These Clinical Guidelines have been created using resources that were current as of the "Reviewed" date noted at the beginning of the document. Clinicians should refer to the manufacturer's Prescribing Information (or equivalent) for the most up-to-date information. While CarepathRx has published these Clinical Guidelines after a close review of available literature and a clinical review process, given the evolving nature and complexity of modern pharmaceutical products, CarepathRx does not and cannot warrant or guarantee that these Clinical Guidelines reflect the objectively best or highest standard of care at any given time.

Nothing within these Clinical Guidelines is intended to supersede or interfere with any individual clinician's decision-making or professional judgment with respect to either (1) prescribing or dispensing the drug or product in question or (2) the overall treatment plan for an individual patient.

Adstiladrin (nadofaragene firadenovec-vncg) Intravesical Instillation Clinical Guideline

Section: Clinical Guideline
Compliance: ACHC Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
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I. BACKGROUND

Adstiladrin (nadofaragene firadenovec-vncg) 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. It delivers a gene for human interferon alfa-2b directly to the bladder urothelium to produce localized anti-tumor effects by enhancing local immune response and cytotoxicity.

To support the effectiveness of nadofaragene firadenovec therapy, patients are premedicated with anticholinergic agents prior to instillation. Anticholinergics help reduce bladder spasms, urgency, and premature voiding, which can significantly improve the retention time of the intravesical therapy. Improved bladder retention allows for optimal contact time between the drug and the urothelium, which is critical to achieving the therapeutic effect of the gene transfer and subsequent interferon alfa-2b expression.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates must be evaluated by the clinician(s) and deemed appropriate to receive care based upon the dispensing pharmacy's admission criteria.

B. Nadofaragene firadenovec is a non-replicating adenoviral vector-based gene therapy. Follow universal biosafety precautions for handling. All doses will be administered through closed system transfer devices (CSTD) in a prescriber's office or urology clinic.

C. Physician orders for nadofaragene firadenovec must include:

1. Drug
2. Dose
3. Route of administration
4. Frequency of administration
5. Orders for pre-medications (anticholinergics)
6. Routine lab monitoring, if applicable

D. Baseline labs or tests prior to starting therapy.

1. Pregnancy tests are recommended for female patients of childbearing age.

E. Patient tolerance to nadofaragene firadenovec treatment is better upon successful completion of a 5-day course on an anticholinergic (e.g. Oxybutynin)

III. PHARMACOLOGY OVERVIEW

Refer to manufacturer's full Prescribing Information for most up to date information

A. Indications: Treatment of adult patients with high-risk BCG-unresponsive NMIBC with CIS, with or without papillary tumors.
B. Dosing: 75 mL via intravesical instillation every 3 months at a concentration of 3×10^{11} vp/mL

C. Dose Adjustment: None

D. Duration- Duration of therapy is dependent on patient response and adverse reactions.

E. Contraindications: Nadofaragene firadenovec is contraindicated in patients with prior hypersensitivity reactions to interferon alfa or to any component of the product

F. Warnings and Precautions:

1. Risk of Muscle Invasive or Metastatic Bladder Cancer with Delayed Cystectomy: In patients with BCG-unresponsive carcinoma in situ (CIS), delaying cystectomy after lack of response or recurrence with nadofaragene firadenovec therapy may lead to progression to muscle-invasive or metastatic bladder cancer, which can be life-threatening. In a clinical study, 14% of patients who underwent delayed cystectomy had muscle-invasive disease. Median time to surgery in these cases was approximately 8 months. Prompt evaluation and surgical consultation are recommended if there is no complete response after 3 months or in cases of recurrence.
2. Risk of Disseminated Adenovirus Infection: Nadofaragene firadenovec may contain trace levels of replication-competent adenovirus. Immunocompromised individuals, including those on immunosuppressants, are at risk for disseminated infection and should avoid direct contact with the medication.
3. Pregnancy and lactation: Nadofaragene firadenovec has not been studied in pregnant women, and no animal reproductive studies have been conducted; therefore, it may pose a risk to the fetus, and pregnancy should be avoided during treatment. Pregnancy status should be verified prior to initiating therapy. It is also unknown whether nadofaragene firadenovec is present in human milk or its potential effects on the breastfed infant or milk production. Clinical decisions regarding breastfeeding should consider the mother's need for treatment alongside the potential risks to the infant. Both male and female patients of reproductive age should use effective contraception during treatment with nadofaragene firadenovec. Females should continue contraception for 6 months after the last dose, while males with female partners of reproductive potential should continue for 3 months after their final dose.

