CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18148/S023

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 18-148/S-023

FEB 25 1999

Dura Pharmaceuticals
7475 Lusk Blvd.
San Diego, CA 92121

Attention: Terry Monk
Labeling Compliance Administrator

Dear Ms. Monk:

Please refer to your supplemental new drug application dated March 29, 1989, received April 7, 1989, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nasalide (flunisolide) Nasal Spray, 25 mcg.

We acknowledge receipt of your submissions dated September 11 and October 27, 1998.

This supplemental new drug application provides for the use of Nasalide (flunisolide) Nasal Spray, 25 mcg as first line therapy for the treatment of the nasal symptoms of seasonal and perennial rhinitis.

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter with the revisions listed below.

1. should be removed from the tradename on all labeling.

2. The following comments pertain to the package insert.

   a. The word should be removed from the first and second sentences of the DESCRIPTION section.

   b. In the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section, the should be replaced with the term "less than the."

   c. The full text of priming and repriming information, as it appears in the patient package insert, should replace the last sentence of the DOSAGE AND ADMINISTRATION section.

3. The following comments pertain to the patient package insert (PPI).

   a. The second sentence of Instruction 1. under "TO PRIME" should be revised to read,

   b. Instruction 1. under "AN IMPORTANT NOTE" should be added to the end of Instruction 1. under "TO PRIME."

   c. The first sentence of instruction 2 under "TO PRIME" should be revised to read,

   d. Instruction 3. under "TO PRIME" should be deleted .

   e. The section titled "Important Information For Patients" should be moved to the beginning of the PPI (before "TO PRIME" and rewritten as follows:

      IMPORTANT INFORMATION ON NASALIDE

      1. You should use Nasalide at regular intervals as directed since its effectiveness depends on its regular use (see below).

      2. It may take one to two weeks before full relief is obtained.

      3. You should contact your physician if symptoms do not improve, if your condition worsens or if sneezing , nasal irritation or bleeding occurs.

      4. You should contact your physician if you know you have been exposed to chicken pox or measles.

These revisions are terms of the supplemental new drug application approval.

The final printed labeling must be identical to the package insert and patient package insert submitted on September 11, 1998, and the carton labeling submitted on October 27, 1998, with the revisions listed above.

Submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-148/S-023." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Sandy Barnes, Project Manager, at (301) 827-1075.

Sincerely,

/S/

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18148/S023

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	18-148/S-023	APPLICATION TYPE:	NDA
SPONSOR:	Dura	PRODUCT/PROPRIETARY NAME:	Nasalide
		USAN / Established Name:	flunisolide
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Intranasal
	Honig	REVIEW DATE:	November 23, 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
September 11, 1998	Sept 11, 1998	PPI	see below under overview

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: The sponsor has made the requested changes to the product label and they are acceptable (see CSO/PM review). The PPI has also been revised to include minor modifications that are also acceptable. The sponsor was requested to include an 'information for patients' section which is based on the same section in the product label. The sponsor's response to this is not in language appropriate for the audience and should be revised as follows:

The section should be titled "IMPORTANT INFORMATION ON NASALIDE" and moved to the beginning of the PPI (ie before 'TO PRIME'). This subsection should be rewritten as follows:

The remainder of the supplement is acceptable.

Outstanding Issues: The sponsor should be asked to make the changes noted above.

Recommended Regulatory Action: Approvable

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: ___x___ Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: 11/23/98

Medical Team Leader: _____ Date: _____

Trovt

OCT 16 1997

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	18-148, S-026BL	APPLICATION TYPE:	Labeling Supplement
SPONSOR:	Dura	PRODUCT/PROPRIETARY NAME:	Nasalide
		USAN / Established Name:	flunisolide nasal solution 0.025%
CATEGORY OF DRUG:	corticosteroid	ROUTE OF ADMINISTRATION:	intranasal
MEDICAL REVIEWER:	Honig	REVIEW DATE:	September 9, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
July 15, 1997	July 16, 1997	Labeling Supplement	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
NA		

Overview of Application/Review: The Project Manager has summarized the proposed changes to the clinical sections of the product label. The revised wording of the ADVERSE REACTIONS section is acceptable. In addition, the following comments should be forwarded to the sponsor:

1. In the CLINICAL PHARMACOLOGY section, the first word should be changed to

2. The INDICATIONS section should be rewritten to read:

3. The first sentence of the second paragraph in the INDICATIONS section should be moved to the CLINICAL PHARMACOLOGY section to follow the paragraph starting

4. The second and third sentences of the second paragraph of the INDICATIONS section should be modified to remove and be moved to the PRECAUTIONS, General subsection and precede the existing sentence regarding localized infections.

