CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20747

CHEMISTRY REVIEW(S)

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

NDA #: 20-747 **DATE REVIEWED:** 10.6.98

REVIEW: 7 **REVIEWER:** P.Maturu

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT # 37	4.30.98	5.4.98	
AMENDMENT # 44	7.29.98	7.30.98	

NAME & ADDRESS OF APPLICANT:
Anesta Corporation, 4745 Wiley Post Way, Suite 650, Salt Lake City, Utah 84116

DRUG PRODUCT NAME

Proprietary:	ACTIQ
Established:	Oral Transmucosal Fentanyl Citrate
Code Name/#:	CAS# 990-73-8
Chem.Type/Ther.Class:	3P

PHARMACOL. CATEGORY/INDICATION: Analgesic for chronic pain in cancer patients tolerant to opioids.
DOSAGE FORM: Lozenge on a stick.
STRENGTHS: 200, 400, 600, 800, 1200 and 1600 mcg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: X Rx ___ OTC
SPECIAL PRODUCTS: ___ Yes X No
Subpart H, restricted distribution.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: USP grade Fentanyl Citrate
N-(1-phenylethyl-4-piperidyl)-propionialide citrate 1:1

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF /	Fentanyl citrate USP	/ —	Okay, as per approved NDA 20195.		

RELATED DOCUMENTS (if applicable): NDA 20-195
CONSULTS: Methods validation work at Philadelphia Lab and San

REMARKS:

Amendment # 37

The applicant's has responded to NA letter dated November 13, 1998. Issues relating to NA action for CMC are the handle change based on Abbott's drawing lacks supporting stability data and process validation, and the handle design based on Abbott's drawing is deficient from the standpoint of safety because it looks like candy and multiple cues be included in the handle design..

The response has 4 parts, namely, (1) the expert opinions from Profs Garnett Peck and Paul Niebergall stating that lozenge stick/handle design based on safety concerns will not effect Fentanyl stability, (2) the personal interviews with 70 children ages 4-8 years on their perceptions of Actiq stating that very few children associated Actiq with candy, (3) the feasibility report for modifying the handle design to show proposal # 6 is easier to insert into the molded product matrix, and (4) an updated 9 months stability data for Actiq prepared with a different lozenge stick.

The proposed lozenge stick design drawing no B-PR3587 on page 4-154 and 4-139, has no potency markings on the stick, and I am assuming that the figure is incorrect and the correct stick design is as per figure 3 on page 4-129.

An expiry date of 9+6 months for Actiq with modified lozenge stick design based on safety concerns is permissible based on the expert opinions and the secondary evidence. The secondary evidence is 9 months of satisfactory real time stability data on one to three Actiq production batches/potency but with a different lozenge stick inserted into the candy matrix. These stability batches are listed as a table on page 4-003, and their stability data is compiled on pages, 4-069 to 4-092 and 4-104 to 4-118. These stability batches were compounded from Fentanyl citrate USP grade, at Abbott's North Chicago mfg. site, packaged in mid 1997 as partial production runs in the proposed child resistant foil package (0.48 mil polyester/adhesive/3 mil valeron/0.6 mil EAA/0.35 mil foil/0.7 mil EAA/1.5 ml linear LDPE).

Amendment # 44

This amendment provides additional stability data, 12 months test results. Therefore, an expiry date of 12+6 months for Actiq with modified lozenge stick design based on safety concerns is permissible based on the expert opinions and the secondary evidence. The secondary evidence is 12 months of satisfactory real time stability data on one Actiq production batch/potency but with a different lozenge stick (see pages 4-010 to 4-033 for stability test results).

It is my understanding that post-approval process validation will be performed on Actiq with the modified lozengestick design based on safety concerns (the stick proposal # 6 , amendment # 37 page 4-129 figure 3, pages 4-139 and 4-154). Stability for process validation batches will be submitted post-approval as annual reports. Tentative expiry data for the distributed Actiq will be 18 months.

Methods validation work was completed only at Philadelphia Lab and the work is in progress at San Juan Lab. Philadelphia lab has concluded that the proposed methods are suitable for regulatory purpose, except for the test for the hydrolytic and oxidative decomposition products. Philadelphia Lab was unable to validate the limit tests for hydrolytic and oxidative decomposition products due to unavailability of reference standards for the decomposition products.

