CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-929

CHEMISTRY REVIEW(S)

NDA #: 20-929 **CHEM. REVIEW #**: 3 **REVIEW DATE**: August 7, 2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	18-NOV-97	20-NOV-97	03-DEC-97
Amendment[BZ]	15-JAN-98	16-JAN-98	21-JAN-98
Amendment[BC]	12-MAY-98	13-MAY-98	19-MAY-98
Amendment[AZ]	07-AUG-98	11-AUG-98	12-AUG-98
Amendment[BC]	30-NOV-98	01-DEC-98	08-DEC-98
Amendment[BC]*	06-MAY-99	07-MAY-99	11-MAY-99
Amendment[AZ]*	09-FEB-00	10-FEB-00	15-FEB-00
Amendment[BC]*	09-JUN-00	09-JUN-00	13-JUN-00
Amendment[BZ]*	10-JUL-00	11-JUL-00	11-JUL-00
Amendment[BC]*	25-JUL-00	26-JUL-00	26-JUL-00
Amendment[BC]*	01-AUG-00	01-AUG-00	01-AUG-00
Amendment[BZ]*	03-AUG-00	04-AUG-00	04-AUG-00
Amendment[BL]*	04-AUG-00	04-AUG-00	04-AUG-00
Amendment[BC]*	04-AUG-00	07-AUG-00	07-AUG-00
Amendment[BC]*	07-AUG-00	07-AUG-00	07-AUG-00

*Subjects of this review.

NAME AND ADDRESS OF APPLICANT:

AstraZeneca LP
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

DRUG PRODUCT NAME:

Proprietary: Pulmicort Respules™
Nonproprietary/USAN: Budesonide Inhalation Suspension
Code Name/#:
Chem.Type/Ther. Class: 1P
Established Name of Drug Substance: [redacted]

PHARMACOL.CATEGORY/INDICATION: Maintenance treatment of asthma and prophylactic therapy in children aged [redacted] to 8 years.

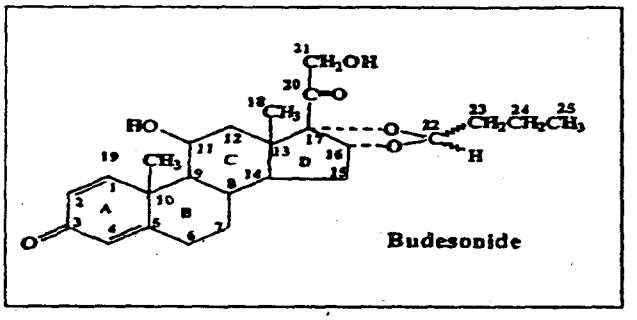
DOSAGE FORM: Inhalation suspension

STRENGTHS: [redacted] 0.25, and 0.5 mg/mL. The suspension is provided in [redacted] ampules, each containing 2 [redacted] mL. A strip of five single dose units is packed into an aluminum foil envelope.

ROUTE OF ADMINISTRATION: Oral Inhalation

Rx/OTC: Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



SUPPORTING DOCUMENTS:
DMFs:

DMF #	Holder	Subject	Date Reviewed	Status	Referenced Section in the NDA
		Type II;	2/11/98 (by Dr. Ng)	Adequate	
		Type II;	1/16/98 (by Dr. Ng)	Adequate	
		Type II;	1/16/98 (by Dr. Ng)	Adequate	
		Type II;	4/21/97(by Dr. Koble)	Adequate	
		Type II;	2/11/98(by Dr. Ng)	Adequate	
		Type III;	7/18/00	Inadequate ***Note 1***	
		Type III;	3/1/00	Inadequate ***Note 2***	
			7/27/00	Adequate	
		Type III	10/2/97&	Adequate	

& Reviewed by Dr. Srinivasachar for supporting NDA 20-755 (Cavaject Injection).

Note 1. Amendment dated May 16, 2000 was reviewed and an IR letter was sent.

Note 2. This DMF has been withdrawn (amendment dated July 25, 2000).

RELATED DOCUMENTS:

IND 44,535: Pulmicort; Budesonide Nebulizing Suspension
NDA 20-233: Rhinocort Nasal Inhaler
NDA 20-244: Pulmicort Turbuhaler
NDA 20-746: Rhinocort Aqua Nasal Spray

CONSULTS:

1. Categorical exclusion of EA is acceptable; FDA's approval of the application increases the use of the active moiety , but the Expected Introduction Concentration of budesonide for all budesonide products at the point of entry into the aquatic environment will be far below than 1 ppb level.