5. The first statement in the OVERDOSAGE section should be amended to include what parameters were investigated that showed no change in acute toxicology studies.

6. The first two paragraphs of the DOSAGE AND ADMINISTRATION section should be deleted as redundant. The last sentence preceding the Adult dosing recommendation (i.e., "Patients should be advised to clear their nasal passages of secretions prior to use") should be moved to be the final statement in the PRECAUTIONS, Information for Patients subsection.

7. Since the accompanying Patient Instructions were not included in this submission, the sponsor should amend them accordingly (see comment above) and submit them for review in the response to the action letter.

Reviewer recommendation: This information should be forwarded to the sponsor in an APPROVABLE letter.

Outstanding Issues: NA

Recommended Regulatory Action: Approvable	N drive location: NDA\18-148\clin\97-07-15.rev
New Clinical Studies: _____ Clinical Hold	_____ Study May Proceed
NDAs:	
Efficacy / Label Supp.: __X__ Approvable	_____ Not Approvable
Signed: Medical Reviewer: /S/	Date: September 9, 1997
Medical Team Leader: for John K. Jenkins, MD	Date: 10/16/97

10/16/97

→ For comment 2 above, the indication should read [ ]

→ In S-026 BL The words [ ] should be added to the sentance regarding chicken pox / measles exposures. This should read: [ ]

/S/ 10/16/97
for
John K. Jenkins

cc: NDA 18-148
Div. File
HFD-570 Henry
Trout
Ng
Williams
Barnes

MAY 2 1997

Trout

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	18-148, S-023	APPLICATION TYPE:	Labeling Supplement
SPONSOR:	Syntex	PRODUCT/PROPRIETARY NAME:	Nasalide
		USAN / Established Name:	flunisolide nasal solution 0.025%
CATEGORY OF DRUG:	corticosteroid	ROUTE OF ADMINISTRATION:	Intranasal
MEDICAL REVIEWER:	Honig	REVIEW DATE:	May 2, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
March 29, 1989	April 7, 1989	Labeling Supplement	Sponsor wishes to change INDICATIONS section

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
NA		

Overview of Application/Review: Nasalide was approved in 1981 for the second-line treatment of seasonal or perennial allergic rhinitis when effectiveness of or tolerance to conventional treatment is unsatisfactory. This was done because there was no extensive safety data available at the time and the only marketed steroid at that time had given rise to concerns regarding HPA axis suppression. This submission contains an analysis of adverse drug reaction reports accumulated over the seven years of marketing of Nasalide. During that time period, 57 additional clinical trials involving 2500 patients were conducted and 9.5 million units were sold. Five (5) adverse reaction reports involving suspected or documented HPA axis effects were received and were included in this submission. In only one of these cases was HPA axis effects documented through assessments of basal and stimulated adrenal function.

Reviewer Impression: All nasal steroids are capable of influencing endogenous adrenal function and all (including Nasalide) are labeled as such. Since the approval of Nasalide, numerous other steroids (new molecules as well as new formulations of marketed drugs) have been approved for the first-line therapy of allergic rhinitis. Since nasalide was not studied in patients who failed to respond to other therapeutic modalities and, in fact, was studied as first-line therapy, it is appropriate for the sponsor to propose that the INDICATION section be modified to be more consistent with labels from other nasal corticosteroid products. That is, the existing labeled INDICATION,

"Nasalide (flunisolide) is indicated for the topical treatment of the symptoms of seasonal and perennial rhinitis when effectiveness of or tolerance to conventional treatment is unsatisfactory."

should be changed to:

Reviewer recommendation: This information should be forwarded to the sponsor in an APPROVAL letter with contingencies.

