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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADSTILADRIN® safely and effectively. See full prescribing information for ADSTILADRIN.

**ADSTILADRIN® (nadofaragene firadenovec-vncc)**  
suspension, for intravesical use

Initial U.S. Approval: 2022

### RECENT MAJOR CHANGES

Dosage and Administration (2.2) 8/2024

### INDICATIONS AND USAGE

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. (1)

### DOSAGE AND ADMINISTRATION

- Premedication with an anticholinergic is recommended before each instillation of ADSTILADRIN. (2.1)
- Administer ADSTILADRIN by intravesical instillation only. (2.1)
- ADSTILADRIN is not for intravenous use, topical use, or oral administration.
- The dose is 75 mL of ADSTILADRIN at a concentration of  $3 \times 10^{11}$  viral particles (vp)/mL, instilled once every three (3) months. (2.1)
- Allow ADSTILADRIN to be left in the bladder for 1 hour following instillation

### DOSAGE FORMS AND STRENGTHS

ADSTILADRIN is a suspension for intravesical instillation, supplied as single-use vials. (3)

ADSTILADRIN is provided in a carton containing four (4) vials. All vials have a nominal concentration of  $3 \times 10^{11}$  viral particles (vp)/mL. Each vial of ADSTILADRIN contains an extractable volume of not less than 20 mL.(3)

### CONTRAINdications

ADSTILADRIN is contraindicated in patients with hypersensitivity to interferon alfa or any component of the product. (4)

### WARNINGS AND PRECAUTIONS

- Delaying cystectomy could lead to the development of metastatic bladder cancer, which can be lethal. (5.1)
- Risk of disseminated adenovirus infection: Persons who are immunocompromised or immunodeficient may be at risk for disseminated infection from ADSTILADRIN due to low levels of replication-competent adenovirus. Avoid ADSTILADRIN exposure to immunocompromised or immunodeficient individuals. (5.2)

### ADVERSE REACTIONS

The most common (>10%) adverse reactions, including laboratory abnormalities (>15%), were glucose increased, instillation site discharge, triglycerides increased, fatigue, bladder spasm, micturition (urination urgency), creatinine increased, hematuria (blood in urine), phosphate decreased, chills, pyrexia (fever), and dysuria (painful urination). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ferring Pharmaceuticals at 1-888-337-7464 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

Immunocompromise/immunodeficiency: Avoid in patients with immunocompromise or immunodeficiency. (8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: xx/xxxx

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

ADSTILADRIN® is 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.

### 2 DOSAGE AND ADMINISTRATION

#### Important Administration Instructions

**ADSTILADRIN is for intravesical instillation only.**

**ADSTILADRIN is not for intravenous use, topical use, or oral administration.**

#### 2.1 Dose

The recommended dose of ADSTILADRIN is 75 mL at a concentration of  $3 \times 10^{11}$  viral particles (vp)/mL instilled once every three (3) months into the bladder via a urinary catheter [*see Dosage and Administration (2.2)*].

Premedication with an anticholinergic is recommended before each instillation of ADSTILADRIN.

#### 2.2 Preparation and Handling

ADSTILADRIN is a non-replicating adenoviral vector-based gene therapy. Follow universal biosafety precautions for handling.

Individuals who are immunosuppressed or immune-deficient, should not prepare, administer, or come into contact with ADSTILADRIN [*see Warnings and Precautions (5)*].

ADSTILADRIN is provided as a sterile frozen suspension.

All four vials of ADSTILADRIN must be thawed and brought to room temperature (20°C to 25°C [68°F to 77°F]) prior to use.

#### WHEN THAWING AT ROOM TEMPERATURE

Frozen ADSTILADRIN vials will thaw in approximately 3 to 5 hours outside the cardboard nest when placed at room temperature (up to 25°C [77°F]) (8 to 10 hours inside the nest).

#### WHEN THAWING IN REFRIGERATOR

Frozen ADSTILADRIN vials will thaw in approximately 4 to 5 hours outside the cardboard nest when placed in the refrigerator (up to 8°C [46°F]) (11 to 13 hours inside the nest). Subsequent time for bringing thawed ADSTILADRIN to room temperature is approximately 2 hours 30 minutes outside of the cardboard nest (6 hours inside the nest).

Do not expose the vials to higher temperatures. Protect from light. DO NOT refreeze.

The vials may be moved between refrigerator and room temperature if the total storage time at each condition is not exceeded (24 hours at room temperature and 7 days refrigerated including thawing time).

#### Inspection and Preparing ADSTILADRIN for instillation

Visually inspect all 4 vials for visible particles and discoloration. The suspension is clear to slightly opalescent and may contain opalescent flecks. Do not use if visible particles or discoloration are observed. Mix gently. Do not shake.

Items required for instillation:

- Four (4) thawed vials of ADSTILADRIN
- Four (4) vented vial adapters suitable for a standard 20 mL vial
- Two (2) standard 50 or 60 mL polypropylene Luer lock syringes or one (1) Luer lock syringe equal to or greater than 75 mL (max 100 mL)
- Two (2) Luer lock adapters
  - One (1) straight, or intermittent, urethral catheter with a proximal funnel opening that will accommodate the Luer lock adapter.
  - Use only catheters made of vinyl/PVC (uncoated or coated with hydrogel), red rubber latex or silicone to instill ADSTILADRIN. Do not use catheters coated or embedded with silver or antibiotics.

1. Using aseptic technique, remove the cap from an ADSTILADRIN vial and attach a vented vial adapter according to manufacturer's instructions.
2. Connect the syringe to the vial adapter and withdraw the contents of the vial into the syringe. Repeat steps 1-2 for the remaining three (3) vials until 75 mL has been withdrawn into one (1) or two (2) syringes.
  - The volumes in the syringes do not have to be equal.
3. Discard any remaining volume according to universal precautions.
  - If unable to administer the suspension shortly after withdrawal, the solution may be stored in syringes for up to 6 hours at room temperature (20°C to 25°C [68°F to 77°F]) protected from light.