The applicant seems to have provided a clinical risk management plan that allows for controlled/restricted distribution, under subpart H. Therefore, multiple cues is no longer an issue.

CONCLUSIONS & RECOMMENDATIONS:

All CMC issues have been satisfactorily addressed. It should be noted however, that the applicant has not yet validated the process for Actiq with the new stick handle. In a letter dated 10.9.98, the applicant has informed the agency that the process validation report for Actiq with the new stick handle and COA will be provided in the first annual report. This is acceptable. Thus, the application is recommended for approval from CMC standpoint. A standard methods validation paragraph should be added asking the applicant to co-operate with the agency with regard to methods validation.

In conclusion, an 18 months expiry date is recommended for Actiq with a modified lozenge stick design based on safety concerns and in the proposed child resistant foil package (0.48 mil polyester/adhesive/3 mil valeron/0.6 mil EAA/0.35 mil foil/0.7 mil EAA/1.5 ml linear LDPE).

/S/

P.Maturu, PhD, Review Chemist

/S/

A.D'Sa, PhD, Chemistry Team Leader

cc:
Org. NDA 20-747
HFD-170/Division File
HFD-170/PMaturu/10.6.98
HFD-170/AD'Sa
R/D Init by: TEAMLEADER
filename:N20747r7.98
APPROVED

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCT, HFD-170

Review of Chemistry, Manufacturing, and Controls

NOV 12 1997

NDA #: 20-747

REVIEW # 6 DATE REVIEW COMPLETED: 11.10.97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	11.4.97	11.5.97	11.7.97 (stability update)

NAME & ADDRESS OF APPLICANT:

Anesta Corp, 4745 Wiley Post Way, Suite 650, Salt Lake City, UT 84116. Drug product is manufactured and distributed by Abbott Laboratories, North Chicago, Illinois 60064.

DRUG PRODUCT NAME

Proprietary: ACTIQ (CII).
Established: Oral Transmucosal Fentanyl Citrate (OTFC).
Code Name/#: CAS# 990-73-8
Chem.Type/Ther.Class: 3P

PHARMACOL. CATEGORY: Analgesic for chronic pain in cancer patients tolerant to opioids (30 min for maximum analgesia; warning: may be habit forming).

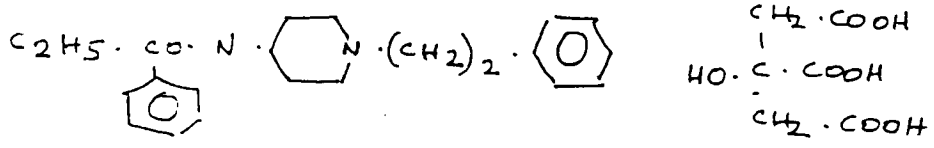
DOSAGE FORM: Raspberry flavored off-white color and conical round shape lozenge with a non-prominant marking of potency on the lozengestick.

Different colors are used as the background for printing ACTIQ on the label, namely, gray for 200 mcg, blue for 400 mcg, orange for 600 mcg, purple for 800 mcg, green for 1200 mcg, and burgundy for 1600 mcg.

STRENGTHS: 200, 400, 600, 800, 1200, and 1600 mcg.
ROUTE OF ADMINISTRATION: Oral transmucosal.
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

N-(1-phenethyl-4-piperidyl)-propionalide citrate (1:1); Fentanyl citrate mol wt is 528.6 (free base mol wt is 336.5); pKas are 7.3 and 8.4. See USP 23 page 654.



REMARKS:

Stability update is for Fentanyl OTF lots manufactured in Sept 96 and April 97 with Actiq handle and CR foil pouch.

. 6 months satisfactory stability at 40C/75%RH was updated for one lot of each strength manufactured in April 97 with Actiq handle and CR foil pouch. These lots were identified as 27-006-JE/200 mcg, 27-007-JE/400 mcg, 27-008-JE/600 mcg, 27-009-JE/800 mcg, 27-010-JE/1200 mcg and 27-011-JE/1600 mcg, and they were FULLY tested for fentanyl potency, decomposition products, moisture, dissolution and appearance.

