CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-271

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-271

FIRM: Zenith Goldline Pharmaceuticals
Attention: Jason A. Gross
140 Legrand Avenue
Northvale, NJ 07647
Tel# (210) 767-1700.
FAX# (800) 631-1583

US authorized agent for:
Steripak Limited, UK
(wholly owned subsidiaries of *IVAX Corp*)

DOSAGE FORM: Inhalation Solution

STREGHTH: 1.0%

DRUG: Cromolyn Sodium

CGMP STATEMENT/EIR UPDATED STATUS: The EER is acceptable for all firms listed as per the EER Summary report dated 11/19/99.

Manufacturing and processing will be performed at:

Steripak Ltd.
4 Pembroke Court Manor Park
Runcorn, Cheshire, U.K.

Packaging and labeling and testing of the referenced drug product will be performed at:

Steripak Ltd.
Goddard Road Astmoor Ind. Es.
Runcorn, Cheshire, U.K.

Manufacturer of the bulk Drug Substance (BDS) DMF

as been added as a contract packager to perform the pouching operation at their facility at:

The following contract laboratories are utilized:

td.

Steripak states they **do not** use services of any contract laboratories in the manufacturing, processing, or labeling.

BIOEQUIVALENCY STATUS: The firm requested a waiver from performing a bioavailability / bioequivalence study due to the quantitative and qualitative similarity of their product with solution (Cromolyn Sodium Inhalation Solution USP) 1%. The Division of Bioequivalence had no further questions after the 4/2/98 sign-off review.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Method validation by the District Laboratory is not required for the approval of the application. The drug substance and drug product are USP. The Phila. D.O. performed verification testing on the drug product and no problems were encountered (refer to the report dated 3/18/98 in Vol. 1.1 of the ANDA).

Steripak provided information and data to support an in-house Method for the determination of impurities and degradants in the drug product. The Method is applicable for release and stability testing. Validation of the method was performed and was found adequate (accuracy, precision, recovery, resolution, linearity, specificity, limit of Quantitation and ruggedness over the stability period were performed). The information is satisfactory.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? The Drug Product (Cromolyn Sodium Inhalation Solution, 10 mg/mL) will be packaged in 3.5 mL containers (strips of 5) with a fill volume of mL. The container is manufactured in from polymer. Strips of 5 ampoules will be placed into a foil pouch

consisting of

with

as the contact surface. The foil pouch contact surface is the same resin as the ampoule).

The foil overwrap demonstrated to be adequate to protect, while not contaminate, the drug product, was not utilized with the exhibit batches. The above-described c/c system will be utilized for production batches.

LABELING: SATISFACTORY. Labeling was found satisfactory as per the 12/22/99 labeling approval summary of Theresa Watkins (see Vol. 4.1).

STERILIZATION VALIDATION (IF APPLICABLE): Acceptable. The drug product is aseptically filled utilizing The product was recommended for approval on the basis of sterility assurance on consult to ONDC Microbiology Staff (Paul Stinavage, Ph.D.) on 12/21/99.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
An exhibit batch #7B3001 of (theoretical yield of ampules) was manufactured on 10/7/97. The entire bulk batch was filled into ampoules. The exhibit batch production records were submitted (refer to Vol. 1.2, pp. 259-410 of the Original 12/11/97 ANDA submission. Steripak also submitted a blank batch record for a proposed production batch.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS exhibit batch manufactured to support this application was made from the same process as the proposed production batches. A exhibit batch was utilized for the stability studies. A proposed production batch size will be utilized.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?: The proposed production batches will be manufactured utilizing the same manufacturing process as the exhibit batch.

Endorsements:
HFD-625/K.Furnkranz/1-5-99
HFD-625/M.Smela/1-5-00 M Smela 1/7/00
V:\firmsam\steripak\ltrs&rev\75271appsum.fkf.doc
F/T by: bc/1-6-00
Approve

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 75271/000**
Priority:
Org Code: **600**
Stamp: **15-DEC-1997** Regulatory Due:
Action Goal:
District Goal: **15-FEB-1999**
Applicant: **STERIPAK**
GODDARD RD, ASTMOOR, RUNCORI
CHESIRE, ENGLAND, UK
Brand Name:
Established Name: **CROMOLYN SODIUM**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **10 MG/ML**

FDA Contacts:

