CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-195/S-002

Trade Name: FENTANYL ORALET 100ug, 200ug and 400ug

Generic Name:(oral transmucosal fentanyl citrate)

Sponsor: Anesta Corp.

Approval Date: May 20, 1996

Indication: Provides for lowering the weight of children who may be administer Fentanyl Oralet from 15 kg.

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APPLICATION: NDA 20-195/S-002

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Application Number:NDA 20-195

APPROVAL LETTER

DEPARTMENT OF HEA[illegible]H & HUMAN SERVICES

Public Health Service

Ref File

NDA 20-195/S-002

Food and Drug Administration
Rockville MD 20857

MAY 20 1996

Anesta Corp.
4745 Wiley Post Way
Suite 650
Salt Lake City, Utah 84116

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your November 28, 1995 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Oralet (oral transmucosal fentanyl citrate) 100 μg, 200 μg, and 400 μg.

The supplemental application provides for lowering the weight of children who may be administer Fentanyl Oralet from 15 kg to not less than 10 kg.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling, in the submission dated November 28, 1995 with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter. The revisions are as follows:

In addition to the above labeling changes, we request that you include in the Precautions and Dosage and Administration sections a statement that use of the product should be limited to infants who are able to follow instructions regarding proper administration.

These revisions are terms of the supplemental NDA approval.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-195/S-002. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, further revision of that labeling may be required.

Please submit one market package of the drug when it is available.

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, please contact:

Millie Wright
Project Manager
(301) 443-4250

Sincerely yours,

/S/

Robert F. Bedford, M.D.
Acting Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Originial NDA 20-195
HFD-170/Divison File
HFD-170/Palmisano
HFD-170/M.Wright
HF-2/MedWatch (with draft labeling)
HFD-2/MLumpkin
HFD-80 (with draft labeling)
HFD-40 (with draft labeling)
HFD-613 (with draft labeling)
HFD-735 (with draft labeling)
District Office
HFD-820

Drafted by M.Wright 5/11/96

RD init by: CPMoody/5-15-96
FD by: PO'Connor/5-16-96

APPROVAL

Doc. N20195.s2ltr (WP 6)

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APPLICATION NUMBER: NDA 20-195/S-002

MEDICAL REVIEW(S)

Division of Anesthesia, Critical Care and Addiction Products
CLINICAL REVIEW

NDA 20-195

Product: Fentanyl Oralet (oral transmucosal fentanyl citrate)

Sponsor: Anesta Corp

Submission Type: Supplement (SE-5) - Use in children weighing 10-15 kg

Date:

Submitted:	11/28/95
Received (CDER):	11/30/95
Review:	2/6/96

CSO: M. Wright

Medical Reviewer: Barbara W. Palmisano M.D.

1. RESUME:

Fentanyl Oralet (oral transmucosal fentanyl citrate) was approved in 1993 for use in a hospital setting as an anesthetic premedication in the operating room or to induce conscious sedation in a monitored anesthesia care setting. The original NDA included 200, 300 and 400 µg dosage forms and approved dosing (5-15 µg/kg) could be used only in children who weighed ≥ 15 kg. Recently a smaller dosage, 100 µg, was approved which will allow use of the approved dosage range in children smaller than 15 kg. This submission is intended to support revision of the label to include children who weigh 10-15 kg.

Material reviewed includes labeling and an 11-page submission of clinical data consisting of safety data for patients weighing 10-14.9 kg. This data was included in the original NDA submission.

Clinical Data - Overview of Safety

Seventy-four of 549 children in the original NDA weighed <15 kg. Twenty-one of these received the approved dosage, 5-15 µg/kg as did 119 children ≥ 15 kg.

Table 1 Adverse Events Following 5-15 µg/kg OTFC
Pediatric Patients >10 kg (N=143)

Adverse Event	Patients 10-14.9 kg (N=21) N (%)	Patients ≥15 kg (N=119) N (%)
pruritis	12 (71)	74 (62)
vomiting	3 (14 %)	13 (11%)
hypoventilation	1 (5%)	6 (5%)

Other adverse events are reported for patients ≥15 kg but no others are reported for the 10-14.9 kg group. This may reflect the small number of patients in the 10-14.9 kg group relative to the ≥15 kg group or the inability to elicit certain effects (i.e., nausea) from the smaller children.