. 12 months satisfactory stability at 25C/60%RH was updated for one lot of low-medium-high strengths manufactured in Sept 96 with Actiq handle and CR foil pouch. These lots were identified as, 20-738-JE/200 mc, 20-739-JE/600 mcg and 20-740-JE/1600 mcg, and they were FULLY tested.

RECOMMENDATIONS AND SUMMARY:

I recommend an extension of shelf life from 9 months to 12 months for Fentanyl OTFC drug product with ACTIQ handle and CR foil pouch package, and concurrence of Ms. Brown's recommendation for approval of mfg site with the understanding of post-approval inspection.

cc:
Orig. NDA 20747
HFD-170/Division File
HFD-170/PMaturu, AD'Sa. JGibbs
filename: N20747r6.97
SATISFACTORY (ACTIQ HANDLE)

/S/

P.Maturu, PhD, Primary Review Chemist

11/12/97

A.D'Sa, PhD, Chemistry Team Leader

Note: The product with ~~the~~ proposed handle (in the Sept. Advisory Committee) has not been manufactured, to date. This action refers to the product submitted in the original NDA.

11/12/97

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCT, HFD-170
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-747 -

REVIEW # 5 **DATE REVIEW COMPLETED: 10.2.97**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	9.22.97	9.23.97	9.25.97

NAME & ADDRESS OF APPLICANT:
Anesta Corp, 4745 Wiley Post Way, Suite 650, Salt Lake City, UT 84116. Drug product is manufactured and distributed by Abbott Laboratories, North Chicago, Illinois 60064.

DRUG PRODUCT NAME
Proprietary: ACTIQ (CII).
Established: Oral Transmucosal Fentanyl Citrate (OTFC).
Code Name/#: CAS# 990-73-8
Chem.Type/Ther.Class: 3P

PHARMACOL. CATEGORY: Analgesic for chronic pain in cancer patients tolerant to opioids (30 min for maximum analgesia; warning: may be habit forming).

DOSAGE FORM: Raspberry flavored off-white color and conical round shape lozenge with a non-prominant marking of potency on the lozengestick.

Different colors are used as the background for printing ACTIQ on the label, namely, gray for 200 mcg, blue for 400 mcg, orange for 600 mcg, purple for 800 mcg, green for 1200 mcg, and burgundy for 1600 mcg.

STRENGTHS: 200, 400, 600, 800, 1200, and 1600 mcg.
ROUTE OF ADMINISTRATION: Oral transmucosal.
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
N-(1-phenethyl-4-piperidyl)-propionalide citrate (1:1); Fentanyl citrate mol wt is 528.6 (free base mol wt is 336.5); pKas are 7.3 and 8.4. See USP 23 page 654.

REMARKS:

1. Abbott drawing for ACTIQ handle with Rx imprint and no potency imprint was submitted on page 3-007 (see enclosed page 3). I have not seen any supporting data, stability and process validation data on production size batches with the modified handle.

2. Stability commitment for full testing at all remaining stability check dates was made on page 3-021 (see enclosed page 4).

3. [redacted] will be ready by October 1997 for inspection rescheduling.

4. Amended EA for the modified handle will not be submitted as stated on page 3-023 (see enclosed page 5).

RECOMMENDATIONS AND SUMMARY:

I RECOMMEND NOT TO APPROVE the handle change based on Abbott drawing alone. I have not seen any supporting data, stability and process validation data on production size batches with the modified handle.

/S/

P.Maturu, PhD, Primary Review Chemist

/S/ 10/2/97

A.D'Sa, PhD, Chemistry Team Leader

cc:
Orig. NDA 20747
HFD-170/Division File
HFD-170/PMaturu, AD'Sa. JGibbs
filename: N20747r5.97
NOT SATISFACTORY (RX HANDLE)

Addendum:

Please Note: This should be labeled as a Major Chemistry Amendment. The company needs to manufacture the product before chemistry review can be adequately done. This issue was brought up in DNDC II team leaders meeting (10/2/97). Adequate manufacturing data and accelerated stability data needs to be submitted before recommending approval. The dosage strength needs to clearly shown on the stick. This was not visible on the engineering drawings or the sample presented at the advisory committee in september.