M. DILLAHUNT	**(HFD-613)**	**301-827-5846**	**, Project Manager**
K. FURNKRANZ	**(HFD-625)**	**301-827-5848**	**, Review Chemist**
M. SMELA JR	**(HFD-625)**	**301-827-5848**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 19-NOV-1999 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 03-NOV-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 03-NOV-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 02-JUN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE STERILITY TESTER**

Establishment:
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:
DMF No:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment: **9617051**
STERIPAK LTD
4 PEMBROKE COURT MANOR PARK
RUNCORN, CHESHIRE, UK
DMF No:
AADA No:

Profile: **SNI** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE PACKAGER**

Establishment: **9617052**
STERIPAK LTD
GODDARD ROAD ASTMOOR IND EST
RUNCORN, CHESHIRE, UK WA7 1TG
DMF No:
AADA No:

Profile: **SNI** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:
DMF No:
AADA No:

Profile: **SNI** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE PACKAGER**

E L E C T R O N I C M A I L M E S S A G E

Date: 15-Dec-1999 01:45pm EST
From: Michael Smela
SMELA
Dept: HFD-625 MPN2 E236
Tel No: 301-827-5848 FAX 301-594-0180

TO: Michelle Dillahunt (DILLAHUNTM)

CC: Kenneth Furnkranz (FURNKRANZ)
CC: Teresa Watkins (WATKINST)

Subject: ANDA 75271

Michelle..

I am closing chemistry for this Steripak cromolyn ANDA. CMC, Bio and EER are OK.

Micro review of the 7/29/99 amendment is pending.

Submission of revised labeling is pending with the applicant which they promise to submit soon.

. se add this to the approvals matrix. Perhaps, you should call them also and advise them that they need to submit the labeling ASAP.

Thanks....Mike

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75271/000**
Priority:
Org Code: **600**
Stamp: **15-DEC-1997** Regulatory Due:
Action Goal:
District Goal: **15-FEB-1999**
Applicant: **STERIPAK**
GODDARD RD, ASTMOOR, RUNCORI
CHESIRE, ENGLAND, UK
Brand Name:
Established Name: **CROMOLYN SODIUM**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **10 MG/ML**

FDA Contacts: **ID = 122344** **, Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-NOV-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 03-NOV-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 02-JUN-1998 by M. FGAS (HFD-322) 301-594-0095

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE STERILITY TESTER**

Establishment:
L SRL
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **9617051**
STERIPAK LTD
4 PEMBROKE COURT MANOR PARK
RUNCORN, CHESHIRE, UK

DMF No:
AADA No:

Profile: **SNI** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**

Establishment: **9617052**
STERIPAK LTD
GODDARD ROAD ASTMOOR IND EST
RUNCORN, CHESHIRE, UK WA7 1TG

DMF No:
AADA No:

Profile: **SNI** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-271** Date of Submission: **December 30, 1998**

Applicant's Name: **Steripak Limited**

Established Name: **Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL**

Labeling Deficiencies:

1. UNIT DOSE CONTAINER (2 mL)

   Satisfactory in final.

2. UNIT DOSE CARTON (60 x 2 mL and 120 x 2 mL)

   Satisfactory in final.

4. PHYSICIAN'S INSERT

   a. TITLE

      We encourage the inclusion of "Rx only" in this section.

   b. PRECAUTIONS

      i. Information for Patients - Include the following to appear as the third paragraph of this subsection:

         Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

c. OVERDOSAGE

i. Revise the second sentence of this section to read as follows:

…demonstrated an extremely low order of toxicity for cromolyn sodium, regardless…

ii. Revise the third sentence of this section to read as follows:

…demonstrated an LD_{50} in the region of 4000 mg/kg.

iii. Revise the fifth sentence of this section to read as follows:

…was 8000 mg/kg, and at this dose level no deaths occurred.

d. HOW SUPPLIED

Revise your net statement of quantity to read as follows:

60 vials per carton. (NDC 0172-6406-49).
120 vials per carton. (NDC 0172-6406-59).

5. PATIENT INSERT

a. CARE AND STORAGE

i. Include the following to appear as the last sentence of paragraph one of this section:

Keep out of the reach of children.

b. INSTRUCTIONS FOR THE USE OF CROMOLYN SODIUM INHALATION SOLUTION USP.

i. **BOLD** the following:

For best results, follow these instructions exactly and observe Care and Storage directions.