2. FUR was submitted on February 16, 2000 for the facilities:

   a). [redacted]

   b). [redacted]

   c). [redacted]

   d). Astra Production Chemicals AB, Soedertalje, Sweden (CFN#9610565); Astra Production Chemicals for micronization.

   e). Astra USA, Inc., 50 Otis Street, Westborough, MA 01581 (CFN#9610565); manufacturing and packaging of the drug product.

   f). [redacted]

   g). [redacted]

   All facilities are acceptable as of July 18, 2000.

3. Applicant has provided [redacted] stability data of [redacted] batches. An expiration dating period of [redacted] was requested based on the stability data of the [redacted] Pulmicort Respules manufactured in Sweden. Data for [redacted] storage at 25°C/60% RH and [redacted] accelerated storage at 40°C/30% RH were provided (page 61, Vol. 1.6). Statistical analysis consult was not requested because all the quantitative values did not indicate any trend to subject to statistical analysis.

4. Microbiology Review of the amendment dated May 12, 1998 is concluded approval (microbiology review dated September 15, 1998).

REMARKS/COMMENTS:

1. Methods validation will be requested ON August 8, 2000.

2. Since there was some difficulty in [redacted]

[redacted] of storage, it is recommended that Pulmicort Respules be stored upright.

3. Pulmicort Respules must be stored protected from light. Pulmicort respules should be stored in the aluminum foil envelope until use.

4. It is stated that all samples, after [redacted] did not meet the appearance test criteria [redacted]. Therefore, the product will be labeled "Do Not Freeze".

5. Applicant has reported that a [redacted] in the labeled dose for lowest strength (0.25 mg) was observed; the source of this [redacted] is related to [redacted] **Applicant has [redacted] and conducted a [redacted] stability study with new Respule design.**

6. Pharm/Tox consult for [redacted] was requested on July 27, 2000. However, Pharm/Tox evaluation was deferred pending completion of the on-going studies to further refine the [redacted] assays and submission of pertinent data by October 12, 2000.

CONCLUSION AND RECOMMENDATION:

The NDA is approvable from CMC standpoints. Applicant should be reminded of their Phase 4 commitments.

/S/

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc: Orig. NDA #20-929
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/MPrucker
HFD-570/JSun
HFD-570/GTrou
R/D Init. by: /S/

doc: NDA 20-929.CR3f

74 Page(s) Withheld

JAN 2 0 1999

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-929 **CHEM. REVIEW #**: 2 **REVIEW DATE**: January 19, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	18-NOV-97	20-NOV-97	03-DEC-97
Amendment[BZ]	15-JAN-98	16-JAN-98	21-JAN-98
Amendment[BC]*	12-MAY-98	13-MAY-98	19-MAY-98
Amendment[AZ]*	07-AUG-98	11-AUG-98	12-AUG-98
Amendment[BC]*	30-NOV-98	01-DEC-98	08-DEC-98

*Subjects of this review.

NAME AND ADDRESS OF APPLICANT:

Astra USA, Inc.
50 Otis Street
Westborough, MA 01581-4500

DRUG PRODUCT NAME:

Proprietary: Pulmicort Respules™
Nonproprietary/USAN: Budesonide Inhalation Suspension
Code Name/#:
Chem.Type/Ther. Class: 1P
Established Name of Drug Substance: [redacted]

PHARMACOL.CATEGORY/INDICATION: Maintenance treatment of asthma and prophylactic therapy in children aged [redacted] to 8 years.

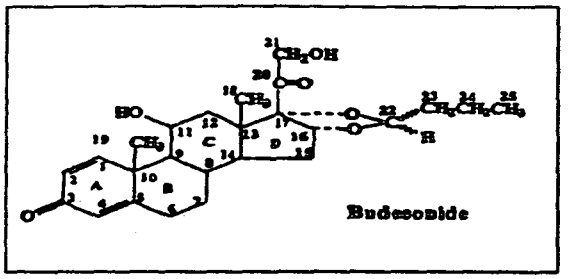
DOSAGE FORM: Inhalation suspension

STRENGTHS: [redacted] 0.25, and 0.5 mg/mL. The suspension is provided in [redacted] ampules, each containing 2. [redacted] mL. A strip of five single dose units is packed into an aluminum foil envelope.