10/7/97

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCT, HFD-170
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-747

REVIEW # 4 **DATE REVIEW COMPLETED: 9.8.97**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	8.29.97	9.2.97	9.5.97
AMENDMENT	7.29.97	8.1.97	9.5.97

NAME & ADDRESS OF APPLICANT:
Anesta Corp, 4745 Wiley Post Way, Suite 650, Salt Lake City, UT 84116. Drug product is manufactured and distributed by Abbott Laboratories, North Chicago, Illinois 60064.

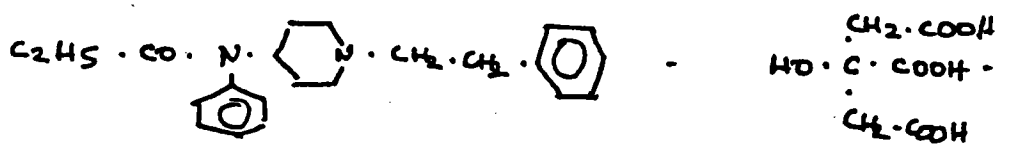
DRUG PRODUCT NAME
Proprietary: ACTIQ (CII).
Established: Oral Transmucosal Fentanyl Citrate (OTFC).
Code Name/#: CAS# 990-73-8
Chem.Type/Ther.Class: 3P
PHARMACOL. CATEGORY: Analgesic for chronic pain in cancer patients tolerant to opioids (30 min for maximum analgesia; warning: may be habit forming).

DOSAGE FORM: Raspberry flavored off-white color and conical round shape lozenge with a non-prominant marking of potency on the lozengestick.

Different colors are used as the background for printing ACTIQ on the label, namely, gray for 200 mcg, blue for 400 mcg, orange for 600 mcg, purple for 800 mcg, green for 1200 mcg, and burgundy for 1600 mcg.

STRENGTHS: 200, 400, 600, 800, 1200, and 1600 mcg.
ROUTE OF ADMINISTRATION: Oral transmucosal.
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
N-(1-phenethyl-4-piperidyl)-propionalide citrate (1:1); Fentanyl citrate mol wt is 528.6 (free base mol wt is 336.5); pKas are 7.3 and 8.4. See USP 23 page 654.



REMARKS:

8.29.97 Amendment: The applicant has submitted SATISFACTORY retest results at 3 months/40 C/75% RH storage conditions for the lots manufactured in April 97. These lots were full production size lots packaged in ACTIQ package and identified as 27-006-JE/200 mcg, 27-007-JE/400 mcg, 27-008-JE/600 mcg, 27-009-JE/800 mcg, 27-010-JE/1200 mcg, 27-011-JE/1600 mcg. These lots were FULLY retested for fentanyl potency, decomposition products, moisture, dissolution and appearance.

7.29.97 amendment: The applicant has provided REQUIRED certification. that ALL stability lots were full production size batches, a stability commitment that post-approval stability updates will be filed as annual reports, a pedigree sheet for stability lots linking ACTIQ drug product lots to | /Fentanyl citrate USP lots, COA for Fentanyl citrate lots, Anesta's QC/QA certification of contractor's reports (child resistant feature testing report dated April 94 with 3 mil Valeron pouch, moisture vapor transmission test report dated May 97), written statement that DEA approval was given in April 97 for 40 C/75% RH stability testing chamber.

SUMMARY:

. Post-implementation of stability studies, we can't concur on stability design dated 23 April 97 (full testing and 4 retests for trend analysis were not done in the stability protocol by Nov 96 filing date).

. The applicant has requested 2 years expiration date, but we can grant only 9 months expiration date (3 mon. data plus 6 months extension) based on the extent of retesting upon release (12th June 97 meeting between ONDC and Anesta/Abbott).

. The applicant has FULLY retested 6 lots at 3 months/40 C/75% RH (INCLUDED DECOMPOSITION PRODUCTS), and PARTIALLY retested 6 lots (EXCLUDED DECOMPOSITION PRODUCTS). CDER POLICY requires 6 months accelerated testing at 40 C/75% RH and 12 months long term RT testing at 25 C/60% RH at NDA filing date (Guidance for Industry, Stability Testing of new drug substances and products, ICH Q1A, September 1994).

. The applicant has placed 12 full size production lots on stability. CDER POLICY requires 18 full size production lots for expiration dating for human drugs (3 lots per potency for 6 potencies; CPG 7130a.04, p.159, Aug 1996).