Outstanding Issues: NA

Recommended Regulatory Action: Approval	N drive location: NDA\18-148\clin\89-03-29.rev
New Clinical Studies: _____ Clinical Hold	_____ Study May Proceed
NDAs:	
Efficacy / Label Supp.: X Approvable	_____ Not Approvable
Signed: Medical Reviewer: /S/	Date: May 2, 1997
Medical Team Leader:	Date: 5/2/97

CC: NDA 18-148
Div File
HFD-570 Honig
Trout
Barnes

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18148/S023

CHEMISTRY REVIEW(S)

OCT 2 1997

CHEMIST'S REVIEW

1

1. ORGANIZATION
HFD-570 DPDP

2. NDA NUMBER
18-148

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Dura Pharmceuticals
5880 Pacific Center Blvd
San Diego, California 92121-4204

4. AF NUMBER

5. SUPPLEMENT (S)
NUMBER(S) DATES(S)

6. NAME OF DRUG	7. NONPROPRIETARY NAME		
Nasalide Nasal Solution, (0.025%)	Flunisolide	SLR-026 SLR-026BL	3/20/95 7/15/97

8. SUPPLEMENT PROVIDES FOR:
Updating the package insert.

9. AMENDMENTS DATES

10. PHARMACOLOGICAL CATEGORY
Anti-inflammatory steroids.

11. HOW DISPENSED
RX X OTC _____

12. RELATED IND/NDA/DMF

13. DOSAGE FORM(S)
Nasal solution

14. POTENCY
0.025% as flusinolide
(25 mcg per spray)

15. CHEMICAL NAME AND STRUCTURE
Flunisolide

16. RECORDS AND REPORTS
CURRENT YES_____NO_____
REVIEWED YES_____NO_____

17. COMMENTS

FT by: LNg 10/1/97
R/D Init. by:
File: 1814826A.REV

18. CONCLUSIONS AND RECOMMENDATIONS
The supplement is approvable from the chemistry, manufacturing and controls perspective. Comments should be forwarded to the applicant.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Linda L. Ng, Ph.D.	/S/	10/1/97

DISTRIBUTION ORIGINAL JACKET NDA18-148 DIVISION FILE HFD-570 REVIEWER LNg CSO [redacted]Trout SUP. CHEMIST GPocchikian

10/2/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 18148/S-023

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA
Label Review

Reviewer: Lawrence F. Sancilio, Ph.D.

Division: PULMONARY DRUG PRODUCTS, HFD-570

Reviewer Completion Date: 1/21/99

NDA No. 18-148

Serial No. /Date/ Type of Submission: 9/11/98

Information to Sponsor: Yes (X), No ( )

Sponsor: Dura Pharmaceuticals

Drug: Nasalide Solution (flunisolide), 0.25%, 25 mcg/spray

Drug Class: Glucocorticoid

Indication: Treatment of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children 6 years and older.

Maximum Recommended Doses: Adults: 0.4 mg/day (0.3 mg/m^2)
Children, 6-14 years old: 0.2 mg/day (0.25 mg/m^2)

The following changes highlighted in **BOLD** and deletions in ~~**strikeout**~~ are recommended in the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the label submitted on 9/11/98. No changes were needed in the other sections related to preclinical data.

RECOMMENDATIONS

The labeling changes recommended were in the Carcinogenesis, Mutagenesis, Impairment of Fertility section as indicated above.

/S/ 1/21/99

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

/S/ Jan 21, 1999

CC:

Original NDA
HFD-570/Division File
HFD-570/CSO/Barnes
HFD-570/LFSancilio
~~NDA 18-340~~

FEB - 5 1998

DIVISION OF PULMONARY DRUG PRODUCTS
PHARMACOLOGY LABELING REVIEW FOR NDA 18,148

Sponsor: Dura Pharmaceuticals

Supplement Number and Date:

SLR/018	13-Aug-86
SLR/018BB	23-Sep-86
SLR/018AF	26-Nov-86
SLR/023	29-Mar-89
SLR/026	20-Mar-95
SLR/026BL	15-Jul-97

Drug Name: Nasalide Nasal Solution (flunisolide) (0.25%, 25 mcg/spray)

Information to be Conveyed to Sponsor: Yes (x), No ( )

Reviewer: Shannon Williams, Ph.D.