ROUTE OF ADMINISTRATION: Oral Inhalation

Rx/OTC: Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



SUPPORTING DOCUMENTS:
DMFs:

DMF #	Holder	Subject	Date Reviewed	Status	Referenced Section in the NDA
		Type II;	2/11/98 (by Dr. Ng)	Adequate	
		Type II;	1/16/98 (by Dr. Ng)	Adequate	
		Type II;	1/16/98 (by Dr. Ng)	Adequate	
		Type II;	4/21/97(by Dr. Koble)	Adequate	
		Type II;	2/11/98(by Dr. Ng)	Adequate	
		Type III	10/2/97&	Adequate	

& Reviewed by Dr. Srinivasachar for supporting NDA 20-755 (Cavaject Injection).

RELATED DOCUMENTS:
IND 44,535: Pulmicort; Budesonide Nebulizing Suspension
NDA 20-233: Rhinocort Nasal Inhaler
NDA 20-244: Pulmicort Turbuhaler
NDA 20-746: Rhinocort Aqua Nasal Spray

CONSULTS:

1. Categorical exclusion of EA is acceptable; FDA's approval of the application increases the use of the active moiety , but the Expected Introduction Concentration of budesonide for all budesonide products at the point of entry into the aquatic environment will be far below than 1 ppb level.

2. FUR was submitted on September 1, 1998 for the facilities:

   a). _____

   b). _____

c). [redacted]

d). Astra Production Chemicals AB, Soedertalje, Sweden; Astra Production Chemicals for micronization.

e). Astra USA, Inc., 50 Otis Street, Westborough, MA 01581; manufacturing and packaging of the drug product.

f). [redacted]

g). [redacted]

h). [redacted]

All facilities except [redacted] and [redacted] are acceptable as of October 7, 1998.

3. Applicant has provided [redacted] stability data of [redacted] batches. An expiration dating period of [redacted] was requested based on the stability data of the [redacted] Pulmicort Respules manufactured in Sweden. Data for [redacted] storage at 25°C/60% RH and [redacted] accelerated storage at 40°C/30% RH were provided (page 61, Vol. 1.6). Statistical analysis consult was not requested because all the quantitative values did not indicate any trend to subject to statistical analysis. However, the applicant reported that under certain conditions, [redacted] This aspect will be discussed with applicant in a separate meeting.

4. Microbiology Review of the amendment dated May 12, 1998 is concluded approval (microbiology review dated September 15, 1998).

REMARKS/COMMENTS:

1. Methods validation by the Agency should be deferred pending resolution of deficiencies in the methods as requested.

2. Since there was [redacted] of storage, it is recommended that Pulmicort Respules be stored upright.

3. Pulmicort Respules must be stored protected from light. Pulmicort respules should be stored in the aluminum foil

envelope until use.

4. It is stated that all samples, [redacted] did not meet the appearance test criteria [redacted]. Therefore, the product will be labeled "Do Not Freeze".

5. Applicant has reported that a [redacted] in the labeled dose for lowest strength (0.25 mg) was observed; the source of this [redacted] is related to [redacted] Investigation is ongoing and a complete technical package is said to be available in December. (Fax dated November 4, 1998).

CONCLUSION AND RECOMMENDATION:

The NDA is not approvable from CMC standpoints. Project manager should convey the CMC comments on page 20 to the applicant.

N.N. EER for two sites listed above under consult 2.g) and h) are currently pending.

/S/

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc: Orig. NDA #20-929
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/SChu
HFD-570/MVogel
HFD-570/GTrout
R/D Init. by: /S/

doc: NDA 20-929.CR2

33 Page(s) Withheld

APR 7 1998

Division of Pulmonary Drug Products

Review of Chemistry, Manufacturing and Controls

NDA #: 20-929 **CHEM. REVIEW #**: 1 **REVIEW DATE**: April 06, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original*	18-NOV-97	20-NOV-97	03-DEC-97
Amendment[BZ]*	15-JAN-98	16-JAN-98	21-JAN-98

*Sujects of this review.

