Nadofaragene firadenovec-vncg (ADSTILADRIN)
National Drug Monograph
September 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Nadofaragene firadenovec is a non-replicating adenoviral vector-based gene therapy for bladder instillation. The replication-deficient adenovirus vector contains a transgene encoding the human interferon alfa-2b (IFNα2b). It delivers a copy of the gene encoding IFNα2b to the bladder urothelium resulting in local expression of the IFNα2b protein for anti-tumor effects.

Indication(s) Under Review in This Document

- Treatment of 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.

Dosage Form(s) Under Review

- Cartons of 4 vials with 3 x 10^{11} viral particles (VP/mL) containing an extractable volume of not less than 20 mL.

Clinical Evidence Summary

Efficacy Considerations

- CS-003 was a single-arm, multicenter, repeat-dose phase 3 trial. Mandatory bladder biopsy at 1 year.
- Adequate BCG therapy: administration of at least five of six doses of induction course plus either of: at least two of three doses of maintenance or at least two of six doses of a second induction course.
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Study Design	ECOG PS	Treatment	Results
CS-003 NCT02773849 Boorjian et al.[1]	Multinational single-arm All tumors resected and TUR for T1 tumors BCG unresponsive:	0-2	75 mL nadofaragene firadenovec by intravesical administration left in bladder	**Primary EP: complete response (CR) in CIS cohort at any time within 12 months of 1st dose.** N=107 CIS plus Ta or T1 N=50 Ta or T1 only Median Age: 71

	• Persistent disease (Ta CIS) after adequate BCG therapy • Recurrence (Ta or T1) after initial tumor-free state after BCG therapy • T1 disease after single induction course of BCG Two cohorts • CIS with or without high-grade Ta or T1 tumors • High grade Ta or T1 tumor cohort without CIS		for 1 hour with rotation, repeat at month 3 , 6, and 9 if no recurrence. If no evidence of disease on 5 biopsies at 12 months, could continue therapy every 3 months. BSC with each dose included anticholinergic to minimize irritative symptoms	**CR in CIS cohort: 53.4%, all at month 3** Duration of response: 9.69 months 23.4% high-grade recurrence free at 12 mos High-grade cohort (Ta or T1 only): 73% high-grade recurrence free at month 3 44% high-grade recurrence free at 12 mos Median duration of recurrence-free survival: 12.4 months Recurrence in entire study group: 69% High-grade NMIBC 61% Progression to MIBC 5% 26% went on to cystoscopy (both cohorts). 24 months OS: 91.9% in CIS cohort

TUR: transurethral resection

Safety Considerations

Safety Results from Clinical Trials:

Table 2: Safety results from clinical trial CS-003 CIS Cohort

Study	Results
	Any AE: 93% **Grade 3-4:** bladder spasm (1%); micturition urgency (1%); syncope (1%); hypertension (1%); urinary incontinence (1%) **Serious AE events:** 11%**:** sepsis, coronary artery disease, hematuria, acute coronary syndrome, brain edema, dehydration, arrhythmia **AEs leading to discontinuation:** bladder spasm (1), discharge around catheter (1), benign neoplasm of the bladder (1) **AEs leading to dose interruption/modification:** 34% **Deaths due to AEs:**0

- **Boxed warnings:** None
- **Contraindications:** prior hypersensitivity to interferon alpha or any component of product.
- **Other warnings / precautions**: Grade 3 or 4 increased glucose in 6% of study patients
- **Adverse reactions**

- **Common** increased glucose, instillation site discharge, increased triglycerides, fatigue, bladder spasm, urinary urgency, increase creatinine, hematuria, decreased phosphate chills, dysuria, pyrexia
- **Serious Adverse events/ Discontinuation:** coronary artery disease, hematuria; discontinuation in 1.9%

Other Considerations

- Studies not conducted in human or animal pregnancy or lactation. Advise patients of reproductive potential of risk to fetus and of breastfeeding. Verify pregnancy status prior to use.
- Must be stored in ≤-60°C freezer; may be stored for up to 3 months at -25°C to -15°C but not passed carton expiration data
- Store for 24 hours at room temperature or refrigerator once removed from freezer.
- Recommend pre-treatment with anticholinergic prior to each instillation.
- Short dating on current packaging with limited allocation

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:** Complete Response in BCG-unresponsive high-risk tumors
- **Effect Size:** 54% (single-arm phase 3 trial) at 3 months; 30% at 12 months
- **Potential Harms:** Low
- **Net Clinical Benefit:** Modest

Other Therapeutic Options

Alternative treatments for BCG unresponsive high-risk non-muscle-invasive bladder carcinoma are listed in table 3 below.

