

MEMORANDUM

Adnan Jaigirdar, MD, FACS
Deputy Director, Division of Clinical Evaluation and
Pharmacology / Toxicology
FDA / CBER / OTAT / DCEPT

BLA	125700/0
Submission Date	June 29, 2022
PDUFA ADD	December 30, 2022
Review Date	December 14, 2022
Product/Trade Name	nadofaragene firadenovec/ADSTILADRIN
Applicant	Ferring Pharmaceuticals A/S
Proposed Indication	ADSTILADRIN is a non-replicating adenoviral vector-based gene therapy indicated for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors
Product Reviewers	Anurag Sharma, PhD (OTAT/DCGT) Zhili Xu, PhD (OTAT/DCGT) Ramjay Vatsan (OTAT/DCGT) Robert Aksamit (OTAT/DCGT)
Pharm / Tox Reviewer	Iwen Wu, PhD (OTAT/DCEPT) Allen Wensky, PhD (OTAT/DCEPT) Alyssa Galaro, PhD (OTAT/DCEPT) Ying Huang
Clinical Reviewers (Clinical studies, Pharmacovigilance, BiMO)	Yuxia Jia, MD (OTAT/DCEPT) Laronna Colbert, MD (OTAT/DCEPT) Daniel Suzman, MD (OND/ODD, OCE) Peter Bross, MD (OTAT/DCEPT) Paul Kleutz, MD (OCE) Adamma Mba-Jonas, MD, MPH (OBPV/DPV) Colonus King (OCBQ/DIS/BIMO) Christine Drabick (OCBQ/DIS/BIMO)
Clin. Pharmacology Reviewer	Xiaofei Wang, PhD (OTAT/DCEPT)
Statistical Reviewer	Jiang (Jessica) Hu, PhD (OBPV/DB)
Regulatory Project Manager	Adrian Fisher (OTAT/DRPM)
Recommendation	Approval

Executive Summary

On September 03, 2019, the Applicant FKD Therapies Oy, submitted a new Biologics License Application (BLA) seeking approval of nadofaragene firadenovec/ADSTILADRIN for the treatment of high-risk, Bacillus Calmette-Guerin (BCG) unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors. ADSTILADRIN is a non-replicating adenoviral vector-based gene therapy containing the human interferon alfa-2b (IFN α 2b) transgene. However, due to deficiencies identified during the review, a complete response letter was issued for the original BLA submission on April 24, 2020. On June 30, 2022, the Applicant, now Ferring Pharmaceuticals A/S, re-submitted the BLA addressing deficiencies identified from the original BLA submission.

In this BLA re-submission, the Applicant is seeking approval for nadofaragene firadenovec/ADSTILADRIN for the indication: treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

Please see the primary review memos for detailed assessment of the original BLA, as well as supplemental review memos evaluating this re-submitted BLA. The review team recommends approval of this BLA for the above indication, and I concur with the review team's recommendation.

Notable Review Highlights

The results from one phase 3, multicenter, single-arm Study (CS-003) form the basis for the safety and efficacy assessment of ADSTILADRIN in patients with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumors. Subjects in this study received ADSTILADRIN, 75 mL intravesical instillation (3×10^{11} vp/mL), once every three months for up to 12 months or until unacceptable toxicity or recurrent high-grade NMIBC. Subjects without evidence of high-grade recurrence could continue to receive ADSTILADRIN treatment every three months.

The primary efficacy outcome measure was complete response (CR) rate at any time (as defined by negative results for cystoscopy [with transurethral resection of bladder tumor or TURBT/biopsies as applicable] and urine cytology). Duration of response (DoR) was a key secondary endpoint. Random bladder biopsy of five sites was conducted in subjects remaining in CR at month 12. The CR rate was 51% (95% CI: 41%, 61%), the median DoR was 9.7 months (range: 3, 52+), and 46% of responding patients remained in complete response for at least one year.

The safety profile of ADSTILADRIN was generally limited to transient bladder-related events. The most common (>10%) adverse reactions, including laboratory abnormalities (>15%), were increased glucose, triglycerides, instillation site discharge, fatigue, bladder spasm, urinary urgency, increased creatinine, hematuria, decreased phosphate, chills, dysuria, and fever. Two warnings were added to labeling. One warning describes the potential risk of progression to muscle-invasive or metastatic urothelial carcinoma with delayed cystectomy in patients with BCG-unresponsive CIS, although the incidence of pathologic upstaging on cystectomy (14%) and progression prior to cystectomy (2%)

were not higher on CS-003 than expected based on historical data. The second warning describes the theoretical risk of disseminated adenovirus in patients with immunocompromise or immunodeficiency. No events related to adenovirus dissemination were observed during the ADSTILADRIN development program.

The overall benefit-risk profile of ADSTILADRIN was acceptable and did not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS).

Recommendations

Approval of ADSTILADRIN for treatment of adult patients with BCG-unresponsive NMIBC with carcinoma in situ (CIS) with or without papillary tumors is recommended.

Adnan Jaigirdar, MD, FACS
Deputy Director
Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research