

Treatment-related effects in male and female dogs that could be attributed to the test article administration included salivation and sedation. No significant local irritation was attributed to disc administration in these three studies with Draize scores of 0.0019, 0.0038, & 0, respectively. Histological examination of cheek mucosa in the study with the free base identified no treatment-related effects. The pharmacokinetic part of these studies demonstrated that fentanyl was effectively delivered through the BEMA formulation (toxicokinetic data reported in section 2.6.5).

In addition, local tolerance was evaluated following buccal administration of a placebo disc or a disc containing fentanyl citrate twice daily, at least 6 hours apart, for 28 days in beagle dogs (Study No. 0436DA76.001). There were no treatment-related lesions attributed to the test article administration noted in samples of oral mucosa examined for this study. More detailed report of this study contained in this section under General toxicology and in the following section 2.6.6.3.

Special toxicology: no studies were conducted.

2.6.6.2 Single-dose toxicity - none reviewed other than GLP local tolerance studies (summaries only reported previously in section 2.6.6.1)

2.6.6.3 Repeat-dose toxicity

Study title: 28-Day buccal toxicity study in dogs with BioErodable MucoAdhesive (BEMA) fentanyl

Key study findings:

- Dogs administered 273 µg BEMA fentanyl bid (546 µg/day) for 28 days exhibited clinical symptoms consistent with the pharmacological action of fentanyl, notably decreased activity, excessive salivation, brown mucous in feces, abnormal gait and stance, emesis, and tremors
- decreased absolute neutrophils, lymphocytes, and monocytes in males
- increased absolute and relative spleen weights (21-50%) and ovary weights (33-74%) in fentanyl-treated animals (histology not performed)
- no NOAEL identified

Study no.: 0436DA76.001

Volume #, and page #: electronic document of 306 pages

Conducting laboratory and location _____

b(4)

Date of study initiation: July 25, 2005 (report date December 13, 2005)

GLP compliance: yes

QA report: yes (x) no ()

Drug, lot #, and % purity: BEMA fentanyl _____, 79077 (pH 6), 79079 (pH 7.25), & 79081 (pH 8.5) – composition (e.g., impurities, etc. not reported) ; PC790 is product patch/disk

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Bulk Product Description	Bulk Product Material Number	Bulk Product Batch Number	Labelled Product Material Number	Labelled Product Batch Number
PC790 BDS, 1.1 cm ² -Formula 1 (Product Patch, 1.1 cm ² , pH ~8)	5000590	34789	5000602	79079
PC790 BDS, 1.1 cm ² -Formula 2 (Product Patch, 1.1 cm ² , pH ~7)	5000591	34787	5000596	79077
PC790 BDS, 1.1 cm ² -Formula 3 (Product Patch, 1.1 cm ² , pH ~9)	5000592	34807	5000601	79081

Methods

Doses:

Group	Dose Level (mcg/dose)	Number of Animals	
		Male	Female
1. Control (Placebo disk)	0	3	3
2. BEMA Fentanyl Citrate, pH 6	273	3	3
3. BEMA Fentanyl Citrate, pH 7.25	273	3	3
4. BEMA Fentanyl Citrate, pH 8.5	273	3	3

Species/strain: Beagle dogs

Number/sex/group or time point (main study): 3/sex

Route, formulation, volume, and infusion rate: buccal, drug on opaque pink disc of 1.1 cm² (Aneva Drug Delivery Systems), bid (right side in morning and left side 6 hours later) for 28 days

Satellite groups used for toxicokinetics or recovery: none

Age: 7-8 months

Weight: 6.5-9.6 kg

Sampling times: none

Unique study design or methodology (if any): none

Observation and Times:

Clinical signs: before dosing and 1-2 hours post dose

Body weights: at randomization and before dosing on days 1, 8, 15, & 22, after dosing on day 28, and fasting weight on day 29 before sacrifice

