at least 90 days. Approximately 75,000 doses of BEMA Fentanyl in the dose range of 200 to 2400 µg were administered.

Deaths, serious adverse events and common adverse events are presented in terms of the length of administration of study drug. Short-term administration is defined as the titration periods of FEN-201 and 202, and the entire FEN-113 (single dose), and long-term administration as the open-label period of FEN-202 and the double-blind period of FEN-201.

The high mortality rate of 22.6% (68 deaths/300 patients) during the development program was not unexpected given that the study population was comprised of patients with advanced/terminal cancer. Fifty-eight deaths occurred during long-term exposure and 10 during short-term. Information provided by the Applicant including narratives, case report forms and relevant datasets were reviewed for each death. None of the deaths were definitely related to the use of BEMA Fentanyl, the vast majority being due to underlying disease, treatment, and/or related complications. There were two deaths as a result of sudden cardiac arrest that although unlikely due to use of study drug, remained unexplained.

A large number of serious adverse events occurred in the safety population reflecting the subjects' poor health and types of treatment administered. There were 29 SAEs in 25 patients during the short-term administration, and 170 SAEs in 106 patients that did not result in death during long-term administration. Narratives, case report forms and relevant datasets were reviewed for each SAE. The overwhelming majority of serious adverse events appeared to be due to cancer and its progression, complications of cancer, and cancer treatment and its complications. None of the SAEs were definitely due to the administration of study drug. Two cases of hypoxia, one case of mucosal inflammation, and one case of vomiting were determined to be possibly related to study drug, however the clinical status of the patients made it more likely that that the events were unrelated. One subject experienced urinary retention that was possibly related to study drug, however it occurred in a setting of increased doses of background opiates.

The incidence of treatment emergent adverse events was 43% during short-term administration and 88% during long-term administration. The most common adverse events occurring during short-term administration were nausea, vomiting, dizziness, and somnolence, and during long-term administration were nausea, vomiting, peripheral edema, dehydration, asthenia, and fatigue. In terms of adverse events that may be opioid-related, the most common during short-term administration were nausea, somnolence and dizziness, and during long-term administration were constipation and nausea.

Most AEs were not related to the dose of BEMA Fentanyl; however nausea and vomiting were more common at the 1200 µg dose. For nausea, the rate in the 1200 µg group was 29.3% whereas the highest rate seen for lower doses was 12.9%; for vomiting the rate at 1200 µg was 26.7% versus a highest rate at lower doses of 9.4%.

Adverse events were more common in females than males (91.9% vs. 84.4%). There did not appear to be an important difference in the rates of AEs between the elderly (76.3%) and those

less than 65 years old (81.4%), however some AEs were more common in the elderly including dizziness (short-term administration), and asthenia, peripheral edema, decreased appetite, confusional state, and hypotension during long-term administration.

There did not appear to be a clinically meaningful relationship between race and the incidence of adverse events, although conclusions are limited by the low number of non-whites enrolled in the trials.

The overall incidence of application site reactions (oral adverse events) was 6.6%. The possible relationship of study drug use to these events is complicated by the fact that stomatitis is a common comorbidity in patients with cancer, either as a result of the underlying disease, treatment, or complications. The rate of application site reactions including only those that **"could possibly" be related to study drug application**, which included stomatitis, mouth ulcer, hypoesthesia, mucosal inflammation, and odynophagia was 4.6%.

First dose safety of BEMA Fentanyl was assessed in studies FEN-113 and FEN-202 following administration of the initial 200mcg dose of study drug. There did not appear to be an increased risk of adverse events, with only two of 111 patients evaluated developing mild somnolence.
There are a number of limitations regarding the interpretation of the safety data for BEMA Fentanyl. They are:

1. Since BEMA fentanyl was being dosed in patients taking around-the-clock opioids for background pain, and the adverse event profile is expected to be similar for all opioids, the determination of causality of adverse events was difficult.
2. The patients enrolled in all trials were extremely ill and were receiving toxic therapies for their underlying conditions. This too made it difficult to assign causality of the adverse events.
3. Because of the cross-over design of the double-blind portion of the efficacy trial, the relationship of the time of the dose of study drug to the time of adverse event was not generally available. Nor was this information was not available for the open-label phases of the studies.

A very important safety concern regarding BEMA Fentanyl is its place among the other two approved treatments for breakthrough pain in cancer patients. Actiq, Fentora, and BEMA fentanyl are all oral transmucosal fentanyl products, have rapid onset and relative short duration of action; however they are not bioequivent. The approximate absolute bioavailability values of the three products (obtained from the product labels) are Actiq 50%, Fentora 65%, and BEMA Fentanyl 71%. Consequently, the drugs are not interchangeable on a microgram per microgram basis.

