

B. Pharmacologic activity

Based on the extensive historical use of approved fentanyl products as analgesics in the United States, no new pharmacology studies were conducted to further evaluate the pharmacologic properties of fentanyl for this 505(b)(2) submission. Thus, the following summary of nonclinical pharmacology is based on publicly available information on fentanyl and approved drug fentanyl products, ACTIQ® (NDA 20-747) and DURAGESIC® (NDA 19-813):

Fentanyl is a potent, short-acting, synthetic opioid analgesic used in anesthesia, post-operative analgesia, and chronic pain management. Fentanyl acts as a μ -opioid receptor agonist with a potency 100-fold greater than that of morphine. It has been widely used for over 3 decades in clinical and veterinary practice, both alone and in combination formulations. Fentanyl is currently available in intravenous, transdermal patch, oral transmucosal, and buccal tablet formulations. In addition, fentanyl has also been administered via transdermal iontophoresis, intranasal, transpulmonary, and epidural routes. Fentanyl has an extremely rapid onset and a duration of action lasting approximately 30 minutes after intravenous administration. Although the response to fentanyl is subject to significant inter-individual variability, there is a direct relationship between the concentration of fentanyl in plasma and its effects.

C. Nonclinical safety issues relevant to clinical use

Under the current submission, the safety of proposed human dose levels is supported by the reference drugs and submitted clinical trials. The nonclinical data doesn't support the maximal human dosing proposed for the drug product in regard to potential local and systemic toxicity.

Assessment of local irritation/tolerance was evaluated at drug application sites following 3 single dosing or 1 two-dose/day 28-day repeated dose application studies at different sites. Dosing in these studies did not mimic potential clinical use for the maximum number of applications (up to 4 per day at the same site) and did not cover the highest proposed dose (1200 μ g up to 4 times per day). While no differing local irritation was attributed to BEMA™ fentanyl administration in these studies when compared with a placebo disc, local tolerance/safety relative to the proposed maximal clinical use cannot be determined using this data as dosing was less than proposed maximal dosing.

Assessment of systemic toxicity was evaluated by a repeated-dose 28-day dermal study was conducted in dogs with BEMA fentanyl. This study was inadequate for assessment of systemic safety as the doses were too small and not applied in a comparable manner as for the proposed drug. However, based on preNDA agreements listed previously (September 15, 2006) for this specific medical indication for management of breakthrough pain in cancer patients who are

already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain and supporting RLDs, there are no nonclinical safety issues that apply to this application's clinical use.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-266

Review number: 1

Document Support #/date/type of submission: 000/October 31, 2007/original
 000/March 11, 2008/BL
 000/May 7, 2008/BL

Information to sponsor: Yes () No (x)

Sponsor and/or agent: BioDelivery Sciences International, 2501 Aerial Center Parkway, Suite 205, Morrisville, NC 27560

Manufacturer for drug substance: _____

b(4)

Reviewer name: Gary P. Bond, Ph.D., DABT

Division name: Division of Anesthesia, Analgesia and Rheumatology Products

Review completion date: July 1, 2008

Drug:

Trade name: ONSOLIST™

Generic name: BEMA™ Fentanyl (name during IND development)

b(4)

Code name: 1130 - _____ USP special

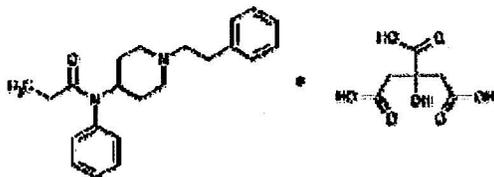
Chemical name: Propanamide *N*-Phenyl-*N*'-[1-(2-phenylethyl)-4-piperidinyl] citrate (1:1)

b(4)

CAS registry number: 990-73-8

Molecular formula/molecular weight: C₂₂H₂₈N₂O•C₆H₈O₇/528.59 (salt),
 336.49 (free base)

Structure:



Relevant INDs/NDAs/DMFs:

IND 62,864 (BEMA fentanyl) _____

b(4)

NDA 20-747 ACTIQ® is a reference drug for this 505(b)(2) application
 - Fentanyl Citrate Oral Transmucosal Lozenge

NDA 19-813 DURAGESIC® is a reference drug for this 505(b)(2) application
 - Fentanyl Transdermal system

DMF _____

b(4)

Drug class: opioid analgesic

Intended clinical population: management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain

Clinical formulation: no issues

Drug Substance

Structural alert status for [redacted] addressed. Per September 15, 2006 meeting [redacted] was a structural alert with post-meeting notes indicating that [redacted] not a structural alert. Regardless, a [redacted] in drug product (specification of [redacted] the maximum recommended dose of 1200 mcg qid would yield a total daily intake (TDI) of [redacted] which is less than the structural alert qualification level for genotoxic impurities of [redacted]

b(4)

b(4)

Table 2.3.S.4-1. Fentanyl Citrate Specification		
Test	Acceptance Criteria	Analytical Procedure
Appearance	White to off-white powder	Visual, STP 101
Identification, IR	Compares to standard	STP 141 USP <197K>
Identification, UV	Compares to standard	USP <197U>
Loss on Drying	≤0.50%	USP <731>
Residue on Ignition	[redacted]	USP <281>
Heavy Metals	≤0.002%	USP <231>
Ordinary Impurities	[redacted]	USP <466>, TLC
Assay Titration	98.0-102.0%	USP Monograph
Assay	98.0-102.0%	HPLC, STP 519
Purity and Related Substances (% w/w):	[redacted]	HPLC, STP 519
[redacted]	[redacted]	
Unknown Related Substances (Each)	[redacted]	
Total Related Substances	[redacted]	

b(4)

b(4)

b(4)