Please revise your physician's insert and patient insert labeling, as instructed above, and submit 12 copies of final printed physician's insert and patient insert labeling. Keep in mind that for insert labeling to be considered as final print, it must be one contiguous document, printed both front and back.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

John L. Gray for/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-271** Date of Submission: **December 11, 1997**

Applicant's Name: **Steripak Limited**

Established Name: **Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL**

Labeling Deficiencies:

1. UNIT DOSE CONTAINER

   a. Delete "1.0%" from the expression of strength.

   b. Include the following statement:

      FOR ORAL INHALATION USE ONLY

2. UNIT DOSE CARTON (30 x 2 mL and 60 x 2 mL)

   a. See comment b under UNIT DOSE CONTAINER.

   b. Replace the "Caution: Federal law..." statement with "℞ only". See section 126 of the FDA Modernization Act of 1997.

   c. Revise the "Usual Dosage" statement to read as follows:

      Read accompanying insert.

   d. Revise to read "PROTECT FROM LIGHT."

4. INSERT

   I. PROFESSIONAL INSERT

   a. GENERAL COMMENT

      When referring to the established name throughout the text of the insert, revise to read "cromolyn sodium" rather than "cromolyn sodium inhalation solution" except where noted below:

i. DESCRIPTION - Utilize "cromolyn sodium inhalation solution" in the first sentence of the first paragraph.

ii. INDICATIONS AND USAGE - Utilize "Cromolyn sodium inhalation solution" in the first paragraph and first sentence of paragraph two.

iii. CONTRAINDICATIONS and WARNINGS (First paragraph).

iv. DOSAGE AND ADMINISTRATION

b. TITLE

Delete "Aqueous Solution for Nebulization" from the title.

c. DESCRIPTION

i. Revise the chemical name to be in accord with the second name listed in USP 23.

ii. Revise to read "molecular formula" rather than "empirical formula".

iii. Revise to read "structural formula" rather than "molecular structure".

iv. Revise to read as follows:

Each 2 mL vial for oral inhalation use only contains 20 mg cromolyn sodium in...

d. CLINICAL PHARMACOLOGY

Last paragraph - Delete the comma that follows exhaled in the last sentence.

e. INDICATIONS AND USAGE

Revise the last sentence of paragraph two to read as follows:

...cromolyn sodium is usually...

f. WARNINGS

Insert the following text as the last paragraph of this section:

Anaphylactic reactions with cromolyn sodium administration have been reported rarely.

g. PRECAUTIONS

i. Information for Patients - Insert the following text as the last paragraph:

For additional information, see the accompanying leaflet entitled Living a Full life with Asthma.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

Delete "and" from this subsection heading and revise to read as follows:

Long-term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg three days per week), hamsters (intraperitoneal administration at doses up to 53 mg/kg three days per week for 15 weeks followed by 17.5 mg/kg three days per week for 37 weeks), and rats (18 months subcutaneous treatment at doses up to 75 mg/kg six days per week) showed no neoplastic effects. These doses correspond to approximately 1, 0.3, and 2 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis.

Cromolyn sodium showed no mutagenic potential in Ames Salmonella/microsome plate assays, mitotic gene conversion in *Saccharomyces cerevisiae* and an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day in males and 100 mg/kg/day in females. These doses are approximately 18 and 10 times, respectively, the maximum recommended adult human daily

inhalation dose on a mg/m^2 basis.

iii. Pregnancy

A) Revise the subsection heading to read "Pregnancy: Teratogenic Effects, Pregnancy Category B".

B) Revise the subsection to read as follows:

...administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg and 164 mg/kg, respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg produced no evidence of fetal malformations. These doses represent approximately 27, 17, and 98 times, respectively, the maximum recommended adult human daily inhalation dose on a mg/m^2 basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

iv. Drug Interaction During Pregnancy - Revise to read as follows:

...sodium alone in doses up to 540 mg/kg (approximately 27 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (approximately 7 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) increased both resorptions and malformations. The addition of cromolyn sodium to isoproterenol appears to have increased the incidence of both resorptions and malformations.

h. OVERDOSAGE

Revise to read as follows:

...demonstrated that toxicity with cromolyn sodium occurs only with very high exposure levels, regardless of whether administration was parenteral, oral or by inhalation. Parenteral administration in mice, rats, guinea pigs, hamsters, and rabbits demonstrated median lethal dose of approximately 4000 mg/kg. Intravenous administration in monkeys also indicated a similar pattern of toxicity. The highest dose administered by the oral route in rats and mice was 8000 mg/kg, (approximately 261 and 130 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis) and at this dose level no deaths occurred. By inhalation, even in long term studies, it proved impossible to achieve toxic dose levels of cromolyn sodium in a range of mammalian species.

i. DOSAGE AND ADMINISTRATION

i. Paragraph one - Replace "children" with "pediatric patients".

ii. Insert the following text as the second paragraph:

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

iii. Insert the following text as the last paragraph:

For additional information, see the accompanying leaflet entitled Living a Full Life with Asthma".

j. HOW SUPPLIED

i. To be in accord with your finished dosage specifications, revise to read "colorless to pale yellow solution".

ii. Revise to read "Protect from light".

iii. Replace the "Caution: Federal law..." statement with the "Rx only". See section 126 of the FDA Modernization Act of 1997.

k. Delete the "Patient's Instructions for Use". This does not appear in the approved labeling of the reference listed drug.

II. PATIENT INSERT

a. GENERAL COMMENT

i. How many patient leaflets are provided in each carton?

ii. Include the illustrations as seen in the approved labeling of the listed drug.

b. ASTHMA MEDICINES, Preventive Medicine - Delete "USP" from the second sentence.

c. HOW TO TAKE CROMOLYN SODIUM

Delete the last sentence.

d. INSTRUCTIONS FOR THE USE OF CROMOLYN SODIUM INHALATION SOLUTION

i. Method of Administration - Delete "USP" from the first sentence and insert the following text as the last paragraph:

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

ii. Inhalation - Revise to read "ten" rather than "fifteen" in the last sentence.

iii. Include the illustrated use of the product as seen in the approved labeling of the listed drug.

Please revise your unit-dose labels, carton and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Cromolyn Sodium Inhalation Solution USP	Zenith Goldline
1%	Northvale, NJ
ANDA #75-271	Submission date: 12/11/1997
Reviewer: Moo Park	
Filename: 75271w.d97	

Review of a Waiver Request

I. Objective

Review of Zenith Goldline's waiver request for its Cromolyn Sodium Inhalation Solution USP, 1%. Reference listed product is Fisons's Intal[R] Nebulizer Solution (Cromolyn Sodium Inhalation Solution USP), 1%.

II. Comments

1. Cromolyn Sodium Inhalation Solution USP, 1%, is a sterile solution for inhalation from a nebulizer. The formulations for Zenith Goldline's test product and Fisons's reference product are compared in Table 1. The formulations are identical.

Table 1. Formulation Comparison

Ingredient	Zenith Goldline's Test,	Fisons's reference,
Cromolyn Sodium USP	20 mg	20 mg
Water for Injection	2.0 mL	2.0 mL

2. Waiver is granted.

III. Deficiency

None.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Zenith Goldline demonstrates that Cromolyn Sodium Inhalation Solution USP, 1%, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Fisons's Intal[R] Nebulizer Solution (Cromolyn Sodium Inhalation Solution USP), 1%.

The firm should be informed of the recommendation.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED MMAKARY
FT INITIALED MMAKARY

Concur: Dale P. Conner Date: 4/2/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-271** Date of Submission: **December 11, 1997**

Applicant's Name: **Steripak Limited**

Established Name: **Cromolyn Sodium Inhalation Solution USP, 20 mg/2 mL**

Labeling Deficiencies:

1. UNIT DOSE CONTAINER

   a. Delete "1.0%" from the expression of strength.

   b. Include the following statement:

      FOR ORAL INHALATION USE ONLY

2. UNIT DOSE CARTON (30 x 2 mL and 60 x 2 mL)

   a. See comment b under UNIT DOSE CONTAINER.

   b. Replace the "Caution: Federal law..." statement with "℞ only". See section 126 of the FDA Modernization Act of 1997.

   c. Revise the "Usual Dosage" statement to read as follows:

      Read accompanying insert.

   d. Revise to read "PROTECT FROM LIGHT."