Table 3 Treatment Alternatives

Treatment	Formulary status	Clinical Guidance	Other Considerations
Nadofaragene firadenovec	TBD	High-risk BCG unresponsive non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors	• Requires storage at ≤-60°C (≤-76°F) • In a freezer -25°C to -15°C up to 3 months without exceeding carton expiration • Store up to 24 hours at room temperature or refrigerated once removed from freezer • Protect vials from light
Gemcitabine sequentially with docetaxel*	F	Can be used for any type of BCG-unresponsive bladder cancer	Only retrospective data; no prospective data; treatment well tolerated in retrospective series
Radical cystectomy*			• High perioperative morbidity • Patients unwilling to have procedure
Pembrolizumab*	F	High-grade, BCG-unresponsive CIS of the bladder for patient ineligible for or decline radical cystectomy	• Systemic therapy • Significant ≥grade 3 toxicities in 13% of patients • Modest durable complete responses

*Current treatment alternative on Oncology Clinical Pathway for Bladder Cancer

Projected Place in Therapy

- In addition to staging by tumor, lymph node, and metastases, bladder cancer is also divided into non-muscle invasive (NMIBC) and muscle invasive (MIBC). Most patients are diagnosed with NMIBC. NMIBC has 3 subgroups based on increasing risk of cancer progression-Ta, T1, and CIS.
- Treatment of NMIBC generally includes removal of visible cancer followed by intravesical BCG therapy. In patients who are BCG-unresponsive (approximately 50% of patients), further therapy options include cystectomy or further intravesical therapy with agents like gemcitabine and docetaxel, but response rates are low. Pembrolizumab received an FDA indication for high risk, BCG-unresponsive CIS disease with or without papillary tumors.[2] There is not standard of care for patients with BCG-unresponsive, NMIBC. Radical cystectomy is potentially curative, but there is a 30-57% complication rate at 90 days post-surgery and 3-4% mortality rate.[3]
- Nadofaragene firadenovec uses a recombinant adenovirus that encodes for interferon alpha-2b gene. Intravesical instillation of interferon alone for bladder cancer produced complete responses that were short lived in previous studies.
- Nadofaragene firadenovec achieved a complete response in 53% of patients with BCG-unresponsive CIS±Ta/T1 disease at 3 months which declined to 24% by 12 months. Results were higher in the Ta/T1 disease alone.
- The primary limitation in the trial is lack of data from a randomized trial. The FDA allows single-arm trials in this population because other therapies are minimally effective. Also, there is some uncertainty about long-term effectiveness. Although pembrolizumab produced a similar rate of complete responses in patients with CIS ±Ta/T1 papillary tumors with a longer duration of response, it is a systemic treatment and was associated with more Grade 3 or 4 Adverse Events and some immune-related adverse events.[4] Results from the cohort including only Ta and T1 disease have not been reported for pembrolizumab.
- Nadofaragene firadenovec offers bladder sparing local therapy for BCG-unresponsive disease in high-risk patients. In the CIS cohort, 29% went on to receive a cystectomy by 12 months. In the Ta/T1 alone cohort 21% received a cystectomy by 12 months. In the clinical trial, the adverse event profile was favorable with only a small percentage experiencing grad 3 or 4 events.
- Due to efficacy and safety, nadofaragene firadenovec is an option for patients with BCG-unresponsive CIS ±Ta/T1 NMIBC.

References

[1]Boorjian SA, Alemozaffar M, Kontey BR et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. Lancet Oncol 2021; 22: 107-17.

[2]Deininger S, Torzsok P, Mitterberger M, et al. From interferon to checkpoint inhibition therapy-a systematic review of new immune-modulating agents in Bacillus Calmette-Guérin (BCG) refractory non-muscle-invasive bladder cancer (NMIBC). Cancers 2022; 14: https://doi.org/10.3390/cancers14030694.

[3]Maibom SL, Joensen UN, Poulsen AM, et al. Short-term morbidity and mortality following radical cystectomy: a systematic review. BMJ Open 2021; 11:e043266.

[4]Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Onc 2021; 22: 919-30.

Prepared September 2023. Contact person: Mark C. Geraci, Pharm.D., BCOP, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing sources for updated information.