CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

CHEMISTRY REVIEW(S)

Trout

DIVISION OF PULMONARY DRUG PRODUCTS

SEP - 8 1999

Review of Chemistry, Manufacturing, and Controls

NDA:	20-746	DATE REVIEWED:	Sep 2, 1999
REVIEW #:	6	RECOMMENDED ACTION:	APPROVAL

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	Jul 29, 1996	Jul 30, 1996	Aug 15, 1996
AMENDMENT	Jun 16, 1997	Jun 17, 1997	Jun 18, 1997
AMENDMENT	Sep 16, 1997	Sep 17, 1997	Sep 22, 1997
AMENDMENT	Sep 30, 1997	Oct 02, 1997	Oct 06, 1997
AMENDMENT	Oct 07, 1997	Oct 08, 1997	Oct 14, 1997
AMENDMENT	Oct 15, 1997	Oct 16, 1997	Oct 22, 1997
AMENDMENT	Feb 27, 1998	Mar 02, 1998	Mar 10, 1998
AMENDMENT	May 14, 1998	May 18, 1998	May 22, 1998
AMENDMENT	Jun 06, 1998	Jun 10, 1998	Sep 25, 1999
AMENDMENT	Jun 15, 1998	Jun 16, 1998	Sep 25, 1999
AMENDMENT	Jul 28, 1998	Jul 29, 1998	Sep 25, 1999
AMENDMENT AC	Dec 23, 1998	Dec 23, 1998	Jan 05, 1999
AMENDMENT	Jan 20, 1999	Jan 21, 1999	Feb 02, 1998
AMENDMENT	Feb 08, 1999	Feb 09, 1999	Feb 16, 1998
AMENDMENT	Feb 19, 1999	Feb 22, 1999	Feb 23, 1998
AMENDMENT	Mar 12, 1999	Mar 15, 1999	Mar 19, 1998
AMENDMENT	Apr 28, 1999	Apr 29, 1999	Apr 30, 1999
AMENDMENT	May 06, 1999	May 07, 1999	May 10, 1999
AMENDMENT	May 18, 1999	May 19, 1999	May 21, 1999
AMENDMENT	May 24, 1999	May 25, 1999	May 25, 1999
AMENDMENT	May 24, 1999	May 25, 1999	May 25, 1999
AMENDMENT	May 24, 1999	May 25, 1999	May 25, 1999
AMENDMENT	May 25, 1999	May 26, 1999	May 28, 1999
AMENDMENT	May 27, 1999	May 28, 1999	May 28, 1999
AMENDMENT	Jun 01, 1999	Jun 01, 1999	Jun 01, 1999
AMENDMENT	Jun 03, 1999	Jun 04, 1999	Jun 08, 1999
AMENDMENT	Jun 08, 1999	Jun 09, 1999	Jun 09, 1999

Subject of this review:

AMENDMENT AZ	Jul 20, 1999	Jul 21, 1999	Jul 26, 1999
AMENDMENT BC	Jul 20, 1999	Jul 22, 1999	Jul 28, 1999
AMENDMENT BL	Jul 30, 1999	Jul 30, 1999	Aug 02, 1999
AMENDMENT BC	Aug13, 1999	Aug16, 1999	Aug19, 1999
AMENDMENT BC	Aug30, 1999	Aug31, 1999	Aug31, 1999

NAME & ADDRESS OF APPLICANT:

Astra USA
50 Otis Street
Westborough, Massachusetts 01581-4500

DRUG PRODUCT NAME

Proprietary:	Rhinocort Aqua Nasal Spray
Nonproprietary/Established/:	Budesonide nasal spray (suspension)
Code Name/#:	CAS #51333-22-3
Chem.Type/Ther. Class:	3S

USAN Name: Budesonide

PHARMACOLOGICAL CATEGORY/INDICATION: Seasonal and perennial allergic rhinitis symptoms - adults and children 6 years and older.

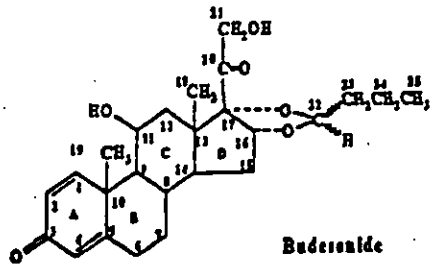
DOSAGE FORM: Nasal spray suspension

STRENGTHS: 64 µg and 32 µg per spray; each spray delivers 50 µL.
Target fill value is 8.6 g (8.4 mL) for 120 metered sprays (64µg and 32µg) and 5.1 g (5.0 mL) for 60 metered spray (32 µg) – total 3 commercial product presentations.
Target fill value is [redacted] for [redacted] metered sprays [redacted] professional sample.

ROUTE OF ADMINISTRATION: Nasal spray; Daily dose: 64µg-256µg;
Minimum dose: 2 sprays (1 per nostril once daily) of 32 µg strength.