4. INSERT

   I. PROFESSIONAL INSERT

   a. GENERAL COMMENT

      When referring to the established name throughout the text of the insert, revise to read "cromolyn sodium" rather than "cromolyn sodium inhalation solution" except where noted below:

i. DESCRIPTION - Utilize "cromolyn sodium inhalation solution" in the first sentence of the first paragraph.

ii. INDICATIONS AND USAGE - Utilize "Cromolyn sodium inhalation solution" in the first paragraph and first sentence of paragraph two.

iii. CONTRAINDICATIONS and WARNINGS (First paragraph).

iv. DOSAGE AND ADMINISTRATION

b. TITLE

Delete "Aqueous Solution for Nebulization" from the title.

c. DESCRIPTION

i. Revise the chemical name to be in accord with the second name listed in USP 23.

ii. Revise to read "molecular formula" rather than "empirical formula".

iii. Revise to read "structural formula" rather than "molecular structure".

iv. Revise to read as follows:

Each 2 mL vial for oral inhalation use only contains 20 mg cromolyn sodium in...

d. CLINICAL PHARMACOLOGY

Last paragraph - Delete the comma that follows exhaled in the last sentence.

e. INDICATIONS AND USAGE

Revise the last sentence of paragraph two to read as follows:

...cromolyn sodium is usually...

f. WARNINGS

Insert the following text as the last paragraph of this section:

Anaphylactic reactions with cromolyn sodium administration have been reported rarely.

g. PRECAUTIONS

i. Information for Patients - Insert the following text as the last paragraph:

For additional information, see the accompanying leaflet entitled Living a Full life with Asthma.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

Delete "and" from this subsection heading and revise to read as follows:

Long-term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg three days per week), hamsters (intraperitoneal administration at doses up to 53 mg/kg three days per week for 15 weeks followed by 17.5 mg/kg three days per week for 37 weeks), and rats (18 months subcutaneous treatment at doses up to 75 mg/kg six days per week) showed no neoplastic effects. These doses correspond to approximately 1, 0.3, and 2 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis.

Cromolyn sodium showed no mutagenic potential in Ames Salmonella/microsome plate assays, mitotic gene conversion in *Saccharomyces cerevisiae* and an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day in males and 100 mg/kg/day in females. These doses are approximately 18 and 10 times, respectively, the maximum recommended adult human daily

inhalation dose on a mg/m^2 basis.

iii. Pregnancy

A) Revise the subsection heading to read "Pregnancy: Teratogenic Effects, Pregnancy Category B".

B) Revise the subsection to read as follows:

...administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg and 164 mg/kg, respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg produced no evidence of fetal malformations. These doses represent approximately 27, 17, and 98 times, respectively, the maximum recommended adult human daily inhalation dose on a mg/m^2 basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

iv. Drug Interaction During Pregnancy - Revise to read as follows:

...sodium alone in doses up to 540 mg/kg (approximately 27 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (approximately 7 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) increased both resorptions and malformations. The addition of cromolyn sodium to isoproterenol appears to have increased the incidence of both resorptions and malformations.

h. OVERDOSAGE

Revise to read as follows:

...demonstrated that toxicity with cromolyn sodium occurs only with very high exposure levels, regardless of whether administration was parenteral, oral or by inhalation. Parenteral administration in mice, rats, guinea pigs, hamsters, and rabbits demonstrated median lethal dose of approximately 4000 mg/kg. Intravenous administration in monkeys also indicated a similar pattern of toxicity. The highest dose administered by the oral route in rats and mice was 8000 mg/kg, (approximately 261 and 130 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis) and at this dose level no deaths occurred. By inhalation, even in long term studies, it proved impossible to achieve toxic dose levels of cromolyn sodium in a range of mammalian species.

i. DOSAGE AND ADMINISTRATION

i. Paragraph one - Replace "children" with "pediatric patients".

ii. Insert the following text as the second paragraph:

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

iii. Insert the following text as the last paragraph:

For additional information, see the accompanying leaflet entitled Living a Full Life with Asthma".

j. HOW SUPPLIED

i. To be in accord with your finished dosage specifications, revise to read "colorless to pale yellow solution".

ii. Revise to read "Protect from light".

iii. Replace the "Caution: Federal law..." statement with the "Rx only". See section 126 of the FDA Modernization Act of 1997.

k. Delete the "Patient's Instructions for Use". This does not appear in the approved labeling of the reference listed drug.

