not take the dose as instructed (please comment). The current lay out of the diary card allows patients to select "a) take it," even if they initially were unable to use the device, but eventually were successful after having used the available support mechanisms. Therefore, more detail needs to be placed in the diary to capture all potential scenarios as they occur. Novartis indicated that they will amend the diary card to record an explanatory comment on when patients used the additional support aids.

The Division stated that patients who have previously used the Certihaler device should not be included in the study. The Division stated that, in order to understand how well the study population reflects the intended patient population, additional demographic data should be collected on the patients, e.g., level of education, socioecomonic status, duration of asthma diagnosis, previous experience with other inhaled drugs, etc. The demographic information currently proposed, i.e. age, gender, race, is not sufficient.

The Division noted that Novartis has indicated that the procedures included in the study reflect the intended "real life" experience of patients. The Division stated that the NDA submission should contain sufficient information on Novartis' plans to ensure that the real life experience of patients will reflect the training and resources available to study participants. For example, Novartis must describe how it will accomplish the initial training for patients, and make the support resources available. The Division asked if Novartis is developing a "trainer" device for use when the product is marketed. Novartis stated that it does plan to develop a trainer device, which will be identical to the drug product except that it will not contain drug.

Novartis asked the Division to comment on how it will determine whether the study demonstrated acceptable device utilization. The Division commented that its conclusions will be based on all of the findings from the study, and will not be based on any one single analysis. If the study shows that patients require various support resources in order to successfully utilize the device, the burden will be on Novartis to explain why this would not be problematic in the marketplace.

Akilah Green,
Senior Regulatory Management Officer

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

/s/

Akilah Green
6/21/05 10:02:14 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-831

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil Aerolizer (formoterol fumarate inhalation powder).

We also refer to MedWatch reports, containing reports of inadvertent oral administration of Foradil Aerolizer capsules for inhalation.

We have reviewed the referenced material and believe that this issue should be addressed through changes to the labeling, including the addition of language such as, "Do not swallow," and "For inhalation only." This language should be prominently displayed in the package insert and on the carton, over wrap and blister cards.

In addition to the suggestion described above, the Division has considered a number of other additional possible solutions to this issue, including, marking the capsule with language similar to that suggested above. We also suggest that you consider a consumer education program to minimize potential user error and maximize patient safety.

Please consider our suggestions and submit a plan for labeling changes for Division comment, prior to submission of a supplement New Drug Application addressing this issue. If you have any questions please contact, Ms. Akilah Green, Regulatory Management Officer, at (301) 827-5585.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury
5/17/05 03:52:55 PM

Memorandum of Meeting Minutes Facsimile Correspondence

Date: May 16, 2005

To: Ann Shea
Senior Associate Director, Regulatory Affairs

Fax: 973-781-3966

From: Akilah Green
Regulatory Project Manager

Subject: NDA 21-592/Foradil Certihaler (formoterol fumarate) Inhalation Powder
April 25, 2005, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on April 25, 2005. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-5585.

MEMORANDUM OF TELECON

DATE: April 25, 2005

APPLICATION NUMBER: NDA 21-592

BETWEEN:

Name: Ann Shea, Drug Regulatory Affairs
Eric Floyd, Ph.D., Drug Regulatory Affairs
Ian Hassan, Ph.D., Project Management
Andre Van As, M.D., Ph.D., Clinical Research
Chad Orevillo, Clinical Research
Orin Tempkin, Ph.D., Regulatory CMC
Michael Belman, Drug Regulatory Affairs, Schering-Plough b(4)
[redacted] Consultant, [redacted]
Inc.

Phone: 1-877-805-0964

Representing: Novartis Pharmaceuticals Corporation

AND

Name: Badrul A. Chowdhury, M.D., Ph.D., Division Director
Eugene Sullivan, M.D., Deputy Director
Richard Nicklas, M.D., Clinical Reviewer
Akilah Green, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

BACKGROUND: Novartis submitted a Type A meeting request dated March 1, 2005, to discuss and clarify items outlined in the Approvable letter dated December 14, 2004. Novartis also submitted a briefing package dated April 8, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to Novartis' questions by fax on April 22, 2005. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Novartis' questions are in **bold italics**; FDA's response is in *italics*; discussion is in normal font.