DISPENSED: X Rx ___ OTC

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



Budesonide

SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status/Review Date	Post-review Update	Reference
[redacted]	[redacted]	Type II, Synthesis of starting material	Adequate 2/11/98 (L.Ng)	No new amendments prior to 5/20/99	Also applicable to NDA 20-441 and N[redacted]

NDA 20-746 *Rhinocort Aqua Nasal Spray Suspension*

Astra USA

		Type II , Starting material	Adequate 5/26/99 (K.Swiss)	No new amendments prior to 6/11/99	Also applicable to NDA 20-441 and N
		Type II, Drug substance	Adequate 4/11/98 (L.Ng)	No new amendments prior to 5/20/99	Also applicable to NDA 20-441 and N
		Type III/I, Tubular glass for container	Adequate 3/18/98 (HFD-580), and 2/18/97 (L.Ng)	Annual update (no significant change) dated 7/13/98 was submitted	
		Type I Glass bottle manufacturer	N/A	N/A	Type I DMF; not reviewed.
		Type III Glass bottle manufacturer	Adequate 8/31/99 (E.Nashed)		This was review of holder's response to DEFICIENCY Letter dated 5/28/99.
		Type III,	Adequate 9/3/99 (E.Nashed/ H.Khorshidi)	Fax from holder, dated 9/3/99	New, tighter specs for extractables (Fax from holder, dated 9/3/99) were reviewed and found adequate.
			Adequate 6/11/99 (K.Swiss)		Holder name changed from
			Inadequate* 7/23/99 (K.Swiss)	Deficiency Letters sent to the holder on 6/14/99	Manufacturing of polypropylene resin was taken over by (DMF
			Adequate 8/16/99 (K.Swiss)	Applicant's response (dated 8/3/99) to IR letter was found adequate.	

* This DMF is not applicable anymore to this NDA since is using only from Owner of this DMF changed from and the scope was limited to resins only. A new DMF was established with a new name for the resin that has an identical composition to

NDA 20-746 *Rhinocort Aqua Nasal Spray Suspension*

Astra USA

RELATED DOCUMENTS :

Type	Number	Owner	Subject
NDA	20-233	Astra USA	Rhinocort Nasal Inhaler (Nasal Aerosol)
NDA	20-441	Astra USA	Pulmicort Turbohaler (DPI)
NDA			
IND		Astra USA	Rhinocort Nasal Inhaler (pMDI) and Aqua Nasal Spray
IND		Astra USA	Pulmicort Turbuhaler
IND		Astra USA	
IND		Astra USA	
IND		Astra USA	

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	Nov 25, 1996	Acceptable 12/20/96	
EER	Oct 14, 1997	Acceptable 10/16/97	Add testing site
FUR	Mar 19, 1999	Acceptable 3/25/99	
EER	May 3, 1999	Acceptable 5/4/99	2 testing sites added
Pharm/Tox	Oct 21, 1996 Apr 21, 1999	Acceptable 11/4/96 Not Acceptable 5/18/99: Limit the acceptance criteria for or conduct	Phase 4 commitment to carry
Microbiology, HFD-160	a. Feb 12, 1997 b. Jul 11, 1997 c. May 4, 1998	NA 3/7/97 Acceptable 8/14/97 Acceptable 5/28/98	
Biometrics, HFD-710	July 3, 1997 April 13, 1999	Acceptable 9/3/97 Acceptable 6/8/99	
Methods Validation	Package in preparation		
EA	Submission dated 8/31/99; (See also 12/23/98 submission).	Acceptable 8/31/99	Categorical exclusion granted, based on the amount of budesonide used in all drug products kg for all products through 2004)
Labeling & Nomenclature Com.	Sept 16, 1996	Acceptable 10/18/96	

NDA 20-746 *Rhinocort Aqua Nasal Spray Suspension*
Astra USA

CONCLUSIONS & RECOMMENDATIONS:

The application is recommended for APPROVAL from the standpoint of chemistry, manufacturing and controls. Detailed reference to Phase 4 commitments submitted on August 30, 1999 should be included in the action letter - See the end of this review for draft letter and copy of the commitments. Comments, if any, resulting from the pending Pharm/Tox consult on [redacted] should be also included.

cc:
NDA 20-746
HFD-570/Division File
HFD-570/ENashed/GPoochikian
HFD-570/GTrout
HFD-570/RAnthracite/LPei
R/D Init by: S\ 9/8/99

/S/
Eugenia Nashed, Ph. D.
HFD-570, Review Chemist

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-746 **DATE REVIEWED:** June 11, 1999