This presents a situation that may result in medication errors on the part of prescribers, pharmacists, and patients, made worse by the fact that all three products have dosage units of the same strength. Within the first year of the approval of Fentora, a Public Health Advisory was issued because of adverse events that occurred due to medication errors related to converting patients from Actiq to Fentora, and deaths related to the use of Fentora in opioid non-tolerant

patients. With a third product on the market, one would expect that occurrence of these errors could potentially increase.

In order to mitigate the occurrence of medication errors, a very strong Risk Management Program must be instituted that includes educating all stakeholders, including prescribers, pharmacists, third-party payers, and patients to be aware of the important differences in bioavailability between Actiq, Fentora, and BEMA Fentanyl. Off-label use, particularly in opioid non-tolerant patients must be monitored, and interventions must be available if a problem develops.

1.3.4 Dosing Regimen and Administration

BEMA Fentanyl is available in five dosage strengths: 200, 400, 600, 800, and 1200 mcg. The Applicant has determined the following scheme for finding the appropriate dose of BEMA Fentanyl and dosing subsequent BTP episodes.

Figure 1: Dose Titration Scheme

b(4)

Source: Applicant's proposed label

Once a successful dose is determined, usage of BEMA Fentanyl should be limited to four or fewer BTP episodes per day which must be separated by at least two hours.

This method of dose finding was used in trials FEN-201 and FEN-202, and appeared to have been successful. Approximately 3% of subjects from FEN-201 and 202 were unable to find an effective dose.

At the beginning of the titration portion of the each trial, subjects were issued a titration package that contained five doses of each of the five strengths of BEMA Fentanyl (200, 400, 600, 800, 1200mcg). Subjects were instructed to only treat their identified "target" breakthrough pain. Dose titration was started with the 200 µg dose of BEMA fentanyl. Subjects were not to take another dose of study drug for 4 hours after their last dose of study medication. Subjects were allowed to use their standard breakthrough pain medication 30 minutes after study drug application for target breakthrough pain episodes that do not respond adequately. The subject was not to have increased their dose without authorization of the investigator or his designee.

b(4)

b(4)

In summary, the proposed titration algorithm is acceptable; The proposed dosing interval of at least two hours and the treatment of up to four BTP episodes per day are acceptable and are supported by findings from FEN-201 and 202. The reader is referred to Section 8.1 in this review for additional detail.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not assessed during the clinical development of BEMA Fentanyl. However, it is known that fentanyl is metabolized mainly via the human CYP3A4 isoenzyme

system; therefore potential interactions may occur when fentanyl is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of fentanyl with any CYP3A4 inhibitor may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression.

The concomitant use of fentanyl with potent CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, and troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of fentanyl.

1.3.6 Special Populations

The use of BEMA Fentanyl in special populations was not assessed in this development program.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The proposed indication for BEMA Fentanyl, an opioid analgesic, is the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

BEMA Fentanyl is a bioerodible mucoadhesive system which delivers fentanyl across the buccal mucosa. The drug product is a flexible, flat, bilayer rectangle with rounded corners, pink on one side and white on the other side. The pink mucoadhesive side containing fentanyl citrate adheres upon contact with the moist buccal mucosa. The white backing layer does not contain drug substance and it minimizes drug release into the oral cavity, maximizing transmucosal diffusion. The dose unit dissolves within 15 to 30 minutes.

BEMA Fentanyl is available in five dose strengths: 200, 400, 600, 800, and 1200 µg fentanyl free base per unit. The concentration of drug substance within the mucoadhesive layer is the same for all product strengths. The fentanyl dose is determined by the dose unit size, defined by the surface area. Each BEMA Fentanyl dose unit is debossed with a product strength identifier on the white backing side and packaged in a child-resistant, [redacted] foil, [redacted] package. b(4)

The proposed trade name, which has been found acceptable by DMETS, is Onsolis, and the established name is [redacted] This product is a new dosage form of fentanyl, which was first approved in 1968 for the intravenous treatment of pain. b(4)

2.2 Currently Available Treatment for Indications

Historically, the treatment of breakthrough pain in cancer patients has consisted of treatment of the pain episode with a short-acting, immediate-release oral opioid (or opioid/non-opioid combination product) consisting of approximately **15% of the patient's total baseline opioid** dose. Typically, morphine, oxycodone, or hydromorphone have been used in this setting, however none of the IR oral opioids are approved for this indication.

There are currently two products approved for BTP in opioid-tolerant cancer patients, Actiq and Fentora.

Actiq (oral transmucosal fentanyl citrate) was approved in November, 1998, specifically for the treatment of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain in. Actiq is a lozenge formulation of fentanyl citrate that, because of the highly lipophilic nature of fentanyl, is rapidly absorbed across the oral mucosa, thereby eliminating the high degree of first-pass metabolism that occurs with oral fentanyl. Because of its pharmacokinetic profile, Actiq provides rapid onset of action

(approximately 15-30 minutes) combined with a relatively short duration of action, both of which make this product suitable for the treatment of a breakthrough pain episode.