G. Pharmacokinetics:

1. Absorption: Interferon alfa-2b protein was detectable in urine for up to 10–12 days post-dose. Most patients had measurable urine levels by Day 2 after instillation.
2. Distribution: Limited systemic distribution. Vector DNA was detected in the urine in some patients up to Day 12 post-dose and was rarely detected in the blood.
3. Metabolism: Not systemically metabolized due to localized intravesical delivery. Interferon alfa-2b expression remains localized to bladder urothelium.

4. Elimination: Primarily through the urinary tract; vector shedding was seen in urine but not consistently in blood. Systemic clearance not clinically significant.

H. Adverse Reactions:

1. Renal: Dysuria (16%), Hematuria (17%), Spasm of urinary bladder (20%), Urethral discharge (33%), Urgent desire to urinate (19%)
2. Other: Fatigue (24%), Fever (15%), Shivering (16%)

I. Drug Interactions: Drug-drug interactions may exist. Consult interaction database for patient specific assessment.

IV. ADMINISTRATIVE GUIDELINES

A. Administer nadofaragene firadenovec via intravesical instillation through a urinary catheter in a sterile, controlled environment.

B. Premedicate the patient with an oral anticholinergic (e.g., oxybutynin) starting five days prior to instillation to reduce the likelihood of bladder spasms and improve retention.

C. Following instillation and holding for 1 hour, the patient should void normally. They should be instructed to disinfect the toilet after each use using bleach, for a duration of 48 hours post-treatment. They should flush the toilet 15 minutes after each void to allow for disinfection.

D. The starter kit includes oral anticholinergic medication and detailed patient education materials covering administration preparation, hygiene, and infection control.

E. Use only catheters made of vinyl/PVC (uncoated or coated with hydrogel), red rubber latex or silicone to instill nadofaragene firadenovec. Do not use catheters coated or embedded with silver or antibiotics.

F. Hazardous handling: **It is the responsibility of the dispensing pharmacy to ensure medication handling is in compliance with organizational policies and procedures. Although biotherapies are excluded from categorization as a hazardous drug by NIOSH, this medication may contain hazardous properties and is recommended to be treated as such. Use universal precautions and treat spills/contaminated non-disposable equipment with virucidal agents (e.g., bleach)."**

V. PROCEDURE

A. Supplies may include but are not limited to:

1. Standard Personal Protective equipment (PPE) appropriate for handling hazardous medications including biohazard waste bag (may be individualized to each prescriber's clinical setting and institutional protocols)
2. Vial Adaptors 20mm CSTD
3. Syringe Units 60mL CSTD
4. Straight Cath Adaptors C CSTD
5. Protective plug caps
6. Nadofaragene firadenovec - Getting started Guide
7. Nadofaragene firadenovec - Treatment Discussion Guide
8. Spill absorbent mat

B. Prescription items: (examples below)

1. nadofaragene firadenovec vials
2. Anticholinergic medication

C. How Supplied: nadofaragene firadenovec is a sterile, clear to opalescent suspension for intravesical instillation, supplied as single-use vials. nadofaragene firadenovec is provided in a carton containing four (4) vials which together have a total nominal concentration of 3×10^{11} viral particles (vp)/mL. Each vial nadofaragene firadenovec contains an extractable volume of not less than 20 mL.