REVIEW #: 5 **RECOMMENDED ACTION:** Approvable

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	Jul 29, 1996	Jul 30, 1996	Aug 15, 1996
AMENDMENT	Jun 16, 1997	Jun 17, 1997	Jun 18, 1997
AMENDMENT	Sep 16, 1997	Sep 17, 1997	Sep 22, 1997
AMENDMENT	Sep 30, 1997	Oct 02, 1997	Oct 06, 1997
AMENDMENT	Oct 07, 1997	Oct 08, 1997	Oct 14, 1997
AMENDMENT	Oct 15, 1997	Oct 16, 1997	Oct 22, 1997
AMENDMENT	Feb 27, 1998	Mar 02, 1998	Mar 10, 1998
AMENDMENT	May 14, 1998	May 18, 1998	May 22, 1998
AMENDMENT	Jun 06, 1998	Jun 10, 1998	Sep 25, 1999
AMENDMENT	Jun 15, 1998	Jun 16, 1998	Sep 25, 1999
AMENDMENT	Jul 28, 1998	Jul 29, 1998	Sep 25, 1999
AMENDMENT AC	Dec 23, 1998	Dec 23, 1998	Jan 05, 1999
AMENDMENT	Jan 20, 1999	Jan 21, 1999	Feb 02, 1998
AMENDMENT	Feb 08, 1999	Feb 09, 1999	Feb 16, 1998
AMENDMENT	Feb 19, 1999	Feb 22, 1999	Feb 23, 1998
AMENDMENT	Mar 12, 1999	Mar 15, 1999	Mar 19, 1998
Subject of this review:			
AMENDMENT	Apr 28, 1999	Apr 29, 1999	Apr 30, 1999
AMENDMENT	May 06, 1999	May 07, 1999	May 10, 1999
AMENDMENT	May 18, 1999	May 19, 1999	May 21, 1999
AMENDMENT	May 24, 1999	May 25, 1999	May 25, 1999
AMENDMENT	May 24, 1999	May 25, 1999	May 25, 1999
AMENDMENT	May 24, 1999	May 25, 1999	May 25, 1999
AMENDMENT	May 25, 1999	May 26, 1999	May 28, 1999
AMENDMENT	May 27, 1999	May 28, 1999	May 28, 1999
AMENDMENT	Jun 01, 1999	Jun xx, 1999	Jun xx, 1999
AMENDMENT	Jun 03, 1999	Jun 04, 1999	Jun 08, 1999
AMENDMENT	Jun 08, 1999	Jun xx, 1999	Jun xx, 1999

NAME & ADDRESS OF APPLICANT:

Astra USA
50 Otis Street
Westborough, Massachusetts 01581-4500

DRUG PRODUCT NAME

Proprietary:	Rhinocort Aqua Nasal Spray™
Nonproprietary/Established/:	Budesonide nasal spray (suspension)
Code Name/#:	CAS #51333-22-3
Chem.Type/Ther. Class:	**3S**
USAN Name:	Budesonide

ANDA Suitability Petition/DESI/Patent Status: Claims eligible for marketing exclusivity under 21 USC 355(c)(3)(D)(ii).

PHARMACOLOGICAL CATEGORY/INDICATION: Seasonal and perennial allergic rhinitis symptoms -- adults and children 6 years and older.

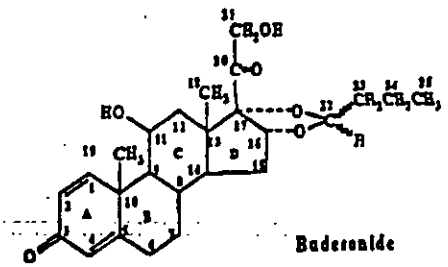
DOSAGE FORM: Nasal spray suspension

STRENGTHS: 64 µg and 32 µg per spray; each 50 µL per actuation.
Target fill value is 8.6 g (8.4 mL) for 120 metered sprays for each of the two commercial products (64µg and 32µg).
Target fill value is [redacted] for [redacted] metered spray [redacted] and 5.1 g for 60 metered spray (32 µg) professional samples.

ROUTE OF ADMINISTRATION: Nasal spray; Daily dose: 64µg-256µg;
Minimum dose: 2 sprays (1 per nostril once daily) of 32 µg.

DISPENSED: X Rx ___ OTC

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



SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status/Review Date	Post-review Update	Reference
[redacted]	[redacted]	Type II, Synthesis of starting material	Adequate 2/11/98 (L.Ng)	No new amendments prior to 5/20/99	Also applicable to NDA 20-441 and N[redacted]
[redacted]	[redacted]	Type II , Starting material	Adequate 5/26/99 (K.Swiss)	No new amendments prior to 6/11/99	Also applicable to NDA 20-441 and N[redacted]