The approval process for Actiq brought to light a situation where the need for a new therapy for cancer breakthrough pain had to be balanced with the management of the potential public risk associated with the marketing of a potent narcotic. This represented a unique circumstance where the population at greatest risk for adverse effects was not the population that would benefit from approval. Since Actiq was intended for use in the home, there was great concern about the appeal of this dosage form to children in the household. The Division was particularly concerned about the accidental or intentional ingestion of the product by children who had mistaken the lollipop formulation for candy.

An Advisory Committee meeting was held in September, 1997, at which time the committee voted that there should be a way found to make Actiq available to those patients who would potentially benefit from it while managing the potential risks to public health. Actiq was ultimately approved in 1998 under 21CFR§314.20 (Subpart H). Use of Actiq was restricted to cancer patients with BTP, and prescribing was restricted to Oncologists and Pain Medicine specialists. In addition, a Risk Management Plan was part of the approval.

Actiq has undergone a number of labeling changes since its approval. They include the addition of a statement advising diabetic patients that Actiq contains two grams of sugar per unit (June 10, 2002); statements added to label based on post-marketing experience regarding the association of Actiq with dental caries, tooth loss, and gum line erosion (September 24, 2004); formulation change to sugar-free (never marketed, September 9, 2005); conversion of patient leaflet (patient package insert) to MedGuide (September 6, 2006); and the addition of pharmacokinetic data for patients 5-15 years of age based on a study carried out in the pediatric population (February 7, 2007).

In September, 2006, Fentora (fentanyl effervescent buccal tablet) was approved for the same indication as Actiq. Also a reformulation of fentanyl, it is a buccal tablet that effervesces as it dissolves over a period of 5 to 40 minutes. Its bioavailability is approximately 20% greater than that of Actiq.

Within a year of its approval, a Public Health Advisory was issued for Fentora. Reports of serious adverse events, including deaths in patients taking Fentora had been reported to the Agency. The reports described prescribing to non-opioid tolerant patients, misunderstanding of dosing instructions, and inappropriate substitution of Fentora for Actiq by pharmacists and prescribers. Additionally, as a result of these reports, changes to the Package Insert and MedGuide were made in February 2008. These modifications, including changes to the Box Warning, strengthen the warnings regarding the use of Fentora in opioid non-tolerant patients including patients with migraines, correct dosing, and the conversion of patients from Actiq to Fentora

2.3 Availability of Proposed Active Ingredient in the United States

There are currently four approved drug products (not including generic forms) in the United States containing the fentanyl moiety. The table below summarizes the important aspects of regulatory and post-marketing experience with these products. The overall adverse event profiles for all of the products is similar (e.g., typical opioid effects of sedation, constipation, respiratory depression, etc...). The table illustrates safety concerns that have occurred in addition to the expected events.

Table 1: Currently Marketed Fentanyl Containing Products

Trade Name/established name	NDA #	Approval date	Major Labeling Changes	Pre and Postmarketing Safety concerns
Sublimaze® (fentanyl injection)	16-619	February 19, 1968	None	None
Duragesic® (fentanyl transdermal system)	19-813	August 7, 1990	-RiskMAP -Medguide -use of overlay -increased warnings re: use in opioid naïve patients	-leaking patches resulting in 2 recalls (2004 and 2008) -lack of adhesion -overdose, misuse and abuse -use in opioid naïve patients
Actiq® (Oral transmucosal fentanyl citrate)	20-747	November 4, 1998	-RiskMAP -Medguide -warnings re: dental caries	-dental caries -accidental pediatric exposures -off-label use in opioid naïve patients -abuse, misuse, overdose
IONSYS® (fentanyl iotophoretic transdermal system)	21-338	May 22, 2006	None	Never marketed due to safety issues regarding the device component
Fentora® (fentanyl buccal tablet)	21-947	September 25, 2006	-increased warnings re: mis-prescribing to opioid naïve patients and improper dosing -RiskMAP was part of original approval	-off label use in opioid naïve patients -improper dosing stemming from fact that this product is not bioequivalent to Actiq and therefore doses are not interchangeable

2.4 Important Issues with Pharmacologically Related Products

All opioids have well established adverse event profiles that include sedation, nausea, vomiting, pruritis, hypotension and constipation. The most serious adverse reactions associated with all opioids include respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension and shock. Abuse, tolerance and physical dependence are other recognized risks associated with this class of drugs.

Because of the high potential of abuse and misuse of opioids, and experience with products such as Oxycontin and Methadone, the Agency now requires that REMS be part of the approval package for high potency opioids, including extended-release formulations.