II. PATIENT INSERT

a. GENERAL COMMENT

i. How many patient leaflets are provided in each carton?

ii. Include the illustrations as seen in the approved labeling of the listed drug.

b. ASTHMA MEDICINES, Preventive Medicine - Delete "USP" from the second sentence.

c. HOW TO TAKE CROMOLYN SODIUM

Delete the last sentence.

d. INSTRUCTIONS FOR THE USE OF CROMOLYN SODIUM INHALATION SOLUTION

i. Method of Administration - Delete "USP" from the first sentence and insert the following text as the last paragraph:

Drug stability and safety of cromolyn sodium inhalation solution when mixed with other drugs in a nebulizer have not been established.

ii. Inhalation - Revise to read "ten" rather than "fifteen" in the last sentence.

iii. Include the illustrated use of the product as seen in the approved labeling of the listed drug.

Please revise your unit-dose labels, carton and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

_____

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Unit Dose Container Label:

Unit Dose Carton Labeling:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Intal®

NDA Number: 18-596

NDA Drug Name: Intal® Nebulizer Solution

NDA Firm: Rhone Poulenc Rorer

Date of Approval of NDA Insert and supplement #:
May 27, 1997/S-026
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels:
Intal labels in file folder.
Basis of Approval for the Carton Labeling:
Intal labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. No foil pouch see FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

*****NOTES/QUESTIONS TO THE CHEMIST:*****

1. **See comment under i. PROFESSIONAL INSERT - HOW SUPPLIED. Do you concur?**

2. **The innovator supplies this product in a foil wrap. This generic firm stated they intend not to provide a foil pouch. Is this acceptable? Has the firm submitted data to show that the product does not need this pouch? Does the container closure prevent the ingress and egress of materials?**

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Intal®; 18-596/S-026; Approved; May 27, 1997, Revised; July 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store between 15° - 30°C (59° - 86°F) and protect from light. Do not use if it contains a precipitate or becomes discolored. Store ampules in foil pouch until ready to use.

   ANDA: Store between 15° - 30°C (59° - 86°F). Protect from direct sunlight. Do not use if solution is discolored or contains a precipitate.

   USP: Preserve in single-unit double-ended glass ampules or in ampules. Label indicates inhalation is not to be used if it contains a precipitate.

4. Product Line:

   The innovator markets their product in 2 mL lastic unit dose ampule with 12 ampules per foil pouch in cartons of 60s and 120 ampules.

   The applicant proposes to market their product in 2 mL containers in cartons or 60s and 30s.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent

with the listing of inactive ingredients found in the statement of components and composition appearing on page 81, Vol. 1.1.

6. All manufacturing will be performed by Steripak Limited, Cheshire England. All outside firms are utilized for testing. See pages 138, 139 and 142, Vol. 1.1.

7. Container/Closure:

   This product will be packaged in 3.5 mL [illegible] containers with a fill volume of 2 mL. See page 424, Vol. 1.2.

8. The solution is described as a colorless to pale yellow in the finished dosage specifications. The HOW SUPPLIED section lists as a colorless solution. See page 492, Vol. 1.2.

9. The firms states on page 49, Vol. 1.1 that it is their intention to supply the product in a non-foil overwrapped presentation. See note to chemist.

Date of Review: **February 11, 1998**

Date of Submission: **December 11, 1997**

Reviewer: [illegible] **Date:** [illegible]

Team Leader: John Grace **Date:** 2/18/98

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cc:

(no cc)
TRS&REV\75271NA1.L

Application: **ANDA 75271/000** Priority: Org Code: **600**
Stamp: **15-DEC-1997** Regulatory Due: Action Goal: District Goal: **15-FEB-1999**
Applicant: **STERIPAK**
GODDARD RD, ASTMOOR, RUNCOR
CHESIRE, ENGLAND, UK
Brand Name:
Established Name: **CROMOLYN SODIUM**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **10 MG/ML**

FDA Contacts: **S. OKEEFE (HFD-617) 301-827-5848 , Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

Establishment:
DMF No:
AADA No:

R

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **20-JAN-1998**
Responsibilities: **FINISHED DOSAGE STERILITY TESTER**

Establishment:
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **20-JAN-1998**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:
STERIPAK LTD
GODDARD ROAD
RUNCORN, CHESHIRE, UK
DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **20-JAN-1998**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:
DMF No:

AADA No:

STERIPAK LTD
4 PEMBROKE COURT MANOR PARK
RUNCORN, CHESHIRE, UK

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **20-JAN-1998**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**