NDA 20-746 *Rhinocort Aqua Nasal Spray Suspension*

Astra USA

		Type II, Drug substance	Adequate 4/11/98 (L.Ng)	No new amendments prior to 5/20/99	Also applicable to NDA 20-441 and N
		Type III/I, Tubular glass for container	Adequate 3/18/98 (HFD-580), and 2/18/97 (L.Ng)	Annual update (no significant change) dated 7/13/98 was submitted	
		Type I Glass bottle manufacturer	N/A	N/A	Type I DMF not reviewed.
		Type III Glass bottle manufacturer	Inadequate 5/28/99 (ENashed)	Fax dated 5/27/99 and letter dated 5/28/99 were forwarded to the applicant	
		Type III,	Inadequate 5/17/99 (E.Nashed)	Fax dated 5/17/99 and letter dated 5/20/99 were forwarded to the applicant	Specs for extractables, Updates. Applicant provided response to similar comment in the NDA application, based on data from
			Adequate 6/11/99 (K.Swiss)		Holder name changed from to
			Inadequate 6/11/99 (K.Swiss)	Deficiency Letters sent to the holder on 6/14/99	No response to letter dated Dec 5, 1996. Acceptance specifications for raw materials, regrinding
			Adequate 6/10/99 (K.Swiss)	IR letter dated 6/14/99 sent to the holder	Acceptance specifications for raw materials, LOA list

* Resin from is not used anymore by Owner of the DMF changed to Also new DMF number was established with a new name for the resin that has identical composition to

NDA 20-746 *Rhinocort Aqua Nasal Spray Suspension*

Astra USA

RELATED DOCUMENTS :

Type	Number	Owner	Subject
NDA	20-233	Astra USA	Rhinocort Nasal Inhaler (Nasal Aerosol)
NDA	20-441	Astra USA	Pulmicort Turbohaler (DPI)
NDA			
IND		Astra USA	Rhinocort Nasal Inhaler (pMDI) and Aqua Nasal Spray
IND		Astra USA	Pulmicort Turbuhaler
IND		Astra USA	
IND		Astra USA	
IND		Astra USA	

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	Nov 25, 1996	Acceptable 12/20/96	
EER	Oct 14, 1997	Acceptable 10/16/97	Add testing site
FUR	Mar 19, 1999	Acceptable 3/25/99	
EER	May 3, 1999	Acceptable 5/4/99	2 testing sites added
Pharm/Tox	Oct 21, 1996 (e-mail) Apr 21, 1999	Acceptable 11/4/96 Not Acceptable 5/18/99: Limit the acceptance criteria for or conduct studies with the impurity	Phase 4 commitment to carry
Microbiology, HFD-160	a. Feb 12, 1997 b. Jul 11, 1997 c. May 4, 1998	NA 3/7/97 Acceptable 8/14/97 Acceptable 5/28/98	
Biometrics, HFD-710	July 3, 1997 April 13, 1999	Acceptable 9/3/97 Acceptable 6/8/99	
Methods Validation	None sent	Deferred, pending adequate methods	Some methods and acceptance criteria under development
Labeling & Nomenclature Com.	Sept 16, 1996	Acceptable 10/18/96	

NDA 20-746 *Rhinocort Aqua Nasal Spray Suspension*
Astra USA

CONCLUSIONS & RECOMMENDATIONS:

The application is considered APPROVABLE from the standpoint of chemistry, manufacturing and controls, providing that all comments are addressed adequately by the applicant and that all supporting DMFs have an adequate status. See the end of this review for draft comments. Also, comments resulting from Pharm/Tox consult should be included in the action letter.

cc:
NDA 20-746
HFD-570/Division File
HFD-570/ENashed/GPoochikian
HFD-570/GTrout
HFD-570/RAnthracite/LPei
R/D Init by /S/ 6/16/99

/S/
Eugenia Nashed, Ph. D.
HFD-570, Review Chemist

APPEARS THIS WAY
ON ORIGINAL

Trust

MAY 22 1999

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-746 **DATE REVIEWED:** May 21, 1999

REVIEW #: 4 **RECOMMENDED ACTION:** Approvable

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	Jul 29, 1996	Jul 30, 1996	Aug 15, 1996
AMENDMENT	Jun 16, 1997	Jun 17, 1997	Jun 18, 1997
AMENDMENT	Sep 16, 1997	Sep 17, 1997	Sep 22, 1997
AMENDMENT	Sep 30, 1997	Oct 02, 1997	Oct 06, 1997
AMENDMENT	Oct 07, 1997	Oct 08, 1997	Oct 14, 1997
AMENDMENT	Oct 15, 1997	Oct 16, 1997	Oct 22, 1997
AMENDMENT	Feb 27, 1998	Mar 02, 1998	Mar 10, 1998
AMENDMENT	May 14, 1998	May 18, 1998	May 22, 1998
AMENDMENT	Jun 06, 1998	Jun 10, 1998	Sep 25, 1999
AMENDMENT	Jun 15, 1998	Jun 16, 1998	Sep 25, 1999
AMENDMENT	Jul 28, 1998	Jul 29, 1998	Sep 25, 1999
Subject of this review:			
AMENDMENT AC	Dec 23, 1998	Dec 23, 1998	Jan 05, 1999
AMENDMENT	Jan 20, 1999	Jan 21, 1999	Feb 02, 1998
AMENDMENT	Feb 08, 1999	Feb 09, 1999	Feb 16, 1998
AMENDMENT	Feb 19, 1999	Feb 22, 1999	Feb 23, 1998
AMENDMENT	Mar 12, 1999	Mar 15, 1999	Mar 19, 1998

NAME & ADDRESS OF APPLICANT:

Astra USA
50 Otis Street
Westborough, Massachusetts 01581-4500

DRUG PRODUCT NAME

Proprietary:	Rhinocort Aqua Nasal Spray™
Nonproprietary/Established/:	Budesonide nasal spray (suspension)
Code Name/#:	CAS #51333-22-3
Chem.Type/Ther. Class:	3S
USAN Name:	Budesonide

ANDA Suitability Petition/DESI/Patent Status: Claims eligible for marketing exclusivity under 21 USC 355(c)(3)(D)(ii).