D. Storage and Handling:

1. Nadofaragene firadenovec is a non-replicating adenoviral vector-based gene therapy and should be handled using universal biosafety precautions.
2. Individuals who are immunosuppressed or immune-deficient should not prepare, administer, or come into contact with nadofaragene firadenovec.
3. **Upon Receipt:** Store nadofaragene firadenovec as a frozen sterile suspension until expiry date printed on carton if freezer temperature ≤ -60°C (≤ -76°F) OR up to 3 months if freezer temperature is -25°C to -15°C (-13°F to 5°F) up to 3 months. Ensure not to exceed the original expiry date printed on the vial and outer carton. Vials must be thawed before use and brought to room temperature (20°C to 25°C / 68°F to 77°F).
4. **Thawing at Room Temperature:** Thaw time is approximately 3–5 hours outside the cardboard nest or 8–10 hours inside the nest.
5. **Thawing in Refrigerator:** Thaw time is approximately 4–5 hours outside the cardboard nest or 11–13 hours inside the nest. After thawing, bring to room temperature over approximately 2.5 hours (or 6 hours if inside the nest).
6. Do not expose nadofaragene firadenovec to temperatures above 25°C (77°F). Protect from light. Do not refreeze once it is thawed.
7. Nadofaragene firadenovec may be moved between refrigerated and room temperature conditions, not exceeding a total of 24 hours at room temperature or 7 days refrigerated, including thaw time.

E. Procedures/Preparation of product, Infusion rates, post infusion monitoring time:

1. Explain to the patient the reasoning for nadofaragene firadenovec use
2. Don gloves.
3. Ensure medication is brought to room temperature before administration and patient has completed anticholinergic medication course. Visually inspect vials for visible particles and discoloration and prepare using CSTD due to hazardous exposure risk. Do not use it if visible particles or discoloration are observed. Mix gently. Do not shake.
4. Counsel patient on warnings, precautions, and potential side effects including but not limited to disseminated infection, instillation site discharge, fatigue, bladder spasm, micturition urgency, hematuria, dysuria, chills, and fever.
5. Using a vinyl, red rubber, or silicone urinary catheter (not silver- or antibiotic-coated), completely empty the bladder prior to instillation.
6. Attach the Luer lock end of the same catheter adaptor to the syringe containing nadofaragene firadenovec and insert the tapered end of the catheter adaptor into the funnel opening of the catheter. Slowly instill 75 mL of nadofaragene firadenovec into the bladder through the catheter, ensuring that the complete volume is administered.
7. After the instillation, nadofaragene firadenovec should be retained in the bladder for 1 hour. During the 1-hour dwell time, the patient should reposition approximately every 15 minutes

from left to right, back and abdomen to maximize bladder surface exposure. If, during the dwell time, the patient exhibits bladder cramping or premature voiding, repositioning of the patient may be adjusted or discontinued.

8. After the 1-hour dwell time, evacuate nadofaragene firadenovec from the bladder as part of routine emptying of the bladder, or the patient may void and completely empty the bladder. Voided urine should be disinfected for 15 minutes with an equal volume of virucidal agent (e.g bleach) before flushing of the toilet.
9. All materials used in the preparation and administration of nadofaragene firadenovec — including catheters, syringes, gloves, and any items contaminated with urine—must be treated as biohazardous waste. Dispose of these items in accordance with institutional hazardous waste guidelines.

VI. CLINICAL MONITORING

A. Prior to therapy:

1. Verify pregnancy status in females of reproductive potential prior to initiation of treatment.
2. Ensure patient completed anticholinergic 5-day course prior to Astiladrin installation.

B. During/After therapy:

1. Assess for adverse effects including disseminated infection, instillation site discharge, fatigue, bladder spasm, micturition urgency, hematuria, dysuria, chills, and fever.
2. Assess treatment effectiveness and confirm achievement of complete response.
3. The pharmacy team will reach out to the MDO around day 60 to confirm that an appointment for patient cystoscopy procedure has been made.

Please refer to the package insert for the most up to date guidance on this medication.

REFERENCES:

Adstiladrin (nadofaragene firadenovec-vncg) [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; August 2024.

United States Pharmacopeia (USP). General Chapter, <797> Pharmaceutical Compounding—Sterile Preparations. (2023) USP-NF. Rockville, MD: United States Pharmacopeia. Accessed April 22, 2025.