Review Date: Feb. 5, 1998

Maximum Recommended Doses:

Adults: 0.400 mg/day (0.25 mg/m^2)
Pediatric patients (ages 6-14 years): 0.200 mg/day (0.30 mg/m^2)

Background: Updates for the nonclinical sections of the labeling were initiated for flunisolide inhalation formulations (Aerobid/Aerobid M, See pharmacology Reviews For NDA 18,340 by this reviewer dated 10/18/96 and 07/21/97). Currently, recommendations regarding the nonclinical sections of the labeling for the flunisolide intranasal formulation (Nasalide) are made. These recommendations in part stem decisions reached by the Division at the meeting of June 17, 1997 and preclinical mutagenicity data contained in the 10th Progress report submitted to IND on 5/17/84 and to IND on 7/2/84 as reviewed by Dr. CJ Sun in a pharmacology review dated 10/1/84.

Labeling Review:

1. Information related to the Carcinogenesis and Impairment of Fertility, currently discussed under two separate headings labeled CARCINOGENESIS: and IMPAIRMENT OF FERTILITY: should be combined under the single heading, "Carcinogenesis, Mutagenesis, Impairment of Fertility:"

The labeling contained under the aforementioned section should be revised as follows:

2. Other labeling sections dealing with nonclinical issues should also be revised to conform with the Division's current labeling standards. Suggested revisions to other sections (Pregnancy and Overdosage) are listed below:

Note: Calculated differences between nonclinical doses and the maximum recommended daily intranasal dose in adults and children are provided in Attachment 1. In addition, expressed

differences represent the average difference between adults and children due to the close proximity between the maximum recommended daily intranasal dose for adults (i.e. 0.25 versus 0.30 mg/m^2 in adults and pediatric patients, respectively). In all cases actual multiples differed from stated multiples by less than 16%.

The labeling section pertaining to the mutagenic potential of flunisolide as recommended above should replace the respective labeling section for Aerobid and Aerobid M (NDA 18,340) which was recommended by this reviewer in Pharmacology reviews for NDA 18,340 dated 10/18/96 and 07/21/97. RECOMMENDATIONS:

1. The labeling for nonclinical sections of the package insert should be revised as follows:

2. Additional revisions of the PREGNANCY and OVERDOSAGE sections should be incorporated into the labeling as are outlined above.

/S/ 2/5/98

Shannon P. Williams, Ph.D.
Pharmacologist

/S/ Feb. 5, 1998

c.c.
Original NDA
HFD-570/Division File/NDA
HFD-570/C.J. Sun
HFD-570/C.S.O./Barnes
HFD-570/S.P. Williams
NDA 18,340

Attachment 1.

Drug: **NDA 18148 Nasalide Intranasal Spray**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	6	0.2	1	0.2	20	0.01	25	0.25
Adult	>12	0.4	1	0.4	50	0.01	37	0.30

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	oral	0.5	3	1.5	5.07	6.00	5	6
rat	diet	0.0025	6	0.015	0.05	0.06	1/20	1/17
hamster			4	0	—	—	—	—
rat	oral	0.001	6	0.006	0.02	0.02	1/49	1/42
extra			—	—	—	—	—	—
Reproduction and Fertility:								
mouse			3	0	—	N/A	—	N/A
rat	oral	0.2	6	1.2	4.05	N/A	4	N/A
rat	oral	0.04	6	0.24	0.81	N/A	1/1	N/A
extra			—	—	—	N/A	—	N/A
Teratogenicity:								
mouse			3	0	—	N/A	—	N/A
rat	oral	0.2	6	1.2	4.05	N/A	4	N/A
rabbit	oral	0.04	12	0.48	1.62	N/A	2	N/A
extra			—	—	—	N/A	—	N/A
extra			—	—	—	N/A	—	N/A
Overdosage:								
mouse			3	0	—	—	—	—
mouse			3	0	—	—	—	—
rat			6	0	—	—	—	—
rabbit			12	0	—	—	—	—
Other: (Describe studies here)								
mouse	iv	4	3	12	40.54	48.00	40	50
dog	1v	4	20	80	270.27	320.00	270	320
dog			20	0	—	—	—	—
rat	iv	4	6	24	81.08	96.00	80	95
extra			—	—	—	—	—	—

DIVISION OF PULMONARY DRUG PRODUCTS
PHARMACOLOGY LABELING SUPPLEMENT REVIEW FOR NDA 18,340 (S004) and NDA 18,148 (S016) (Addendum to Pharmacology Review for NDA 18-340 dated 10/18/96)

Sponsor: Syntex Labs

Drug Name: Aerobid/Aerobid M (fllunisolide) Inhaler System

Information to be Conveyed to Sponsor: Yes (x), No ( )

Reviewer: Shannon Williams, Ph.D.