PHARMACOLOGICAL CATEGORY/INDICATION: Seasonal and perennial allergic rhinitis symptoms - adults and children 6 years and older.

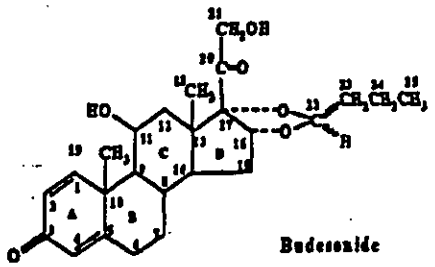
DOSAGE FORM: Nasal spray suspension

STRENGTHS: 64 µg and 32 µg per spray; each 50 µL per actuation.
Target fill value is 8.6 g (8.4 mL) for 120 metered sprays for each of the two commercial products (64µg and 32µg).
Target fill value is [redacted] for [redacted] metered sprays [redacted] and 5.1 g for 60 metered spray (32 µg) professional samples.

ROUTE OF ADMINISTRATION: Nasal spray; Daily dose: 64µg-256µg;
Minimum dose: 2 sprays (1 per nostril once daily) of 32 µg.

DISPENSED: X Rx ___ OTC

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



Budesonide

SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status/Review Date	Date Reviewed	Reference
		Type II, Synthesis of starting material	Adequate 2/11/98 (L.Ng)	5/20/99: No new amendments	Also applicable to NDA 20-441 and N
		Type II , Starting material	Adequate 4/21/97 (D.Koble)	5/20/99: Annual report dated 4/20/98 was submitted (upgraded specs, minor manuf. changes)	Also applicable to NDA 20-441 and N Review pending
		Type II, Drug substance	Adequate 4/11/98 (L.Ng)	5/20/99: No new amendments	Also applicable to NDA 20-441 and N
		Type III/I, Tubular glass for container	Adequate 2/18/97 (L.Ng) and 3/18/98 (HFD-580)	5/20/99: Annual update (no significant change) dated 7/13/98 was submitted	

		Type I Glass bottle manufacturer	N/A	N/A	Type I DMF not reviewed.
		Type III Glass bottle manufacturer	Inadequate 2/2/99 (W.Berlin)	5/20/99: Annual update dated 5/15/99 was submitted. No response to Deficiency Letter dated 2/4/99 was provided.	Lack of and for the bottles (ref to USP<661>)
		Type III,	Inadequate 5/17/99 (E.Nashed)	Fax dated 5/17/99 and letter dated 5/20/99 were forwarded to the applicant	Specs for extractables, updates
			Adequate 10/20/97 (L.Ng)	5/20/99: Amendment dated 12/9/98 and Annual report dated 11/25/98 were submitted	DMF was found Adequate for Flovent Discus (N D.Koble) and Serevent Disc (N20-692, R.Lostritto) Review of the amendment is pending
			Inadequate 10/23/97 (L. Ng)	Letters informing of the inadequate status of this DMF were sent to the holder of DMF 5/20/99) and to the applicant (5/6/99)	Await response to letter dated Dec 5, 1996
			Adequate 2/18/99 (HFD-180)	5/10/99: No new amendments	Review evaluated response to our Letter dated 6/17/98

RELATED DOCUMENTS :

Type	Number	Owner	Subject
NDA	20-233	Astra USA	Rhinocort Nasal Inhaler (Nasal Aerosol)

NDA 20-746 *Rhinocort Aqua Nasal Spray Suspension*

Astra USA

NDA	20-441	Astra USA	Pulmicort Turbohaler (DPI)
NDA			
IND		Astra USA	Rhinocort Nasal Inhaler (pMDI) and Aqua Nasal Spray
IND		Astra USA	Pulmicort Turbuhaler
IND		Astra USA	
IND		Astra USA	
IND		Astra USA	

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	Nov 25, 1996	Acceptable 12/20/96	
EER	Oct 14, 1997	Acceptable 10/16/97	Add testing site
FUR	Mar 19, 1999	Acceptable 3/25/99	
EER	May 3, 1999	Acceptable 5/4/99	2 testing sites added
Pharm/Tox	Oct 21, 1996 (e-mail) Apr 21, 1999	Acceptable 11/4/96 Not Acceptable 5/18/99	Limit the acceptance criteria for
Microbiology, HFD-160	a. Feb 12, 1997 b. Jul 11, 1997 c. May 4, 1998	NA 3/7/97 Acceptable 8/14/97 Acceptable 5/28/98	
Biometrics, HFD-710	July 3, 1997 April 13, 1999	Acceptable 9/3/97 Pending	Evaluation of acceptance limits for impurities and And is pending
Methods Validation	None sent	Deferred pending adequate methods	Some methods and acceptance criteria under development
Labeling & Nomenclature Com.	Sept 16, 1996	Acceptable 10/18/96	

