CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20746/000 Priority: 3S Org Code: 570
Stamp: 30-JUL-1996 Regulatory Due: 21-JAN-2000 Action Goal: District Goal: 30-MAR-1997
Applicant: ASTRA PHARMS
725 CHESTERBROOK BLVD
WAYNE, PA 190875677
Brand Name: RHINOCORT AQUA (BUDESONIDE)NASAL SPRAY
Established Name:
Generic Name: BUDESONIDE
Dosage Form: SPR (SPRAY)
Strength: 32 & 64 MCG

FDA Contacts:
G. TROUT (HFD-570) 301-827-1050 , Project Manager
E. NASHED (HFD-570) 301-827-1050 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 04-MAY-1999 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 25-MAR-1999 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 16-OCT-1997 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 20-DEC-1996 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: 9612840
ASTRA PHARMACEUTICAL PRODU
STRANGNASVAGEN 20
SODERTALJE, , SW
DMF No:
AADA No:

Profile: ADM OAI Status: NONE Responsibilities: DRUG SUBSTANCE MICRONIZER
Last Milestone: OC RECOMMENDATION FINISHED DOSAGE MANUFACTURER
Milestone Date 25-MAR-1999 FINISHED DOSAGE RELEASE TESTER
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 25-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: 1220331
ASTRA USA INC
50 OTIS ST
WESTBOROUGH, MA 015814500
DMF No:
AADA No:

Profile: ADM OAI Status: NONE Responsibilities: FINISHED DOSAGE PACKAGER
Last Milestone: OC RECOMMENDATION FINISHED DOSAGE RELEASE TESTER
Milestone Date 19-MAR-1999 FINISHED DOSAGE STABILITY TESTER
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 19-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 19-MAR-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-MAY-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 22-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: INTERMEDIATE MANUFACTURER

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ASTRA®
Astra USA

July 24, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Re: Rhinocort® (budesonide) Aqua Nasal Spray
Original New Drug Application
NDA 20-746
Patent Information

Dear Sir or Madam:

The applicant of the above-referenced application number declares that there are no patents which claim budesonide or which claim a method of using budesonide and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of budesonide.

This product is the subject of this application for which approval is being sought. If approved, Rhinocort Aqua will be eligible for marketing exclusivity pursuant to the provisions of 21 U.S.C. § 355(c)(3)(D)(ii).

Very truly yours,

Charles E. Yon
General Counsel

CEY/eaw

APPEARS THIS WAY
ON ORIGINAL

MAILING ADDRESS:
Astra USA, Inc.
P.O. Box 4500
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OFFICE:
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Westborough, MA

TEL:
508 366-1100

FAX:
508 366-7406
TELEX:
6810105-Cable/Astrapharm

Consult #681 (HFD-570)

RHINOCORT AQUA NASAL SPRAY budesonide aqua nasal spray

RHINOCORT is an approved trademark for use on this product and NASAL SPRAY is an acceptable USP dosage form descriptor, therefore the Committee only considered the term "AQUA". The term AQUA adjacent to the trademark is acceptable if this is a distinct aqueous formulation differing from the original RHINOCORT formulation. The use of "aqua" in the established name is not in conformance with USP dosage form descriptors for established names and should not be used. The established name should be (budesonide nasal spray).

The LNC has no reason to find the proposed name proprietary name unacceptable.

/S/ 10/18/96, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 20-746 SUPPL #

Trade Name Rhinocort Aqua Generic Name budesonide

Applicant Name AstraZeneca HFD # 570

Approval Date If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

20746

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

_____NO_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# __20-233_____ __Rhinocort (budesonide) Nasal Spray_____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?
YES /__X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/
(The sponsor submitted literature, but did not include the statement that publicly available data would not independently support approval of the application)

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(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

05-3038, 05-3039

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

05-3038, 05-3039

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4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # [redacted] YES /_X__/ ! NO /___/ Explain: (NOTE: The applicants name has changed several times but they were the sponsor of the studies).

! _____

Investigation #2 !