Review Date: July 21, 1997

Background: Recommendations for revision of the carcinogenicity section of the labeling for Aerobid (flunisolide) to incorporate the results of an oral rat carcinogenicity study (Report No. SS/049/85, Doc # RS-3999 AT3427) were submitted to the Executive Carcinogenicity Assessment Committee (Exec CAC) for discussion on Dec 03, 1996. At the Dec 03 meeting, the Exec CAC recommended that additional pairwise analysis be conducted separating out the three control groups. These additional analyses were conducted with the results presented to the Exec CAC on June 2, 1997. At the June 2 meeting members of the Exec CAC requested that the Sponsor provide the following additional information:

1) any differences in the treatment and/or examinations of control groups

2) the number of pathologists which examined the data

3) "contemporary" control data (i.e. data from the same strain and laboratory for the time period succeeding that of the study for up to 7 years or 10 studies)

4) additional statistical analyses on the combination of mammary gland benign adenomas and malignant carcinomas in females.

The Division met on June 17, 1997 in order to discuss the status of the labeling update and the recommendations made by the Exec CAC at the June 2 meeting. This addendum provides the Division's conclusions reach at the June 17, meeting along with final recommendations regarding revision of the carcinogenicity section of the labeling.

SUMMARY AND EVALUATION:

The incidence of three tumor types were previously identified as being statistically elevated using both the trend test (See Carcinogenicity Statistical Review and Evaluation by Mordecai Friedberg dated April 10, 1987) and by pairwise analysis (See Statistical review and

Evaluation Carcinogenicity by Barbara Bono, dated Aug 12, 1996). These included: liver malignant hepatocellular carcinoma in males and in females, mammary gland benign adenoma and pancreas benign islet cell adenoma.

It was recommended that all three of the aforementioned tumor types be incorporated into the labeling (See Pharmacology review by this reviewer, dated 10/18/96). On DEC 3, 1996, the Exec. CAC recommended that additional pairwise statistical analysis be conducted on these three tumor types, but using only one of the three control groups (the one which most closely resembled historical control data) and not to the combined incidence .

Additional pairwise analyses with each of the individual control groups were recently completed (See Statistical Review and Evaluation Carcinogenicity by Ms. Barbara Bono dated 4/9/97). Comparisons with each of the control groups was deemed necessary since the control group which most closely resembled historical control data (garnered from the literature) was different, depending on which tumor type was being examined.

Results from the additional comparisons varied according to the control group used for the comparison and the tumor type examined, with the incidence of no tumor being consistently elevated across each of the three control groups.

The results of above pairwise analyses were presented to the CAC on June 2, 1997, at which time it was recommended that the sponsor provide additional information regarding the following:

1) "contemporary" control rates for the incidence of spontaneous neoplasms (i.e data from the same strain and laboratory for the time period succeeding that for the study for up to 7 years or 10 studies).

2) any differences in the treatment and/or examinations of the control groups.

The following summarizes the committee's discussion's and recommendations regarding each of the three tumor types discussed at the June 2, meeting:

<u>Pancreas Islet cell Carcinoma</u>: In regard to the pancreas islet cell adenomas (incidence of 0-2-2-2-4-8 in C_1-C_2-C_3 -LD-MD-HD ; i.e. 18.1%, observed in high dose females,) the committee noted that the incidence in the pooled control groups was comparable to that reported in the literature for female Sprague Dawley Rats average = 3.9%, Range = 0.0-8.3%). Thus the committee recommended that any statistical comparisons made on this tumor type be made using the total incidence from the pooled control groups (incidence = 4/165 or 4.2%), since this overall incidence approximated that reported in the literature.

Liver Hepatocellular Carcinoma: The committee, noted that the combined incidence of hepatocellular carcinoma and hepatic nodules (regarded as adenomas) was not significantly different between treated and control groups.

Mammary Gland Benign Adenoma: In regard to the increased incidence in mammary gland adenomas (incidence of 14.5% in females a the high dose) the Committee recommended that an additional trend analysis be performed on the combined incidence of benign mammary gland adenomas and mammary malignant adenocarcinomas be conducted.