NDA 20-746 *Rhinocort Aqua Nasal Spray Suspension*
Astra USA

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is approvable from the standpoint of chemistry, manufacturing and controls. However, the CMC deficiencies (as summarized in the draft letter at the end of this review) should be adequately addressed by the applicant before the approval of the NDA.

cc:
NDA 20-746
HFD-570/Division File
HFD-570/ENashed/GPoochikian
HFD-570/GTrout
HFD-570/RAnthracite/LPei
R/D Init by: ES 6/22/99

File: 20746rev4.doc

ES

Eugenia Nashed, Ph. D.
HFD-570, Review Chemist

APPEARS THIS WAY
ON ORIGINAL

Tacrolimus

JUN 17 1998

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-746 **DATE REVIEWED:** June 16, 1998

REVIEW #: 3 **RECOMMEND ACTION:** Approvable

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	July 29, 1996	July 30, 1996	August 15, 1996
AMENDMENT	June 16, 1997	June 17, 1997	June 18, 1997
AMENDMENT	September 16, 1997	September 17, 1997	September 22, 1997
AMENDMENT	September 30, 1997	October 2, 1997	October 6, 1997
AMENDMENT	October 7, 1997	October 8, 1997	October 14, 1997
AMENDMENT	October 15, 1997	October 16, 1997	October 22, 1997
Subject of this review:			
AMENDMENT	February 27, 1998	March 2, 1998	March 10, 1998
AMENDMENT	May 14, 1998	May 18, 1998	May 22, 1998

NAME & ADDRESS OF APPLICANT:
Astra USA
50 Otis Street
Westborough, Massachusetts 01581-4500

DRUG PRODUCT NAME

Proprietary:	Rhinocort Aqua Nasal Spray™
Nonproprietary/Established/:	Budesonide nasal spray (suspension)
Code Name/#:	CAS #51333-22-3
Chem.Type/Ther. Class:	3S
USAN Name:	Budesonide

ANDA Suitability Petition/DESI/Patent Status: Claims eligible for marketing exclusivity under 21 USC 355(c)(3)(D)(ii).

PHARMACOLOGICAL CATEGORY/INDICATION: Seasonal and perennial allergic rhinitis symptoms- adults and children 6 years and older.

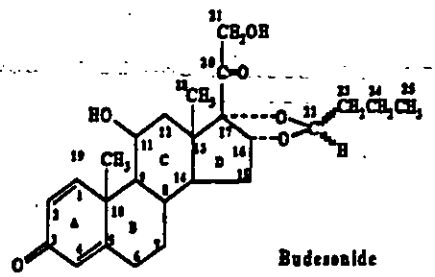
DOSAGE FORM: Nasal Spray suspension

STRENGTHS: 64 µg and 32 µg per spray; 50 µL per actuation. 8.6 g (8.4 mL) for 120 metered sprays each commercial size. [redacted] for [redacted] metered sprays for professional size [redacted] µg); [redacted] metered sprays [redacted]

ROUTE OF ADMINISTRATION: Nasal; 2 sprays per nostril once daily; 128 µg recommended starting dose.

DISPENSED: X Rx ___ OTC

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



Budesonide

SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference
		Type II, Synthesis of starting material	Acceptable	2/13/98	NDA 20-441/S-001
		Starting material (Type II)	Acceptable	4/21/97; chem review by D. Koble	
		Drug substance (Type II)	Acceptable	2/13/98	NDA 20-441/S-001
		Tubular glass for container	Acceptable	2/18/97	DMF review 1 CR #1, p. 12
		Glass bottle manufacturer (type I)	N/A	N/A	Type I DMF not reviewed.
		Glass bottle manufacturer (type III)	Acceptable	2/20/97	DMF review 1 CR #1, p. 12

[redacted]	[redacted]	[redacted]	Inadequate	10/24/97 Open	DMF review #1. Await data
[redacted]	[redacted]	[redacted]	Acceptable	10/20/97	DMF review #1. CR #2, p. 31
[redacted]	[redacted]	[redacted]	Inadequate	10/23/97	DMF review #5. DMF [redacted] review #1
[redacted]	[redacted]	[redacted]	Inadequate	6/16/98	DMF review #1.

