ONSOLIS (fentanyl buccal soluble film)

NDA 22-266

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: BioDelivery Sciences international
2501 Aerial Center Parkway
Suite 205
Morrisville, NC 27560

Indication: For the Management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Presentation: The drug product is a flat bilayer rectangle with round corners, pink on one side and white on the other side. The pink mucoadhesive layer contains the drug substance, fentanyl citrate, and the white backing layer controls the erosion rate and residence time of the dosage form in the mouth. Each individual unit is sealed in a multilayer [redacted] including foil. The package material is a [redacted] multilayer [redacted] b(4)

EER Status: **Acceptable**

Consult:	EA:	Categorical exclusion provided in the NDA
	Pharm. Tox.:	Acceptable July 21, 2008
	Clin. Pharm.:	Acceptable July 18, 2008
	Biometrics:	Acceptable June 27, 2008
	Methods Validation	Not recommended
	Microbiology:	N/A

Original Submission:	**October 31, 2007**
Re-submissions:	N/A
Post-Approval Agreements:	None beyond the typical stability commitment.

Drug Substance

The drug substance is the citrate salt of the active component fentanyl. Fentanyl citrate, a well characterized compound, is supplied and manufactured by [redacted]. Chemistry, Manufacture and Controls' (CMC) information is referred to [redacted], proprietary Type [redacted] Drug Master File (DMF) [redacted] b(4)
The DMF was reviewed and found adequate.
Chemical name, structural formula, molecular formula, molecular weight of the drug substance is provided below.

[redacted] b(4)

Molecular Formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$
Molecular Weight: Fentanyl citrate salt: 528.59, Fentanyl free base: 336.49
Chemical Names:
Propanamide *N*-Phenyl-*N*-[1-(2-phenylethyl)-4-piperidyl] citrate (1:1)

The specifications for fentanyl citrate drug substance that will be used by the drug product manufacturer, Aveva Drug Delivery Systems (Aveva), comprise Appearance (visual), Identification (IR and UV spectroscopy), Loss on Drying (USP <731>), Residue on Ignition (USP <281>), Heavy Metals (USP <231>), Ordinary Impurities (TLC), Assay (titration and HPLC), and Purity and Related Substances (HPLC). The content of fentanyl citrate, calculated on dry basis, is 98.0–102.0 %. The acceptance criteria for Related Substances such as the [redacted] is NMT [redacted] for each of them, and NMT [redacted] for [redacted] The content of Unknown Related Substances (each) is [redacted] and the total content of Related Substances does not exceed [redacted] fentanyl specifications meet USP fentanyl citrate monograph. b(4)

The drug substance will be stored in [redacted] container closure systems, either [redacted]. Based on stability data, a [redacted] retest date has been granted for the drug substance. b(4)

Conclusion

Drug substance: The drug substance is satisfactory.

Drug product

The drug product ONSOLIS, fentanyl buccal soluble film, is a flat bilayer rectangle with round corners, pink on one side and white on the other side. The pink mucoadhesive layer contains the drug substance, fentanyl citrate, and the white backing layer controls the erosion rate and residence time of the dosage form in the mouth. The white backing layer does not contain drug product, and it minimizes drug release into the oral cavity, maximizing transmucosal diffusion. The drug product is designed to provide drug release through the buccal mucosa when the pink side is placed on the inside of the cheek. The composition of the drug substance within the mucoadhesive layer is the same for all product strengths. The drug product units are designed to erode over a period of approximately 30 minutes.

The drug product is manufactured mainly by [redacted] b(4)

[redacted] The units are packaged by [redacted] in preprinted pouches, and the pouches are boxed. The thickness of the film product is fixed by design (mucoadhesive and backing layer thickness

The drug product is available in five strengths: 200, 400, 600, 800, and 1200 mcg (µg) fentalyl free base per unit. Fentanyl citrate, the drug substance, is contained in the mucoadhesive layer. The excipients sodium benzoate [redacted] b(4)
methylparaben [redacted], propylparaben [redacted]
[redacted] citric acid [redacted], vitamin E [redacted], hydroxypropyl cellulose [redacted], hydroxyethyl cellulose [redacted], and [redacted] water [redacted] b(4)
are found in both mucoadhesive and backing layers (common excipients). Besides the common excipients, the mucoadhesive layer contains propylene glycol [redacted], ferric oxide [redacted], monobasic sodium phosphate [redacted] sodium hydroxide [redacted] b(4)
[redacted], tribasic sodium phosphate [redacted], polycarbophil [redacted], and carboxymethylcellulose [redacted]. In addition to the common excipients, the backing layer has titanium dioxide [redacted] saccharin sodium [redacted], and peppermint oil [redacted]. All excipients meet compendial requirements.

Drug product specifications include appearance (visual), identification (RP HPLC and UV-Vis Spectroscopy), assay (RP HPLC), Purity (HPLC), content uniformity (RP HPLC), unit weight (gravimetry), pH (potentiometry), Dissolution (RP HPLC), water content (Karl Fischer titration), microbial limits (USP <61>), and pouch integrity (expansion under pressure reduction in a vacuum enclosure). The acceptance criteria for purity requires that the content of the impurities [redacted] b(4)
and [redacted] not to exceed [redacted], and [redacted] (w/w) respectively, any unknown impurity no more than [redacted], and the total impurity content should be lower than [redacted] (w/w).

Based on the available data, 18 months at the storage condition and 6 months under accelerated condition, a 24-month expiry dating is granted by the Agency.

Overall Conclusion:
From a CMC perspective, the application is recommended for **approval.**

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