The aforementioned recommendations were discussed in an internal Division meeting on June 17, 1997 with the following discussions and decisions were reached:

1. Additional information garnered from the original study report (Report No. SS/049/85) indicated no difference in how each of the three control groups were treated in the study and that two pathologists were responsible for the histological analyses performed in the study.

2. It was decided not to pursue the CAC's requests for data on the rates for the incidence of spontaneous neoplasms in "contemporary" control groups, based on the age of the study (Completed study dated 7/30/85), the transfer of ownership (at least three times), and existence of literature reports describing the incidence of spontaneous neoplasms in Sprague Dawley rats taken from studies contemporary in time to the current study.

3 It was also decided not to request additional statistical analysis for the combined incidence of mammary tumors in females, based on the existence of both trend test and pairwise analyses for both the mammary gland benign adenoma and malignant adenocarcinoma.

4. It was recommended that both the increased incidence of pancreas islet cell adenoma and mammary gland benign adenoma in females at the high dose be incorporated into the labeling.

5. Finally, the division decided to rescind its original recommendation for incorporation of hepatocellular carcinomas into the labeling since the total combined incidence of hepatocellular carcinomas and hepatic nodules (benign adenomas) failed to reveal a treatment-related effect.

In regard to the aforementioned decisions reached by the Division at the meeting of June 17, 1997, the following recommendations regarding revision of the "Carcinogenesis, Mutagenesis, Impairment of Fertility:" section of the labeling are made.

Redacted 1

pages of trade secret and/or confidential commercial information

RECOMMENDATIONS:

1. The labeling section related to studies on the carcinogenic and mutagenic potential of flunisolide as well as its ability to impair fertility should be revised as follows:

2. Additional revisions of the PREGNANCY and OVERDOSAGE sections should be incorporated into the labeling as are outlined above.

/S/ 7/21/97

Shannon P. Williams, Ph.D.
Pharmacologist

July 21, 1997

/S/

c.c.
Original IND
HFD-570/Division File/NDA
HFD-570/C.J. Sun
HFD-570/C.S.O./Barnes
HFD-570/S.P. Williams
N:\NDA\18,340\PHARM\94-6-8.RE2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 18148/S023

ADMINISTRATIVE DOCUMENTS

Record of Telephone Conversation

Date: May 1, 1998

NDA No: NDA 18-148/SLR-026

Product Name: Nasalide Nasal Solution, 25 mcg
Firm Name: Dura Pharmaceuticals
San Diego, California 92121-4204

Telecon Initiated by: Firm

Name and Title of Person with whom conversation was held:
Terrie Munk, Drug Regulatory Affairs.

Telephone No: (619)-784-6338

Content:

The teleconference call was initiated because of supplement SLR-013 for updating the package insert. The firm wanted some clarification of FDA's request. Terrie Munk, Malcolm Hill and JoAnn of Dura Pharmaceuticals and myself were in a teleconversation call.

Firm inquired if the request for weight of the formulation for each spray is to update their specification. I assured them that this is just to standardize the package insert and all firms are asked the same information in their package insert. They understood and will look into the volume delivery data for the target value. They were unclear what the density of the formulation solution is. They inquired about the words "at least", "CFC free" and "approximately". I told them that all firms are treated the same as far as the PI wording is concerned. They are more comfortable with our request and will amend the PI. They would like to add the word "solution" to the drug product in the description section for clarification (as opposed to suspension product). I don't see any issue with their proposal but told them that Gretchen will confirm since this is a team decision.

/S/

Linda L. Ng, Ph.D.
HFD-570

cc: NDA 18-148
HFD-570/Division File
HFD-570/GPoochikian
HFD-570/LNg
HFD-570/GTrout
R/D Init. by: 5/9/98

F/T by: LLN 5/1/98
File: N18148A.TEL

MEMORANDUM OF TELECON

DATE: March 30, 1998

APPLICATION NUMBER: N18-148

DRUG PRODUCT: Nasalide (flunisolide) Nasal Spray

PARTICIPANTS:
FDA: Gretchen Trout Project Manager

Dura: Terry Monk

BACKGROUND: The Division sent a facsimile to Dura on March 13, 1998, requesting numerous revisions to the labeling. Dura was requested to submit revised labeling as an amendment to supplement 023. Ms. Monk telephoned to clarify several points.