NAME AND ADDRESS OF APPLICANT:

Astra USA, Inc.
50 Otis Street
Westborough, MA 01581-4500

DRUG PRODUCT NAME:

Proprietary: Pulmicort Respules™
Nonproprietary/USAN: Budesonide Inhalation Suspension
Code Name/#: -
Chem. Type/Ther. Class: 1P
Established Name of Druc Substance: [redacted]

PHARMACOL. CATEGORY/INDICATION: Maintenance treatment of asthma and prophylactic therapy in children aged [redacted] to 8 years.

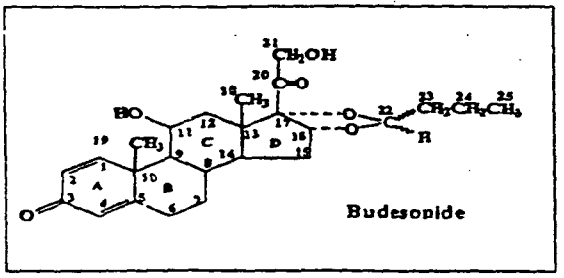
DOSAGE FORM: Inhalation suspension

STRENGTHS: [redacted] 0.25, and 0.5 mg/mL. The suspension is provided in [redacted] ampules, each containing 2 [redacted] mL. A strip of five single dose units is packed into an aluminum foil envelope.

ROUTE OF ADMINISTRATION: Oral Inhalation

Rx/OTC: Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



SUPPORTING DOCUMENTS:

DMFs:

DMF #	Holder	Subject	Status	Date Reviewed	Referenced Section in the NDA
		Type II;	adequate	2/11/98 (by Dr. Ng)	
		Type II;	adequate	1/16/98 (by Dr. Ng)	
		Type II;	adequate	½0/98 (by Dr. Ng)	
		Type II;	adequate	4/21/97 (by Dr. Koble)	
		Type II;	adequate	2/11/98 (by Dr. Ng)	
		Type III	adequate	10/2/97	

& Reviewed by Dr. Srinivasachar for supporting NDA 20-755 (Cavaject Injection).

RELATED DOCUMENTS:

IND 44,535: Pulmicort; Budesonide Nebulizing Suspension
NDA 20-233: Rhinocort Nasal Inhaler
NDA 20-244: Pulmicort Turbuhaler
NDA 20-746: Rhinocort Aqua Nasal Spray

CONSULTS:

1. Labeling and Nomenclature Committee was consulted and found the proposed trade mark acceptable. However, the Committee ruled that the established name should be "budesonide inhalation suspension" (3/5/98).

2. Applicant has submitted a categorical exclusion based on the fact that the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion. However, actual calculation which should include all the budesonide containing products are not provided.

3. EER request was submitted on January 13, 1998 for the facilities;

[redacted]; Astra Production Chemicals AB, Soedertalje, Sweden; Astra Production Chemicals for micronization. The drug products will be manufactured and packaged at Astra USA, Inc., 50 Otis Street, Westborough, MA 01581. The contract testing facility ([redacted] for the [redacted] USP also requested for inspection. The EER is pending.

4. Biometrics consult was not requested for the following reasons: Applicant has requested [redacted] expiration dating period(25°C/60% RH) and actual data for [redacted] storage at 25°C/60% RH and [redacted] accelerated storage at 40°C/30% RH for [redacted] Pulmicort are provided. Although only [redacted] data of primary stability (25°C/40%RH and 40°C/15%RH) are available, evaluation of the supporting stability data suggests no particular trends in pH, assay, and impurities; pH drops in [redacted], and remains steady for [redacted] Impurities are barely quantifiable until [redacted] and picks up a little bit at [redacted]

5. Microbiology Review dated March 16, 1998 indicates that the application is approvable. However, "Microbiology Deficiencies and Comments" will be conveyed to the applicant.

REMARKS/COMMENTS:

1. Methods validation by the Agency should be deferred pending resolution of deficiencies in the methods as requested.

2. Since there was [redacted] of storage, it is recommended that Pulmicort Respules be stored upright.

3. Pulmicort Respules must be stored protected from light. Pulmicort respules should be stored in the aluminum foil envelope until use.

4. Polysorbate issue, its suitability at the intended concentration for inhalation use is under pharm/tox review.

CONCLUSION AND RECOMMENDATION:
The NDA is not approvable from CMC standpoints. CMC deficiencies as well as microbiology comments should be conveyed to the applicant.

/S/

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc: Orig. NDA #20-929
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/SChu
HFD-570/MVogel
HFD-570/GTrol
R/D Init. by: [illegible]
doc: NDA 20-929.CR1

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