Drug Product

The drug product is in the form of a BEMA (BioErodable MucoAdhesive) that contains 200, 400, 600, 800, or 1200 µg of fentanyl free base. Although inactive ingredient/excipient carboxymethylcellulose (CMC) present at [redacted] at 1200 µg drug product or [redacted] if dose qid) in the drug product is only approved at [redacted] CMC is considered qualified based and oral CMC calcium and sodium approved at [redacted] In addition, all excipients considered qualified based on historical oral use, 28-day buccal study in dogs, and literature review per prior Agency agreement (September

b(4)

15, 2006). The components of the BEMA are also at levels which are at or below approved levels or considered qualified as noted above.

Table 2.3.P.1-2. Unit Composition (mg/Unit)

Component	% wt/wt Dry Weight	Strength (µg Fentanyl Free Base)				
		200	400	600	800	1200
Fentanyl Citrate						
Water						
Propylene Glycol						
Sodium Benzoate						
Methylparaben						
Propylparaben						
Ferric Oxide						
Citic Acid						
Vitamin E						
Monobasic Sodium Phosphate						
Sodium Hydroxide						
Tribasic Sodium Phosphate						
Polycarophil						
Hydroxypropyl Cellulose						
Hydroxyethyl Cellulose						
Carboxymethylcellulose						
Titanium Dioxide						
Saccharin Sodium						
Peppermint Oil						
Total Weight (mg)						

b(4)

b(4)

b(4)

b(4)

The disc has a bilayer structure composed of a bioadhesive layer and a backing layer. The two layers are bonded together and fentanyl is incorporated into the bioadhesive layer, which contacts the buccal mucosa. The flexible BEMA disc adheres readily to the mucosa, where it softens upon contact with moisture, rapidly becoming unnoticeable. As the BEMA product delivers the dose of fentanyl, the disc dissolves, so that there is no requirement to remove the disc from the mucosa. The backing layer of the disc minimizes drug release into the oral cavity and maximizes delivery to the mucosal tissue.

b(4)

Table 2.3.P.1-3. Approximate Dimensions

Strength (µg)	Area (cm ²)	Weight (mg)	Length (mm)	Width (mm)	Thickness Mucoadhesive (mm)	Thickness Backing (mm)	Thickness Total (mm)
200							
400							
600							
800							
1200							

b(4)

b(4)

Figure 2.3.P.1-2 Drug product dimensions.

Route of administration: buccal

Disclaimer: Tabular and graphical information are constructed by the sponsor unless cited otherwise. Sponsor's summary text may be used for descriptive purposes when no new studies have been conducted or, for new studies, if in agreement with reviewer's review and assessment.

Data reliance for this 505(b)(2) application: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-266 are owned by BioDelivery Sciences International or are data for which BioDelivery Sciences International has obtained a written right of reference. Any information or data necessary for approval of NDA 22-266 that BioDelivery Sciences International does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that BioDelivery Sciences International does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-266.

Studies reviewed within this submission:

Toxicology:

28-Day buccal toxicity study in dogs with BioErodable MucoAdhesive (BEMA) fentanyl (study 0436DA76.001)

Local tolerance:

Evaluation of the pharmacokinetics of BEMA™-fentanyl free base after application to the buccal mucosa in dogs (study ATLS-138)

Evaluation of the pharmacokinetics of BEMA™-fentanyl after application to the buccal mucosa in dogs (study ATLS-141)

b(4)

A single-dose toxicokinetics and toxicity study in dogs given BEMA™ - fentanyl — applied to the buccal mucosa (study ATLS-159)

b(4)

Studies not reviewed within this submission:

All other submitted studies. Sponsor summary data has been used for these studies which do not impact on the nonclinical safety assessment of the proposed drug.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 Primary pharmacodynamics

2.6.2.3 Secondary pharmacodynamics

2.6.2.4 Safety pharmacology

2.6.2.5 Pharmacodynamic drug interactions

Based on the extensive historical use of fentanyl as in FDA-approved analgesic products in the United States including the reference drugs ACTIQ® (NDA 20-747) and DURAGESIC® (NDA 19-813), no new pharmacology studies were conducted to further evaluate the pharmacologic properties of fentanyl.

Clinically relevant descriptions are contained in the proposed labels which are based on RLD labels.

2.6.3 PHARMACOLOGY TABULATED SUMMARY – N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The pharmacokinetics (PK) of fentanyl have been extensively studied after administration by various routes. For this submission, fifty-seven non-GLP formulation screening studies were performed in the dog in which the dose, salt form, pH, time of loading, and disc surface area were varied to determine their effects on the systemic absorption of fentanyl from BEMA Fentanyl. Three GLP PK-local tolerance studies were conducted with BEMA Fentanyl! — (as used in the BEMA Fentanyl drug product) or BEMA Fentanyl free base in which clinical observations, test article administration site observations, and toxicokinetic monitoring were performed for up to 24 hours after application. All formulations produced measurable systemic exposures to fentanyl, with concomitant signs of sedation in the dogs. No significant adverse events or local irritation were attributed to drug administration in these studies. The drug was well-tolerated with sedation being the consistent treatment-related effect attributed to test article administration. BEMA Fentanyl containing fentanyl citrate achieved slower and more prolonged plasma levels of fentanyl than formulations containing BEMA Fentanyl free base.

b(4)