Food consumption: daily

Ophthalmoscopy: pretreatment period, pre terminal sacrifice on day 29

EKG: predosing period, pre terminal sacrifice on day 29 with 8 lead apparatus

Hematology: predosing period, pre terminal sacrifice on day 29

Hematology Parameters	
Red Blood Cell Count (RBC) and Morphology	Platelet count (PLT)
White Blood Cell Count (WBC)*	Hematocrit (HCT)
Mean Corpuscular Hemoglobin (MCH)	Hemoglobin (HGB)
Mean Corpuscular Hemoglobin Concentration (MCHC)	Reticulocyte Count (Retic)
Mean Corpuscular Volume (MCV)	

*Total and differential white blood cell counts, including neutrophils, basophils, eosinophils, monocytes, lymphocytes and large unstained cells

Coagulation Parameters	
Activated Partial Thromboplastin Time (APTT)	Prothrombin Time (PT)

Clinical chemistry: pre-dosing period, pre-terminal sacrifice on day 29

Clinical Chemistry Parameters	
Alanine Aminotransferase (ALT)	Globulin (calculated)(GLOB)
Albumin (ALB)	Glucose (GLU)
Albumin/Globulin ratio (calculated)(A/G)	Phosphorus (PHOS)
Alkaline Phosphatase (ALP)	Potassium (K)
Aspartate Aminotransferase (AST)	Sodium (NA)
Calcium (CA)	Total Bilirubin (T-BIL)
Chloride (CL)	Total Protein (TP)
Cholesterol (CHOL)	Triglycerides (TRIG)
Creatinine (CREAT)	Urea Nitrogen (BUN)

Urinalysis: none

Gross pathology: day 29

Organ weights:

Organs Weighed	
Adrenals	Testes
Brain	Ovaries
Heart	Spleen
Kidneys	Thyroids/parathyroids
Liver	

Histopathology: Only evaluation was of oral mucosa (all animals) Other tissues stored.

Adequate Battery: yes (), no (x)

Peer review: yes (), no (x)

The histopathology evaluation was only adequate for local, site of application effects. Although any gross lesions were to be evaluated, which did not occur, without inclusion of organs for microscopic evaluation determination of systemic toxicity/safety cannot be determined.

Eyes and testes in Bouin's fixative, rest in 10% neutral buffered formalin. Slide preparation and histopathological evaluation conducted by _____

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Tissues Collected	
Cardiovascular	Urogenital
Aorta	Kidneys
Heart	Urinary Bladder
Digestive	Ovaries
Salivary gland(s)	Uterus

Tongue	Cervix
Esophagus	Vagina
Stomach	Testes
Small Intestine	Epididymides
Duodenum	Prostate
Jejunum	Endocrine
Ileum	Adrenals
Large Intestine	Pituitary
Cecum	Thyroid/Parathyroid
Colon	Skin/Musculoskeletal
Rectum	Skin
Pancreas	Mammary Gland
Liver	Skeletal Muscle (thigh)
Gallbladder	Femur with articular surface
Respiratory	Nervous/Special Sense
Trachea	Eye with optic nerve
Larynx	Sciatic Nerve
Lung with mainstem bronchus	Brain
Lymphoid/Hematopoietic	Spinal Cord - cervical
Sternum with bone marrow	Spinal Cord - midthoracic
Thymus	Spinal Cord - lumbar
Spleen	Lacrimal Glands
Lymph Nodes	Other
Mandibular	Unique Animal Identifier (not for evaluation)
Mesenteric	Gross Findings
	Oral mucosa (treated and untreated)

Results: NOTE – all animals except controls received same dose of fentanyl though formulations were different.

Mortality: none

Clinical signs: all fentanyl treated animals exhibited expected symptoms of decreased activity, excessive salivation, brown mucous in feces, abnormal gait and stance, emesis, and tremors

Body weights: body weight changes over the treatment period were +4, -5, -10, & -7% (males) and +2, -8, -10, & -9% (females) for control and 3 treatment groups, respectively

Food consumption: daily food consumption was reduced in all treatment groups compared to control group throughout the study with some daily values being up to 30% of control values

Ophthalmoscopy: nothing remarkable

EKG: nothing remarkable

Hematology:

- all groups: decreased WBCs both sexes and neutrophils (females only)
- treatment groups only: decreased absolute neutrophils (males), lymphocytes (males), and monocytes (males)
- no treatment effect on erythrocyte morphology or coagulation parameters.