RELATED DOCUMENTS :

Type	Number	Owner	Subject
NDA	20-233	Astra USA	Rhinocort Nasal Inhaler (Nasal Aerosol)
NDA	20-441	Astra USA	Pulmicort Turbohaler
IND	[redacted]	Astra USA	Rhinocort Nasal Inhaler (pMDI) and Aqua Nasal Spray
IND		Astra USA	Pulmicort Turbuhaler
IND		Astra USA	[redacted]
IND		Astra USA	
IND		Astra USA	

APPEARS THIS WAY
ON ORIGINAL

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	November 25, 1996	Acceptable 12/20/96	
EER	October 14, 1997	Acceptable 10/16/97	Add testing site
Microbiology, HFD-160	a. February 12, 1997 b. July 11, 1997 c. May 4, 1998	NA 3/7/97 Acceptable 8/14/97 Acceptable 5/28/98	
Biometrics, HFD-710	July 3, 1997	Acceptable 9/3/97	
Methods Validation	None sent		Inadequate information
Labeling & Nomenclature Com.	September 16, 1996	Acceptable 10/18/96	

CONCLUSIONS & RECOMMENDATIONS:
The application as submitted is approvable from the standpoint of chemistry, manufacturing and controls. However, deficiencies as summarized in the attached draft letter to applicant, chemistry portion should be resolved by the applicant before approval of the NDA.

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 20-746
HFD-570/Division File
HFD-570/LNg/5-20-98; 6-16-98
HFD-570/GTrout
HFD-570/GPoochikian
R/D Init by: LS 6/17/98

filename:

/S/

Linda Ng, Ph. D.
HFD-570, Review Chemist

Trout

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA:	20-746	**DATE REVIEWED:**	October 24, 1997
REVIEW #:	2	**RECOMMEND ACTION:**	Approvable

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	July 29, 1996	July 30, 1996	August 15, 1996

Subject of this review:

AMENDMENT	June 16, 1997	June 17, 1997	June 18, 1997
AMENDMENT	September 16, 1997	September 17, 1997	September 22, 1997
AMENDMENT	September 30, 1997	October 2, 1997	October 6, 1997
AMENDMENT	October 7, 1997	October 8, 1997	October 14, 1997
AMENDMENT	October 15, 1997	October 16, 1997	October 22, 1997

NAME & ADDRESS OF APPLICANT: Astra USA
50 Otis Street
Westborough, Massachusetts 01581-4500

DRUG PRODUCT NAME

Proprietary:	Rhinocort Aqua Nasal Spray™
Nonproprietary/Established/:	Budesonide nasal spray (suspension)
Code Name/#:	CAS #51333-22-3
Chem.Type/Ther.Class:	3S
USAN Name:	Budesonide

ANDA Suitability Petition/DESI/Patent Status: Claims eligible for marketing exclusivity under 21 USC 355(c)(3)(D)(ii).

PHARMACOLOGICAL CATEGORY/INDICATION: Seasonal and perennial allergic rhinitis symptoms- adults and children 6 years and older.

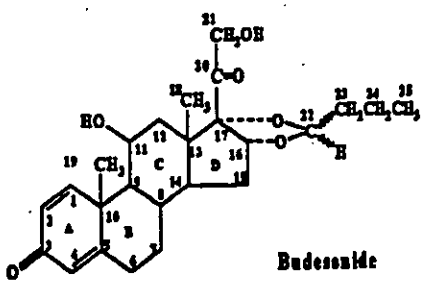
DOSAGE FORM: Nasal Spray suspension

STRENGTHS: 64 µg and 32 µg per spray; 50 µL per actuation.
8.6 g for 120 metered sprays each commercial size.
[redacted] for [redacted] metered sprays for professional size [redacted] µg only);

ROUTE OF ADMINISTRATION: Nasal; 2 sprays per nostril once daily; 256 µg recommended starting dose.

DISPENSED: X Rx ___ OTC

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



Budesonide

SUPPORTING DOCUMENTS:

APPEARS THIS WAY ON ORIGINAL

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference
		Type II, Synthesis of starting material	Inadequate	8/29/97	
		Starting material (Type II)	Acceptable	4/21/97; chem review by D. Koble	
		Drug substance (Type II)	Inadequate	8/29/97	
		Tubular glass for container	Acceptable	2/18/97	DMF review 1 CR #1, p. 12
		Glass bottle manufacturer (type I)	N/A	N/A	Type I DMF not reviewed.
		Glass bottle manufacturer (type III)	Acceptable	2/20/97	DMF review 1 CR #1, p. 12
			Inadequate	10/24/97	DMF review #1. CR #2, item 7.g
			Acceptable	10/20/97	DMF review #1. CR #2, p. 31
			Inadequate	10/23/97	DMF review #5 DMF review #1

RELATED DOCUMENTS :

Type	Number	Owner	Subject
NDA	20-233	Astra USA	Rhinocort Nasal Inhaler (Nasal Aerosol)
NDA	20-441	Astra USA	Pulmicort Turbohaler
IND		Astra USA	Rhinocort Nasal Inhaler (pMDI) and Aqua Nasal Spray
IND		Astra USA	Pulmicort Turbuhaler

IND [redacted] Astra USA
IND Astra USA
IND Astra USA [redacted]