Item 3.1
Novartis asks, "Is the outcome of the actions taken by Novartis, outlined below, acceptable to the Agency for approval of the NDA?"

Response:
The single dose study that you have submitted is not adequate to address the concerns raised by the previous studies. A repetitive dose study similar to study 2306 is necessary. The demographics of the individuals in the study should be consistent with asthma

patients in clinical practice and the duration of the study should be for the life of the device.

In regard to the revised patient instructions, the Division suggests that the patient in picture 6 should be pictured with his head level, rather than leaning back. In addition it should be clarified that the steps after step 1 do not have to be performed with the inhaler on a level surface, such as a table.

Novartis asked what the Agency's concerns were with regard to their new patient use study. Novartis stated that the Agency's December 14, 2004, approvable letter suggested that the instructions used in the previous patient use study were unclear and patients did not understand how to use the device. Novartis indicated that they felt that they had revised the instructions so that the device could be used appropriately.

The Division noted that Novartis has yet to demonstrate that the revised instructions are in fact effective in improving the ability of patients to operate the device successfully. In the studies previously submitted, it was apparent that patients were having difficulty using the device, despite the fact that participation in these studies required that the patients be able to understand and demonstrate the correct use of the device at the start of the study. The Division understands that Novartis has made efforts to improve the instructions, and that, on the basis of the data from the new, single-"dose" study, Novartis believes that the revised instructions are superior. However, given the experience from the previous studies, it will be necessary to demonstrate that the new instructions are effective in a patient use study similar to Study 2306.

Novartis noted ~~that in studies~~ 2304 and 2306, 83% and 86% of patients, respectively, took every dose over the three-week period, 95% missed three doses or less, and 98% missed less than 6 doses. Novartis' impression was that patients successfully used the device.

The Division stated that the interpretation depends on how one analyzes the data. In study 2306, which enrolled 154 patients, 6 patients discontinued because they could not use the device; some of these patients, demonstrated correct use of the device but were unable to get a dose. In addition, this study only enrolled patients who demonstrated that they were able to use the device. Therefore, if even well trained individuals who had to demonstrate that they knew how to use the device in order to enter the study could not use the device correctly during the subsequent course of the study, there is a very good possibility that patients in clinical practice will not be able to correctly use the device.

Novartis asked what failure rate the Division would find acceptable in a future multidose in-use study. The Division responded that the goal would be to have no reported failures. The Division noted that, a clinical trial is a very artificial setting and would likely underestimate the number of problems that could occur with clinical use. To address this, the Division stated that the study population should reflect the intended market population, and that the extent of training used in the study should reflect the training proposed for use in the market.

The Division noted that in Study 2306 one subject (Center 501, Subject 01) could not get a dose from the device and the counter did not work for four days. Despite the fact that this appeared to be a patient reported malfunction, this case was not reported along with the five other cases of "apparent malfunction," in which subsequent in vitro testing did not reveal a device malfunction. Instead, this case was reported as "the subject experienced problems using the device and therefore missed multiple doses of study medication." The Division suggested that Novartis explore why this case was reported in a separate category.

At the conclusion of the meeting, Novartis stated that they will design a multidose, patient use study and submit it to the Division for review. Upon review of the protocol by the Division, the project manager will set up a teleconference or fax comments to Novartis.

Item 3.2
Novartis would like to clarify which patients were included in the Agency's calculations in Items 7 and 8 of the December 14, 2004, approvable letter.

7. [redacted]

8. [redacted] b(4)

Response:
Your proposal is acceptable. Listed below are our proposed labeling revisions:

[redacted] b(4)

b(4)

Item 3.3
Novartis requests clarification on whether the format for the proposed safety update, which would not include new tables for integrated safety data, is acceptable.

Response:
This is acceptable. However, all adverse events (not just serious adverse events and premature discontinuations due to an adverse event) must be reported for all studies, where such data was not previously reported under the NDA.