Hematology changes compared to baseline values over the treatment period in dogs receiving buccal BEMA fentanyl for 28 days bid				
	Patch only	273 µg fentanyl (pH 6)	273 µg fentanyl (pH 7.25)	273 µg fentanyl (pH 8.5)
Males				
# white blood cells	-5%	-33%	-45%	-24%
# neutrophils	-10%	-46%	-54%	-15%
# lymphocytes	No change	+2%	-22%	-40%
# monocytes	+15%	-29%	-54%	-16%
Females				
# white blood cells	-33%	-46%	-30%	-37%
# neutrophils	-47%	-48%	-31%	-44%

Clinical chemistry: nothing remarkable

Urinalysis: not conducted

Gross pathology: nothing remarkable

Organ weights: slight increase in absolute and relative spleen weights and ovary weights in fentanyl treated animals (histology not performed)

Organ weight changes compared to controls after treatment period in dogs receiving buccal BEMA fentanyl for 28 days bid				
		273 µg fentanyl (pH 6)	273 µg fentanyl (pH 7.25)	273 µg fentanyl (pH 8.5)
Males				
Spleen	absolute	+24%	+21%	+34%
	relative	+44%	+38%	+50%
Testes	absolute	-8%	+13%	-23%
	relative	+20%	+30%	-10%
Females				
Spleen	absolute	+37%	+33%	+26%
	relative	+48%	+49%	+31%
Ovaries	absolute	-53%	-55%	-74%
	relative	-33%	-33%	-67%

Histopathology: nothing remarkable for oral mucosa (only tissue examined)

Toxicokinetics: not conducted

2.6.6.4 Genetic toxicology – nothing new submitted/reviewed (see referenced drugs for fentanyl). Summaries in section 2..6.6.1.

2.6.6.5 Carcinogenicity – nothing new submitted/reviewed (see referenced drugs for fentanyl)

2.6.6.6 Reproductive and developmental toxicology – nothing new submitted/reviewed (see referenced drugs for fentanyl). Summaries in section 2.6.6.1.

2.6.6.7 Local tolerance – see summaries in section 2.6.6.1

2.6.6.8 Special toxicology studies – nothing new submitted/reviewed (see referenced drugs for fentanyl)

2.6.6.9 Discussion and Conclusions

While local toxicity was not observed in the submitted nonclinical studies, the single or twice daily (28-day study) applications were not adequate to cover proposed applications of up to 4 times/day. In regards to the 28-day repeat-dose study, as noted in the minutes of the meeting of September 15, 2006 for IND 62,864 (BEMA fentanyl), the data provided does not fully address the safety concerns as the nonclinical study is considered inadequate for the following reasons:

1. The product used was the lowest-strength disc formulation,
2. The disc was administered twice daily while the clinical usage would be expected to allow for 4 applications per day, and
3. The disc was rotated between two sites while there is no requirement that the disc is rotated in clinical studies

Therefore, the 28-day study performed does not accurately mimic the clinical usage of the product and does not provide sufficient local exposure to allow a full evaluation of the potential safety concerns with clinical use. Single dose pharmacokinetic studies for dogs (see section 2.6.5 tables; no 28-day dog pharmacokinetic data) also did not support systemic exposure levels as the highest values were a C_{max} of 6.76 ng/mL and an AUC of 16.71 ng•h/mL at the maximum dose tested while single dose human values were a C_{max} of 2.19 ng/mL and an AUC of 20.43 ng•h/mL at a 1200 µg dose, ¼ of the proposed maximum dose. Assuming linearity, a maximum proposed human dose rate of 4 times/day at 1200 µg/dose would result in human exposures in excess of those received by the dogs, thereby identifying inadequate human safety margins. On this basis, for this 505(b)(2) application, safety for potential systemic exposures that result from the proposed use and indication for the submitted drug are covered by reference drugs DURAGESIC® and ACTIQ®. Potential local toxicity is also covered by ACTIQ® with an application rate of up to 6 times/day, clinical experience with ONSOLIST™, and clinical monitorability of local effects.