. EA and FONSI for ACTIQ were concurred by M. Nancy Sager.

. EER for ACTIQ is still pending (EES/_ /not ready for inspection).

. MV work for ACTIQ is in progress at FDA labs.

. Lack of multiple cues for visual identification of ACTIQ will be addressed at ALSAC Meeting 17 Sept 97.

/S/

cc:
Orig. NDA 20747
HFD-170/Division File
HFD-170/PMaturu, AD'Sa. JGibbs
filename: N20747r4.97

P.Maturu PhD. Primary Review Chemist
9/12/97
A.D'Sa,PhD, Chemistry Team Leader

SATISFACTORY FOR 9 mon EXPIRY/NOT SATISFACTORY FOR 2 YR EXPIRY

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCT, HFD-170
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-747

REVIEW # 3 **DATE REVIEW COMPLETED: 7.16.97**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	6.19.97	6.20.97	
AMENDMENT	6.20.97	6.23.97	
AMENDMENT	6.27.97	6.30.97	
AMENDMENT	7.10.97 (FAX)		

NAME & ADDRESS OF APPLICANT:
Anesta Corp, 4745 Wiley Post Way, Suite 650, Salt Lake City, UT 84116. Drug product is manufactured and distributed by Abbott Laboratories, North Chicago, Illinois 60064.

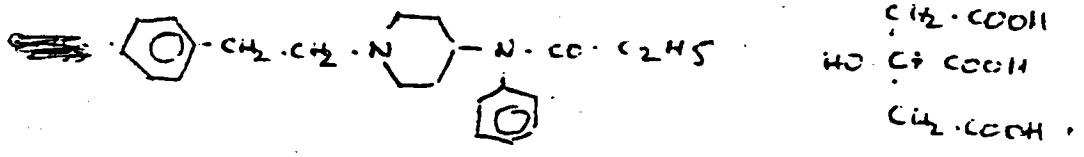
DRUG PRODUCT NAME
Proprietary: ACTIQ (CII).
Established: Oral Transmucosal Fentanyl Citrate (OTFC).
Code Name/#: CAS# 990-73-8
Chem.Type/Ther.Class: 3P
PHARMACOL. CATEGORY: Analgesic for chronic pain in cancer patients tolerant to opioids (30 min for maximum analgesia; warning: may be habit forming).

DOSAGE FORM: Raspberry flavored off-white color and conical round shape lozenge with a non-prominant marking of potency on the lozengestick.

Different colors are used as the background for printing ACTIQ on the label, namely, gray for 200 mcg, blue for 400 mcg, orange for 600 mcg, purple for 800 mcg, green for 1200 mcg, and burgundy for 1600 mcg.

STRENGTHS: 200, 400, 600, 800, 1200, and 1600 mcg.
ROUTE OF ADMINISTRATION: Oral transmucosal.
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
N-(1-phenethyl-4-piperidyl)-propionalide citrate (1:1); Fentanyl citrate mol wt is 528.6 (free base mol wt is 336.5); pKas are 7.3 and 8.4. See USP 23 page 654.



REMARKS:

AMENDMENT dated 6.19.97 is a resubmission of foil pouch labels for 200,400,600,800,1200 and 1600 mcg, and it is SATISFACTORY.

- AMENDMENT dated 6.20.97 is for updated stability data in the proposed market package. 3 moths stability up date is for 20-882-JE/200 mcg, 20-883-JE/600 mcg and 20-884-JE/1600 mcg manufactured in Nov 96; and 6 months stability up date is for 20-738-JE/200 mcg, 20-739-JE/600 mcg and 20-740-JE/1600 mcg manufactured in Sept 96. These lots were stored at 25 C but NOT TESTED FOR DECOMPOSITION PRODUCTS.

- AMENDMENT dated 6.27.97 is for two Anesta's unaudited reports generated by their contractors. (1) 1st report dated 5th May 97 is for moisture barrier testing (vapor transmission for 6 mil thick barrier in units of gm per 100 sq inch per day with MoCon test instrument). (2) 2nd report dated 13 April 94 is for child resistant feature testing (3 mil Valeron and 200 children).

  FAX dated 7.10.97 to inform Anesta's preference to launch in Fentanyl OTFC in ACTIQ package with shorter expiry date.