Item 3.4
Novartis requests that the resubmission be considered as a Class 1 Resubmission:

Response:
This determination will be made at the time of resubmission. However, it appears that the resubmission will require review of data from a clinical study, and therefore not qualify as a Class 1 resubmission.

If you have any questions, please contact Ms. Akilah Green, Regulatory Project Manager, at 301-827-5585.

Akilah Green
Regulatory Project Manager

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

/s/

Akilah Green
5/16/05 01:39:59 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: April 22, 2005

To: Ann Shea Associate Director, Regulatory Affairs	**From:** Akilah Green Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Drug Products
Fax number: 973-781-3966	**Fax number:** 301-827-1271
Phone number: 862-778-4567	**Phone number:** 301-827-5585

Subject: NDA 21-592 Response to meeting package questions

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES XNO

Below are the FDA responses to your questions (in bold italics) regarding Foradil Certihaler (formoterol fumarate) Inhalation Solution. You have the option of canceling our meeting of April 25, 2005, if these answers are clear to you. If you choose to have the meeting (or change it to a teleconference), notify the Division of the specific questions for discussion and we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please notify the Division as soon as possible whether you are canceling the meeting.

Item 3.1
Novartis asks, "Is the outcome of the actions taken by Novartis, outlined below, acceptable to the Agency for approval of the NDA?"

Response:
The single dose study that you have submitted is not adequate to address the concerns raised by the previous studies. A repetitive dose study similar to study 2306 is necessary. The demographics of the individuals in the study should be consistent with asthma patients in clinical practice and the duration of the study should be for the life of the device.

In regard to the revised patient instructions, the Division suggests that the patient in picture 6 should be pictured with his head level, rather than leaning back. In addition it should be clarified that the steps after step 1 do not have to be performed with the inhaler on a level surface, such as a table.

Item 3.2
Novartis would like to clarify which patients were included in the Agency's calculations in Items 7 and 8 of the December 14, 2004, approvable letter.

7.

8.

b(4)

b(4)

Response:
Your proposal is acceptable. Listed below are our proposed labeling revisions:

b(4)

Item 3.3
Novartis requests clarification on whether the format for the proposed safety update, which would not include new tables for integrated safety data, is acceptable.

Response:
This is acceptable. However, all adverse events (not just serious adverse events and premature discontinuations due to an adverse event) must be reported for all studies, where such data was not previously reported under the NDA.

Item 3.4
Novartis requests that the resubmission be considered as a Class 1 Resubmission:

Response:
This determination will be made at the time of resubmission. However, it appears that the resubmission will require review of data from a clinical study, and therefore not qualify as a Class 1 resubmission.

Item 3.2
Novartis would like to clarify which patients were included in the Agency's calculations in Items 7 and 8 of the December 14, 2004, approvable letter.

9.

b(4)

b(4)

Response:
Your proposal is acceptable. Listed below are our proposed labeling revisions:

b(4)

If you have any questions, please contact Ms. Akilah Green, Regulatory Project Manager, at 301-827-5585.

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

/s/

Akilah Green
4/22/05 03:03:12 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: March 9, 2005

To: Ann Shea Associate Director, Regulatory Affairs	**From:** Akilah Green Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Drug Products
Fax number: 973-781-3966	**Fax number:** 301-827-1271
Phone number: 862-778-4567	**Phone number:** 301-827-5585

Subject: NDA 21-592 Information Request letter

Total no. of pages including cover: 5

Comments:

Document to be mailed: X YES NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your December 17, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil Certihaler (formoterol fumarate) Inhalation Powder.

We also refer to your submission dated June 24, 2004.

We have reviewed the draft Patient Instructions for Use document and educational campaign materials in your June 24, 2004, submission for Foradil Certihaler and have the following comments and information requests to assist you in responding to our December 14, 2004, approvable letter.

General Device Comments

1.

2.

b(4)

3.

4

Patient Instructions for Use

2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Badrul Chowdhury
3/9/05 04:10:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sepracor Foradil Certihaler (formoterol fumarate) Inhalation Powder.