The following are Ms. Monk's questions, and my answers.

1. **Will Dura need to implement similar changes to the labeling for Nasarel?**

   Yes, Dura should submit a supplement providing for similar revisions to the Nasarel labeling.

2. **What timeframe does Dura have to make the changes? Dura is specifically concerned about the change in the name to "Nasal Spray" because this also effects all of their packaging and promotional material.**

   The Division is requesting that the changes be made within 6 months, or the next printing, whichever comes first.

Note: The following issues were covered in a second telephone call on the same day.

3. **Will the Division be issuing an industry-wide letter requesting that name of other Nasal Solution products be changed to "Nasal Spray"?**

   No, the Division is not sending out a general letter, however as supplements are submitted with labeling changes we are consistently requesting that the name be changed to "Nasal Spray." Several products have already changed their name, however the labeling may not yet be in use.

4. **Is the Division distinguishing between solutions and suspensions?**

   No, all solutions and suspensions are being changed to "Spray."

5. **With regard to the six month timing, this is acceptable to Dura for labels, cartons, and package inserts; however, for the promotional material for Nasarel they have more than a six month supply. Can Dura wait until the next printing, even if it is longer than six months?**

   I suggested that Dura submit a counter proposal estimating how long it would take them to exhaust their supply of Nasarel promotional material.

6. **In the DESCRIPTION section, the Division had added wording that stated each action of the unit delivers a metered droplet spray of "100 mg formulation" containing 25 mcg of flunisolide. Dura was confused about the units of measurement - volume vs. Mass.**

   The first measurement should indicate the weight of a single spray, the second should indicate the amount of flunisolide that is within the one spray. If the Division's calculations are incorrect, Dura should insert appropriate numbers and measurements.

In addition to the above discussion, I informed Ms. Monk that there was another change which the Division would like to be made to the labeling which had not been indicated in the facsimile: [ ] should be changed to [ ]

Ms. Monk indicated that Dura would begin working on the revisions.

/S/

Gretchen Trout
Project Manager

MEMORANDUM

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

DATE: May 8, 1997

FROM: Gretchen Trout
Project Manager

SUBJECT: Memo to file

TO: NDA 18-148

A submission dated March 29, 1989 was submitted to NDA 18-148 requesting approval for a change to the package insert. This submission was coded as a labeling supplement (SLR-023). During a project manager review of open labeling supplements for this NDA, it was determined that the revision to the package insert requested in this supplement actually constituted a change in the indication for this product, and therefore should have been coded as an efficacy supplement. The document room was requested to change the code from SLR-023 to SE2-023.

/S/

Gretchen Trout
Project Manager

cc: Orig. NDA
Div. File
HFD-570/Trout
HFD-570/Barnes
HFD-570/Honig

PROJECT MANAGER LABELING REVIEW

NDA 18-148/S-023

Applicant: Dura Pharmaceuticals

Drug: Nasalide (flunisolide) Nasal Spray, 25, mcg

Date of submissions: AL - September 11, 1998 and October 27, 1998

Background: The FDA sent a facsimile to Dura on March 13, 1998, requesting that Dura submit revised labeling as an amendment to S-023. S-023 provides for the use of Nasalide as first line therapy for the topical treatment of the symptoms of seasonal and perennial rhinitis. The facsimile incorporated labeling revisions from the reviews of labeling supplements S016, S-018, and S-026 and efficacy supplement S-023. Additional labeling revisions were discussed in a May 1, 1998, telephone conversation between our chemist and the applicant.

On September 11, 1998 Dura submitted a package insert and "patient's leaflet of instructions" to S-023 (the efficacy supplement) in response to the March 13, 1998, facsimile. On October 27, 1998 Dura submitted revised carton labeling.

I compared the package insert submitted on September 11, 1998 to the labeling revisions requested by facsimile on March 13, 1998, and in the May 1, 1998 telephone conversation. The following differences were noted.

1. (was added to the tradename of the product.

2. The phrase "a target of" was added to the last line of the third paragraph of the DESCRIPTION section.

3. The Priming and repriming information was added to the DOSAGE AND ADMINISTRATION section by reference to the "patient leaflet of instruction".