- EA deficiencies were communicated to Anesta in a fax dated 5.5.97, but I have not seen Anesta's's response.

cc:
Orig. NDA 20747
HFD-170/Division File
HFD-170/PMaturu, AD'Sa
HFD-820/JGibbs

filename: N20747r3.97
WITHHOLD APPROVAL

/S/
P.Maturu,PhD, Primary Review Chemist

/S/ 7/15/97
A.D'Sa,PhD, Chemistry Team Leader

This review does not change the previous recommendation which was to withhold approval.

7/15/97

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCT, HFD-170
Review of Chemistry, Manufacturing, and Controls

NDA #: 20747

REVIEW #2 **DATE REVIEW COMPLETED: 5.22.97**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	4.23.97	4.25.97	
AMENDMENT	3.27.97	3.28.97	4.14.97
AMENDMENT	3.21.97	3.24.97	
AMENDMENT	1.13.97	1.14.97	

NAME & ADDRESS OF APPLICANT:
Anesta Corp, 4745 Wiley Post Way, Suite 650, Salt Lake City, UT 84116. Drug product is manufactured and distributed by Abbott Laboratories, North Chicago, Illinois 60064.

DRUG PRODUCT NAME
Proprietary: ACTIQ (CII).
Established: Oral Transmucosal Fentanyl Citrate (OTFC).
Code Name/#: CAS# 990-73-8
Chem.Type/Ther.Class: 3P

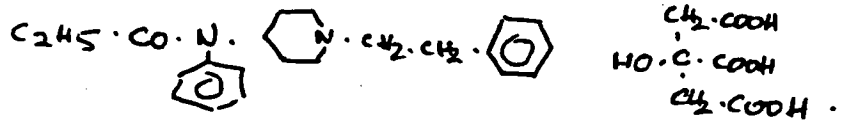
PHARMACOL. CATEGORY: Analgesic for chronic pain in cancer patients tolerant to opioids (30 min for maximum analgesia; warning: may be habit forming).

DOSAGE FORM: Raspberry flavored off-white color and conical round shape lozenge with a non-prominant marking of potency on the lozengestick.

Different colors are used as the background for printing ACTIQ on the label, namely, gray for 200 mcg, blue for 400 mcg, orange for 600 mcg, purple for 800 mcg, green for 1200 mcg, and burgundy for 1600 mcg.

STRENGTHS: 200, 400, 600, 800, 1200, and 1600 mcg.
ROUTE OF ADMINISTRATION: Oral transmucosal.
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
N-(1-phenethyl-4-piperidyl)-propionalide citrate (1:1); Fentanyl citrate mol wt is 528.6 (free base mol wt is 336.5); pKas are 7.3 and 8.4. See USP 23 page 654.



REMARKS:

AMENDMENT dated 4.23.97: Response is not SATISFACTORY.

The conflict is with regard to the required number of lots, potencies, and storage conditions for expiration dating for NDA 20747 Fentanyl citrate lozenges. The applicant wants approval on the basis of testing of one lot per potency for 3 out of 6 potencies stored at 25 C and 40 C. Approval on this basis meant ONDC has to grant a waiver from the requirement for stability testing on 3 lots per potency for 6 potencies, as per CPG 7132a.04.

To diffuse this conflict, a recommendation was made to the applicant to switch the container-closure to the container-closure used in NDA 20195 for Fentanyl citrate lozenges. However, this recommendation was rejected by the applicant. To comply with ICH recommendation for stability testing, a recommendation was made to the applicant to conduct stability tests on samples stored at 25 C/60% RH and 40 C/75% RH. However, this storage condition was rejected by the applicant. See `market product stability protocols' for 6 potencies, SEE ENCLOSED PAGE 25.

AMENDMENT dated 3.27.97: Response is SATISFACTORY.

The applicant has used the established name as `oral transmucosal fentanyl citrate' but the `Labeling and Nomenclature Committee' has initaly disallowed it and made a recommendation to use `fentanyl citrate lozenges'. This recommendation is based on USP nomenclature. However, the applicant has disagreed with this recommendation. Labeling committee has changed its initial position based on the precedence with NDA 20195 for Fentanyl citrate lozenges for use of established name as `oral transmucosal fentanyl citrate', coupled with the arguments presented by the applicant - lozenges are meant for `topical action' and not for `systemic action' and rebuttal on pages 15-153 to 164 from the `Law Offices of Burditt & Radizius'.