2.6.6.10 Tables and Figures – see individual sections

2.6.7 TOXICOLOGY TABULATED SUMMARY – see individual summaries and reviews

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

While the submitted nonclinical data (local and systemic toxicity after single doses and twice daily doses for 28-days) does not support the proposed clinical dosing, clinical safety is supported for the proposed dosing and indication based on the reference drugs, clinical experience, and monitorability (local toxicity). Also, due to the severity of the indication being sought and the ability to monitor and evaluate local buccal effects in clinical studies, repeat of the buccal toxicity study in the dog will not be required to address this concern. The local tolerance studies were also less than optimal to assess local effect as exposure conditions compared to the proposed drug as 1 dose was applied 1 time compared to up to 4 doses per day with the proposed drug product over multiple days. Again, this will not need to be repeated for the above reasons.

Unresolved toxicology issues: none for this submission

Recommendation: NDA approval is recommended.

Suggested labeling: (For nonclinical-based label sections sponsor's proposed labeling agrees with Actiq reference label except for animal:human dose ratios, which remain unchanged from reference label because differing bioavailability between Actiq and Onsolis result in comparable absorption at proposed doses.)

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Signatures (optional):

Reviewer: Gary P. bond, Ph.D., DABT

Supervisor: Adam M. Wassermann, Ph.D. Concurrence Yes No

APPENDIX/ATTACHMENTS - none

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Gary Bond
7/2/2008 08:43:50 AM
PHARMACOLOGIST

Adam Wasserman
7/2/2008 10:57:00 AM
PHARMACOLOGIST
I concur with Dr. Bond.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

Division of Anesthesia, Analgesia, and Rheumatology Products

NDA Number: 22-266

Applicant: BioDelivery Sciences
International

Stamp Date: 10/31/2007

Drug Name: BEMA™ Fentanyl (Bioerodable Mucoadhesive Fentanyl Citrate)

IS THE PHARM/TOX SECTION OF THE APPLICATION FILEABLE? Yes [X] No []

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are final reports of ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? Have electronic files of the carcinogenicity studies been submitted for statistical review?	X		No carcinogenicity data required.
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	X		
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
7	For a 505(b)(2) submission, has the sponsor identified a referenced product?	X		ACTIQ® - NDA 20-747
8	For a 505(b)(2) submission, has the sponsor submitted patent certification information to support the information referenced in the proposed drug product labeling?	X		
9	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	X		
10	Based upon a cursory review, do the excipients appear to have been adequately qualified?	X		While inactive ingredient/excipient carboxymethylcellulose (CMC) at _____ at 1200 mcg drug product or _____ if dose qid) in drug product - approved oral suspension with _____, and oral dose of _____ as CMC calcium and sodium approved at _____ and all excipients considered qualified based on historical oral use, 28-day buccal study in dogs, and literature review per prior Agency agreement (September 15, 2006).
11	Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)?		X	None required - Structural alert for _____

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			addressed. Per September 15, 2006 meeting (PPA not structural alert) and again at June 28, 2007 preNDA meeting. At _____ in drug product (specification of ≤ _____, maximum recommended dose of 1200 mcg qid would yield less than genotoxicity qualification requirement of _____
12	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X	
13	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X	
14	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	X	
15	From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.	X	
16	If the NDA is fileable, are there any filing review issues that need to be conveyed to Sponsor? If so, specify:	X	

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Reviewing Pharmacologist: Gary P. Bond, Ph.D.

Team Leader: Adam M. Wasserman, Ph.D.

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this page is the manifestation of the electronic signature.**

/s/

Gary Bond
12/10/2007 07:40:06 AM
PHARMACOLOGIST

Adam Wasserman
12/10/2007 01:15:43 PM
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