4. No description of a safety clip was included in the HOW SUPPLIED section.

The current review chemist, Chong-Ho Kim, Ph.D., has no objection to the addition of the phrase "a target of" and there is no safety clip for this product, therefore only comment 1 and 3 above should be conveyed to the applicant.

The March 13, 1998 facsimile also requested that Dura update and submit the patient instructions for use for FDA review. I compared The "patient leaflet of instructions" submitted on September 11, 1998, to the last approved "patients leaflet of instructions" and there are no changes other then those highlighted by the applicant in their submission.

The applicant submitted a revised carton label on October 27, 1998. There are a number of differences between the carton labeling submitted on October 27, 1998 and the last approved

carton label (Original NDA approval, September 24, 1981). Minor differences include removal of the "Usual Dose", addition of the temperature in centigrade and some formatting changes. The major change is the deletion of instructions for assembly and priming of the unit. When Nasalide was approved in 1981, the container and the pump were packaged in the same box but not assembled. The drug product had a 3 month expiration period after assembly. On April 21, 1986 supplement S-007, which provided for a revised formulation and a new pump, was approved. The chemistry review for S-007 also included a review of annual report R-08 dated December 10, 1985 which contained full 24 month stability data for the assembled pump. The approved labeling in 1986 still contained assembly instructions. Annual report R-012 dated December 8, 1989 contained revised labeling to market the product as an assembled unit, therefore the assembly instructions were not on the carton. The presentation of the assembled unit with a 24-month expiration period is acceptable.

Recommendations:

The Medical Officer should review the revisions to the patients leaflet of instructions and the Chemist should review the revision to the patients leaflet of instructions and the carton labeling. If the revisions are acceptable the supplement should be approved with the following labeling requests.

1. We recommend that you remove from the tradename on all labeling.

2. The full text of the Priming and repriming information should be added to the DOSAGE AND ADMINISTRATION section of the package insert.

Following the approval of supplement S-023, labeling supplements S-016, S-018 and S-026 should be acknowledged and retained.

/S/

Sandy Barnes
Project Manager

cc:OrigNDA 18-148/S-023
DivFile
HFD-570S. Barnes
Initialed by CA 11-20-98

EXCLUSIVITY SUMMARY FOR NDA # _18-148_____ SUPPL #_S-023___

Trade Name _Nasalide Nasal Spray Generic Name _flunisolide__

Applicant Name Syntex_____ 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 /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) ___SE2__

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 /___/ NO /_X_/

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

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 /_X_/ NO /___/

If yes, NDA #_20-409_. Drug Nam: Nasarel_____.

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 /___/

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 /___/ NO /___/

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

NDA# _____ _____

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."

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 /___/ 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 /___/ 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 /___/

(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 /___/

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:

_____

_____

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.

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 /___/

Investigation #2 YES /___/ NO /___/

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 /___/

Investigation #2 YES /___/ NO /___/

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"):

_____ _____

_____ _____

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 # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !
!

IND # _____ YES /___/ ! 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 /___/

If yes, explain: _____

_____

/S/ 2/19/99

Signature Date

Title: Project Manager

/S/ 4/9/99

Signature of Office/ Date

Division Director

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

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	18148	**Trade Name:**	NASALIDE (FLUNISOLIDE) SOLUTION.
Supplement Number:	23	**Generic Name:**	FLUNISOLIDE
Supplement Type:	SE2	**Dosage Form:**	
Regulatory Action:	AP	**Proposed Indication:**	indicated for the treatment of nasal symptoms of seasonal and perennial rhinitis

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

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

COMMENTS:
Approved down to 6 years of age

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

/S/ 2/19/99

Signature Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18148/S023

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-148/S-028

FEB 5 1998

DURA PHARMACEUTICALS, INC.
7475 LUSK BLVD
SAN DIEGO, CA 92121

Attention: DARLENE ROSARIO
ASSOCIATE DIRECTOR
REGULATORY AFFAIRS

Dear:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: NASALIDE NASAL SOLUTION 0.025%

NDA Number: 18-148

Supplement Number: S-028

Date of Supplement: JANUARY 26, 1998

Date of Receipt: JANUARY 28, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on MARCH 29, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Attention: Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 18-148/028
HFD-570/Div. Files
HFD-570/CSO/SANDRA BARNES

filename:

SUPPLEMENT ACKNOWLEDGEMENT