AMENDMENT dated 3.21.97: Response is not satisfactory for items 7 and 8 dealing with expiration dating and stability testing.

CMC information request was sent for 10 items, by a fax dated 3.6.97 and followed with a division letter dated 3.21.97. Applicant has responded with CMC information on the clinical materials used in pivotal clinical studies, such as, chromatograms for the 2 Fentanyl citrate lots 04368-KA and 12847-KA used for compounding the 3 stability lots for expiration dating (item 1, SEE ENCLOSED PAGES 15-22), chromatograms for Fentanyl citrate lozenges (item 2, SEE ENCLOSED PAGES 7-14), U.S.P. quality test results for the container-closure system (item 3), chromatograms for Fentanyl citrate lozenges stored for 3 months at 40 C in proposed container-closure system (item 4), linkages from clinical protocol no to drug product lot no to drug substance lot no (item 5), one page publication on medicated candies by Dyer with poor print quality (item 6), deleted compression molded lozenge patent as requested (item 9), and

a rebuttal to comply with a fentanyl assay in dissolution fluids (item 10).

AMENDMENT dated 1.13.97: Response is not satisfactory.

Updated stability with test results for one lot per potency for 3 out of 6 potencies packaged in proposed container-closure system and stored for 3 months at 40 C. Tested for Fentanyl citrate assay and NOT TESTED (NT) for hydrolytic degradation products and oxidative decomposition products (SEE ENCLOSED PAGES 4-6). Marketing authorization request is for 2 year expiration date is supported with lots manufactured in Sept 96 for the NDA filing in November 96, and they are identified as lots 20738-JE/200 mcg, 20739-JE/600 mcg and 20740-JE/1600 mcg. This is the only relevant data.

Significantly different foil laminates are used for the construction of pouches for packaging Fentanyl citrate lozenges for the two indications, NDA 20747 for chronic pain indication and NDA 20195 Fentanyl citrate lozenges for pediatric sedation. Polyester/foil/Extrel 335 polypropylene laminate is used for NDA 20915 and Polyester/Valeron/white ethylene acrylic acetate/foil/ethylene acrylic acetate/linear low density polyethylene laminate is used for NDA 20747.

Non-prominent marking of potency on stick is another troubling issue in the approval of container-closure system for NDA 20747. Prominent marking of potency is recommended by the Drug Advisory Committee.

CONCLUSIONS & RECOMMENDATIONS:

Recommends `withhold of approval' for failure to test adequate number of batches as the basis for Expiration Dating for NDA 20747 Fentanyl citrate lozenges.

The applicant has disagreed to make a switch to NDA 20195 container-closure configuration, that is, disk shaped flange/paddle handle, with overcap polypropylene, polyester/foil/Extrel 335 polypropylene foil pouch. The applicant has not provided any moisture permeation rate to show superiority or equivalency for the 2 container-closure systems, approved NDA 20195 Fentanyl citrate lozenges and current NDA 20747 Fentanyl citrate lozenges.

EA deficiencies were communicated in a fax dated 5.5.97, and I have not seen the response.

/S/ 5.22.97
P.Maturu,PhD, Primary Review Chemist

/S/ 10/10/97
A.D'Sa,PhD, Chemistry Team Leader

cc:
Orig. NDA 20747
HFD-170/Division File
HFD-170/PMaturu, AD'Sa, K Nolan
HFD-820/JGibbs

filename: N20747r2.97
WITHHOLD APPROVAL

This review may have already been recorded CSO - please note.

20-747

FEB 26 1997
DIV. File

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCT, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 20747

REVIEW # 1 DATE REVIEWED: 1.28.97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	11.11.96	11.13.96	11.22.96

NAME & ADDRESS OF APPLICANT:
Anesta Corp, 4745 Wiley Post Way, Suite 650, Salt Lake City, UT 84116.

Drug product will be manufactured and distributed by Abbott Laboratories, North Chicago, Illinois 60064.