IND # [redacted] YES /_X__/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

/S/ 9/16/99
Signature Date
Title: Project Manager

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/30/99
Signature of Office/ Date
Division Director

cc: Original NDA 20716 Division File HFD-93 Mary Ann Holovac

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20746	**Trade Name:**	RHINOCORT AQUA (BUDESONIDE)NASAL SPRAY
Supplement Number:		**Generic Name:**	BUDESONIDE
Supplement Type:		**Dosage Form:**	Spray; Nasal
Regulatory Action:	PN	**Proposed Indication:**	The management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children six years of age and older

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
____Children (25 Months-12 years)
____Adolescents (13-16 Years)
_X_Other Age Groups (listed): 6-adult

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are submitted and under review

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This is a new NDA providing for the indication specified above. The Division is approving the application with labeling down to 6 years of age. The DIvision has issued a written request to the sponsor requesting safety studies to obtain information in patients down to two years of age. The sposnor has requested an amendment to the WR. This is currently under negotiation (9/16/99)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, GRETCHEN TROUT

/S/
Signature

9/16/99
Date

ASTRA®
Astra USA

Debarment Certification

This certifies that Astra USA, Inc. has not used in any capacity any person identified by the United States Food and Drug Administration on the recent Debarment List.

Further, we certify that Astra USA, Inc. will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

The following is a list of all relevant convictions (for which a person can be debarred) as described in section 306 (a) and (b). The list covers the past five (5) years for persons employed and/or affiliated with Astra USA, Inc. (including contractors) and responsible for the development of data and information to support approval of NDA 20-746 for Rhinocort® (budesonide) Aqua Nasal Spray.

Person	Date of Conviction	Charge
None	None	None

Dennis J. Bucceri
Vice President
Drug Regulatory Affairs

6/18/96
Date

MAILING ADDRESS:
Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

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50 Otis Street
Westborough, MA

TEL:
508 366-1100

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508 366-7406
TELEX:
6810105-Cable/Astrapharm

Division Director's Memorandum

Date:	Thursday, September 30, 1999
NDA:	20-746
Sponsor:	AstraZeneca
Proprietary Name:	Rhinocort Aqua (budesonide) Nasal Spray

Introduction: This is the fourth cycle of review for this NDA for Rhinocort Aqua, an aqueous suspension corticosteroid drug product for topical nasal administration. The drug substance – budesonide - is already contained in a CFC-based nasal spray – Rhinocort Nasal Aerosol. The main issues holding up final approval of this application have been CMC considerations (reliability of dosing, stability considerations, etc) and the last divisional action was on Jun 22nd, 1999.

Chemistry/Manufacturing and Controls: This application is for two dosage strengths – a 32 mcg and a 64 mcg product. The major CMC issues have been resolved, however a number of phase 4 commitments regarding primarily related to setting final specifications based on the post-approval production experience are contained in the action letter and have been committed to by the sponsor.

Pharm/tox: A remaining issue at the time of the last action was the qualification of [redacted] of budesonide. The sponsor made a reasonable assessment of safety risk based on assuming this [redacted] and therefore justified their current specifications. They have an outstanding commitment to complete and submit both a [redacted] by November 30, 1999.

Biopharmaceutics: There are no new issues for this cycle and the product is approvable from the biopharmaceutics standpoint.

Clinical / Statistical: See Dr. Anthracite's reviews for details. In this cycle, there were no new safety data due to the short turn around of the response. The product is approvable clinically, especially given the restrictions of dosing agreed to by the sponsor for pediatrics (i.e., no more than 128 mcg/day in children less than age 12). Note that the sponsor did do an open-label, but well controlled growth study that confirms a growth effect of higher doses (256 mcg/day) in the range of suppression seen with other corticosteroid drug products (0.78 cm/year). Given that this dose was not approvable in FDA's view, we will require a phase 4 commitment to study the approved dose range and to submit labeling according to the results.

EERs: The appropriate EERs for the drug substance/product production sites and testing sites are all current, with inspections dated 5-4-99 and 3-25-99. The EER overall recommendation is acceptable for both of those dates (as they had been in prior inspections in 1996 and 1997).

Labeling: The sponsor has made all labeling changes requested by FDA, most notably recommending lower starting doses and limiting the recommended maximum dosing in pediatric patients 6 – 11 years of age to 128 mcg per day (rather than the [redacted] originally sought). This decision to limit this top dose was based on their being no defined

incremental benefit to these higher doses, but there were clearly incremental safety signals of concern – including growth suppression.

Conclusions: This NDA as submitted and subsequently amended will be approved. There will be a clinical phase 4 commitment for a [redacted] for several CMC issues needed to arrive at final specifications, and there is a remaining commitment to address the [redacted] issue.

/S/

Robert J. Meyer, MD 9/30/99
Director
Division of Pulmonary and Allergy Drug Products.

APPEARS THIS WAY
ON ORIGINAL

CC: NDA 20746
Div. File