A total of 406 children received OTFC in a higher than approved dose, including 53 patients 10-14.9 kg.

Table 2 Adverse Events Following>15 µg/kg OTFC
Pediatric Patients >10 kg (N=406)

Adverse Event	Patients 10-14.9 kg (N=53) N (%)	Patients ≥15 kg (N=353) N (%)
pruritis	37 (70)	253 (72)
vomiting	7 (13 %)	47 (13%)
hypoventilation	6 (11%)	23 (7%)
sweating	4 (8%)	11 (3%)

Other adverse effects are reported with a frequency of 1 (2%) for patients 10-14.9 kg: bradycardia, dizziness, emotional lability, headache, laryngismus, nausea, stupor, vasodilation.

The adverse event profile for approved and higher-than-approved dosages in the 10-14.9kg group is not worse than current labeling: hypoventilation (11%), pruritis (56%), vomiting (34%), nausea (17%).

Overview of Efficacy

No new efficacy data is presented.

Labeling Review

*Recommendation regarding labeling: Include in **Precautions** and **Dosage and Administration** sections a statement that use of the product should be limited to infants who are able to follow instructions regarding proper administration.*

Conclusions

Fentanyl is a well known product with a long history of use in small infants. Its effects in small infants are not different from those in older children and adults. The most common serious adverse event associated with fentanyl is hypoventilation. Smaller children are at the same degree of risk for this as older children and adults. Use of OTFC is contraindicated except in environments in which hypoventilation can be recognized and effectively managed so there is no consequence to the patient.

There is no clinical rationale to exclude children weighing 10-15 kg from the label now that a suitable dosage form is available. Use should be restricted to children who are at a sufficient developmental stage to follow instructions on proper consumption.

Recommendations

We recommend approval of revised labeling with additions noted above.

/S/

2/22/96

Barbara W. Palmisano MD

/S/

2/26/96

Peer Reviewer

Orig NDA #20-195
HFD-170/Div File
HFD-170/BPalmisano
HFD-170/D.Wright
HFD-502
HFD-340
F/T by

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APPLICATION NUMBER: NDA 20-195/S-002

ADMINISTRATIVE DOCUMENTS

DV NK

APR 14 1996

Review of Labeling

NDA 20-195/S-002

Sponsor: Anesta Corp.

Drug: Fentnyl Oralet (oral transmucosal fentanyl citrate)

Date:

Letter Date:	November 28, 1995
CDER Date:	November 30, 1995
Review Date:	February 26, 1996/Medical Officer April 14, 1996/Project Manager

Type of Submission: SE5-002 (efficacy supplement) submitted 11/28/95

Material Reviewed: Draft labeling (DL) submitted with the11/28/95 efficacy supplement (SE5-002) and the Final Printed labeling (FPL) approved May 2, 1996 for efficacy supplement (SE2-001).

Discussion:

The efficacy supplement submitted 11/28/95 proposed to lower the weight limit from 15 kg to 10 kg. Changes in the DL, as a result of this lower weight limit applies to 4 sections of the package insert: the Black Box Warning, the Contraindications Section, the Precautions Section, and the Dosage and Administrations Section. The DL accompanying SE5-002 was compared to the FPL submitted 1/26/96 and approved May 2, 1996 for SE2-001. (SE2-001, approved October 8, 1995, provided for the addition of a 100 μg dosage). The changes were as follows:

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

NDA 20-195/S-002

Other Comments

Dr. Palmisano reviewed the DL (see Attachment) and recommended that and additional statement be included in the Precaution and Dosage Administration sections that limits the use of the product to infants who are able to follow instructions regarding proper administration.

Conclusion

Further comparison of the DL submitted with SE5-002 (dated 11/28/95)to the FPL submitted for SE2-001 (approved May 2, 1996) revealed only editorial changes.

Recommendation

I recommend that the DL submitted November 28, 1995 be approved with the provision that the Sponsor be requested to add the statement requested by Dr. Palmisano in their FPL.

/S/

Millie Wright
Project Manager

/S/

Concur: Corinne P. Moody
Acting Chief
Project Management Staff

Attachment (1)

cc:
Original NDA 20-195
HFD-170/Division File
HFD-170/M.Wright
HF-2/Red Watch