DRUG PRODUCT NAME

Proprietary: ACTIQ (CII).
Established: Oral Transmucosal Fentanyl Citrate (OTFC).
Code Name/#: CAS# 990-73-8
Chem.Type/Ther.Class: 3P

PHARMACOL. CATEGORY: Analgesic for chronic pain in cancer patients tolerant to opioids (30 min for maximum analgesia; warning: may be habi forming).

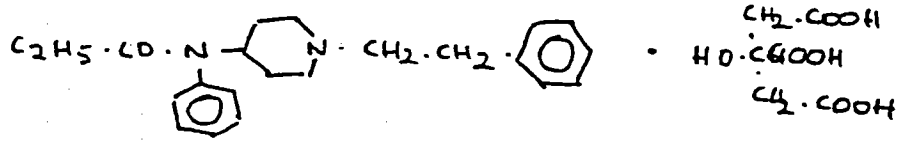
DOSAGE FORM: off-white color and conical round shape lollipop. Lollipop is on a white plastic stick without the disk shaped flange/paddle handl and without the overcap. Lollipop stick is in a child resistant foil pouch (16 CFR 1700). Lollipop is in contact with foil pouch.

To prevent product mix up, different colors were chosen for the child resistant foil pouch, namely, gray for 200 mcg, blue for 400 mcg, orang for 600 mcg, purple for 800 mcg, green for 1200 mcg, and burgundy for 1600 mcg.

Exclusivity claim was based on US Patents 4671953 and 5288497 assigned to University of Utah Research Foundation, Salt Lake City, Utah.

STRENGTHS: 200, 400, 600, 800, 1200, and 1600 mcg.
ROUTE OF ADMINISTRATION: Oral transmucosal.
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
N-(1-phenethyl-4-piperidyl)-propionalide citrate (1:1); Fentanyl citrate mol wt is 528.6 (free base mol wt is 336.5); pKas are 7.3 and 8.4. See USP 23 page 654.



N-(1-phenethyl-4-piperidyl)-propionalide citrate (1:1); Fentanyl citrate mol wt is 528.6 (free base mol wt is 336.5); pKas are 7.3 and 8.4. See USP 23 page 654.

REMARKS:

Marketing authorization request for Fentanyl OTFC with 2 year expiry date was supported with one month stability for 3 stability lots in the proposed market package (without the overcap, without the paddle handle, and Pet/Valeron/Foil/LLDPE pouch material). Executed batch records were submitted for these 3 stability lots, 20738-JE/200 mcg/9.16.96, 20739-JE/600 mcg/9.17.96 and 20740-JE/1600 mcg/9.18.96. A review of the executed batch records has indicated the usage of 2 lots of drug substance, 04368-KA and 12847-KA, and an incomplete packaging of only 720 units out of 60,000 units.

A significant change has occurred from Phase III clinical material to proposed marketing request. Phase III clinical material has non-market package (with the overcap, with the paddle handle, and Polyester/Foil/Polypropylene pouch material). One year of partial testing results were submitted on Phase III clinical material, 03-919-DH/200 mcg; 03-920-DH/400 mcg; 03-921-DH/600 mcg; 03-922-DH/800 mcg; 03-923-DH/1200 mcg; 03-924-DH/1600 mcg. Partial stability testing has meant the exclusion of hydrolytic degradation products test and oxidative degradation products test.

Lemon and raspberry flavored Fentanyl OTFCs were used in Phase II clinical testing. Biobatch was 66865-DH/800 mcg, to link 2 different formulations (lemon flavor formulation and raspbery flavor formulation). Biobatch record was not submitted.

Phase I clinical material was subjected to following tests for quality, weight uniformity, GC assay with papaverine as internal standard, and GC retention time as identity (Fentanyl citrate USP was supplied by [redacted]). This IND original file was reviewed on 11.12.85 in HFD-160 by Dr. John Gibbs. See enclosed chemists review notes.

CONCLUSIONS & RECOMMENDATIONS:

CMC section for NDA 20747 is INADEQAUTE.

The following CMC information is requested.

cc:
Original N.D.A. 20-747
HFD-170/Div. File
HFD-170/PMaturu, AD'Sa, Mwright
FileName:N20747
Primary Review Chemist, P. Maturu, Ph.D. /S/ 1-25-97

Chemist, Team Leader, AD'Sa, Ph.D. /S/ 2/26/97