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	November 25, 1996	Acceptable 12/20/96	
EER	October 14, 1997	Acceptable 10/16/97	Add testing site
Microbiology, HFD-160	a. February 12, 1997 b. July 11, 1997	NA 3/7/97 Acceptable 8/14/97	
Biometrics, HFD-710	July 3, 1997	Acceptable 9/3/97	
Methods Validation	None sent		Inadequate information
Labeling & Nomenclature Com.	September 16, 1996	Acceptable 10/18/96	

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is approvable from the standpoint of chemistry, manufacturing and controls. However, deficiencies as summarized in the attached draft letter to applicant, chemistry portion should be resolved by the applicant before approval of the NDA.

cc:
NDA 20-746
HFD-570/Division File
HFD-570/LNg
HFD-570/GTrout
HFD-570/GPoochikian
R/D Init by: LS 10/27/97

filename:

[redacted]
LS1

Linda Ng, Ph. D.
HFD-570, Review Chemist

FEB 28 1997

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 20-746 **DATE REVIEWED:** February 24, 1997

REVIEW #: 1 **RECOMMEND ACTION:** Not approvable

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	July 29, 1996	July 30, 1996	August 15, 1996

NAME & ADDRESS OF APPLICANT: Astra USA
50 Otis Street
Westborough, Massachusetts 01581-4500

DRUG PRODUCT NAME

Proprietary:	Rhinocort Aqua Nasal Spray™
Nonproprietary/Established/:	Budesonide nasal spray (suspension)
Code Name/#:	CAS #51333-22-3
Chem.Type/Ther.Class:	3S
USAN Name:	Budesonide

ANDA Suitability Petition/DESI/Patent Status: Claims eligible for marketing exclusivity under 21 USC 355(c)(3)(D)(ii).

PHARMACOLOGICAL CATEGORY/INDICATION: Seasonal and perennial allergic rhinitis symptoms- adults and children 6 years and older.

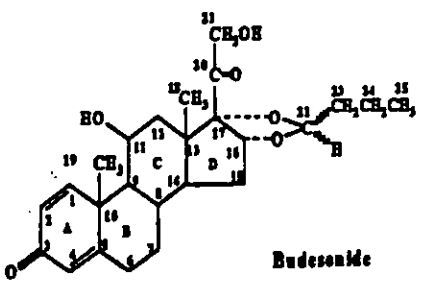
DOSAGE FORM: Nasal Spray suspension

STRENGTHS: 64 µg and 32 µg per spray; 50 µL per actuation. 8.6 g for 120 metered sprays each commercial size. [redacted] for [redacted] metered sprays for professional size [redacted] µg only);

ROUTE OF ADMINISTRATION: Nasal; 2 sprays per nostril once daily; 256 µg recommended starting dose.

DISPENSED: X Rx ___ OTC

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



Budesonide

SUPPORTING DOCUMENTS:

DMF #	Holder Name	Subject	Status	Date Reviewed	Reference
[redacted]	[redacted]	Type II, Synthesis of starting material	Pending	Inadequate 11/17/96; Response being reviewed	
[redacted]		Starting material (Type II)	Pending	Inadequate 4/30/96; Response being reviewed	
[redacted]		Drug substance (Type II)	Pending	Inadequate 10/17/96	
[redacted]		Tubular glass for container	Acceptable	2/18/97	DMF review 1 CR #1, p. 12
[redacted]		Glass bottle manufacturer (type I)	N/A	N/A	Type I DMF not reviewed.
[redacted]		Glass bottle manufacturer (type III)	Acceptable	2/20/97	DMF review 1 CR #1, p. 12
[redacted]	[redacted]	[redacted]	Pending	2/20/97 Letter sent	CR #1, p. 13

RELATED DOCUMENTS :

Type	Number	Owner	Subject
NDA	20-233	Astra USA	Rhinocort Nasal Inhaler (Nasal Aerosol)
NDA	20-441	Astra USA	Pulmicort Turbohaler
IND	[redacted]	Astra USA	Rhinocort Nasal Inhaler (pMDI) and Aqua Nasal Spray
IND		Astra USA	Pulmicort Turbuhaler
IND		Astra USA	[redacted]
IND		Astra USA	
IND		Astra USA	

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	November 25, 1996	Acceptable 12/20/96	
Microbiology, HFD-160	February 12, 1997	Pending	
Biometrics, HFD-710	None sent		Inadequate information
Labeling & Nomenclature Com.	September 16, 1996	Pending	

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not acceptable from the standpoint of chemistry, manufacturing and controls. Deficiencies as summarized in the attached draft letter to applicant, chemistry portion should be forwarded to the applicant.

cc:
NDA 20-746
HFD-570/Division File
HFD-570/LNg; 2/14/97; revised 2/28/97
HFD-570/GTrout
HFD-570/GPoochikian
R/D Init by: LS 2/28/97

filename:

/S/

Linda Ng, Ph. D.
HFD-570, Review Chemist

APPEARS THIS WAY
ON ORIGINAL