We also refer to your March 1, 2005, correspondence, received March 2, 2005, requesting a meeting to discuss items 1, 7, and 8 of the approval letter dated December 14, 2004, and the format of a safety update.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date:	April 25, 2005
Time:	12:30-2:00 PM
Location:	Parklawn Building 5600 Fishers Lane, 3rd Floor Conference Room TBD Rockville, Maryland 20857
CDER participants:	Badrul A. Chowdhury, M.D., Ph.D., Division Director, Eugene Sullivan, M.D., Deputy Director Richard Nicklas, M.D., Clinical Reviewer Richard Lostritto, Ph.D., Chemistry, Manufacturing, and Controls Team Leader Craig Bertha, Ph.D., Chemistry, Manufacturing, and Controls Reviewer Akilah Green, Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Akilah.Green@fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an

escort to the conference room: my number, 301-827-5585; the division secretary, (301)-827-1050.

Provide the background information for this meeting (three copies to the NDA and 7 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by April 11, 2005, we may cancel or reschedule the meeting.

If you have any questions, call Akilah Green, Regulatory Project Manager, at (301) 301-827-5585.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Akilah Green
3/7/05 04:36:48 PM
Signed for Sandy Barnes

Office of Drug Safety

MEMO

To: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

From: Kimberly Culley, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina Mahmud, R.Ph., Team Leader
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

CC: Akilah Green
Project Manager, Division of Pulmonary and Allergy Drug Products
HFD-570

Date: December 30, 2004

Re: ODS Consult 03-0011-2 and 03-0011-3, Foradil Certihaler Patient Instructions for Use and Educational Campaign, NDA 21-592

This memorandum is in response to a November 28, 2004 and December 4, 2004 request from your Division for a review of the Patients Instructions for Use and Educational Campaign for the drug product, Foradil Certihaler.

In the review of the Patients Instructions for Use and Educational Campaign, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. General Device Concerns

1.

2.

b(4)

3.

4

5

2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Kimberly Culley
2/3/05 09:36:23 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
2/3/05 09:51:01 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/3/05 02:05:23 PM
DRUG SAFETY OFFICE REVIEWER

FAX

from:

Orin Tempkin, Ph.D.
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

Global Regulatory CMC
Phone: (862) 778-6949
FAX: (973) 781-3320

To: Ms. Akilah Green, Regulatory Project Manager

Location: FDA

FAX: (301) 827-1271

Date: 22-Nov-2004 4 pages (incl. cover sheet)
Re: Foradil Certihaler, NDA 21-592

COMMENTS:

Dear Ms. Green,

Kindly refer to your fax of 17-Nov-2004 to Ann Shea regarding an additional CMC question on Foradil Certihaler. Attached, please find Novartis's response, including our proposal for tightened magnesium stearate specific surface area acceptance criteria.

Novartis will follow up with the hard copy submission.

Thank you for your attention.

Sincerely,

Orin Tempkin

Novartis Pharmaceuticals Corporation
Global Regulatory CMC
One Health Plaza
East Hanover, NJ 07936-1080

Tel 862 778 8300
Fax 973 781 6325

NOVARTIS

22-Nov-2004

Badrul Chowdhury, MD, Director
Division of Pulmonary and Allergy
Drug Products/HFD-570
Office of Drug Evaluation II
Attn: Document Control Room 10B-45
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-592
Foradil Certihaler (formoterol fumarate inhalation powder)

Response to FAX dated 17-Nov-2004 – Chemistry, Manufacturing and Controls

Dear Dr. Chowdhury:

Kindly refer to the Division's fax of 17-Nov-2004 to Ms. Ann Shea, listing an additional CMC question on Foradil Certihaler. Novartis is now providing a response to this question.

Should you have any comments or questions regarding this submission or any other CMC issues, please contact me directly at (862) 778-6949; FAX (973) 781-3320. If there are any general or clinical-related issues, please contact Ms. Ann Shea, the DRA Therapeutic Area representative at (862) 778-4567.

Sincerely,

Orin Tempkin, Ph.D.
Associate Director
Global Regulatory CMC

Attachments
Submitted in duplicate

cc: Mr. Michael C. Rogers, Division of Emergency and Investigational Operations, FDA (cover letter only)

21592 22Nov2004.doc