Treat any ADSTILADRIN spills or unused portion with a virucidal agent (such as sodium hypochlorite with 0.5% active chlorine or 6% hydrogen peroxide solution) for 15 minutes. Disposable materials that have come into contact with ADSTILADRIN should be placed in biohazard containers for destruction. Non-disposable equipment may be decontaminated according to the facility's standard operating procedures. [see *Patient Counseling Information (17)*].

## 2.3 Bladder instillation of ADSTILADRIN

1. Premedication with an anticholinergic before each instillation of ADSTILADRIN is recommended.
2. ADSTILADRIN must be brought to room temperature before administration [*see Dosage and Administration (2.2)*].
3. Before administering ADSTILADRIN to the patient, insert one straight, or intermittent, urinary catheter with a proximal funnel opening that will accommodate the Luer lock adapter.
4. Use only catheters made of vinyl/PVC (uncoated or coated with hydrogel), red rubber latex or silicone to instill ADSTILADRIN. Do not use catheters coated or embedded with silver or antibiotics.
5. Use the catheter to completely empty the patient's bladder before instillation of ADSTILADRIN. Do not remove the catheter.
6. Attach the Luer lock end of the same catheter adapter to the syringe containing ADSTILADRIN and insert the tapered end of the catheter adapter into the funnel opening of the catheter.
7. Slowly instill 75 mL of ADSTILADRIN into the bladder through the catheter, ensuring that the complete volume is administered.
8. After the instillation, ADSTILADRIN 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.
9. Evacuate ADSTILADRIN from the bladder as part of routine emptying of the bladder, or the patient may void and completely empty the bladder after 1 hour has elapsed.
10. Voided urine should be disinfected for 15 minutes with an equal volume of virucidal agent before flushing of the toilet. [*see Patient Counseling Information (17)*].

## 3 DOSAGE FORMS AND STRENGTHS

ADSTILADRIN is a sterile, clear to opalescent suspension for intravesical instillation, supplied as single-use vials.

ADSTILADRIN is provided in a carton containing four (4) vials. All vials have a nominal concentration of  $3 \times 10^{11}$  viral particles (vp)/mL. Each vial of ADSTILADRIN contains an extractable volume of not less than 20 mL.

## 4 CONTRAINDICATIONS

ADSTILADRIN is contraindicated in patients with prior hypersensitivity reactions to interferon alfa or to any component of the product [*see Description (11)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risk of Muscle Invasive or Metastatic Bladder Cancer with Delayed Cystectomy

Delaying cystectomy in patients with BCG-unresponsive CIS could lead to development of muscle invasive or metastatic bladder cancer, which can be lethal. The risk of developing muscle-invasive or metastatic bladder cancer increases the longer cystectomy is delayed in the presence of persisting CIS.

Of the patients with CIS treated with ADSTILADRIN on Study CS-003 who underwent subsequent radical cystectomy and for whom pathologic data were available, 14% (n = 6) had muscle-invasive (T2 or greater) disease at cystectomy. Median time from persistence or recurrence of CIS to cystectomy in these patients was 235 days (range 38 to 582 days). Two additional patients who did not undergo cystectomy experienced progression to muscle-invasive disease during the treatment period.

If patients with CIS do not have a complete response to treatment after 3 months or if CIS recurs, consider cystectomy.

### 5.2 Risk of Disseminated Adenovirus Infection

Immunocompromised persons, including those receiving immunosuppressant therapy, may be at risk for disseminated adenovirus infection because of the possible presence of low levels of replication-competent adenovirus in ADSTILADRIN. Individuals who are immunosuppressed or immune-deficient should not come into contact with ADSTILADRIN.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ADSTILADRIN was evaluated in Study CS-003, a multicenter, single-arm, open-label study in 157 U.S. patients [*see Clinical Studies (14)*] with high-risk BCG-unresponsive NMIBC, 107 of whom had BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumors.

Patients received 75 mL (3 x 10<sup>11</sup> vp/mL) ADSTILADRIN administered intravesically once every 3 months for up to 12 months [*see Clinical Studies (14)*]. All patients with an absence of high-risk recurrence or progression were offered continued treatment every 3 months beyond 12 months. The median number of instillations of ADSTILADRIN was 2 (range 1 to 5).

Serious adverse reactions occurred in 11% of patients who received ADSTILADRIN. Serious adverse reactions occurring in >1% of patients included coronary artery disease and hematuria (blood in urine).

Permanent discontinuation of ADSTILADRIN due to an adverse reaction occurred in 3 (1.9%) patients. Adverse reactions that resulted in permanent discontinuation of ADSTILADRIN included bladder spasm, instillation site discharge, and benign neoplasm of the bladder.

Dosage interruptions of ADSTILADRIN due to an adverse reaction occurred in 54 (34%) patients. Adverse reactions in >10% of patients that required dosage interruption included instillation site discharge, bladder spasm, and micturition urgency.

The most common (>10%) adverse reactions, including laboratory abnormalities (>15%), were glucose increased, instillation site discharge, triglycerides increased, fatigue, bladder spasm, micturition (urination) urgency, creatinine increased, hematuria (blood in urine), phosphate decreased, chills, dysuria, and pyrexia (fever).

Tables 1 and 2 summarize adverse reactions and laboratory abnormalities, respectively, in patients on ADSTILADRIN in CS-003.

Clinically relevant adverse reaction in <10% of patients who received ADSTILADRIN include syncope (fainting) (1.3%).

**Table 1: Adverse Reactions (>10%) in Patients with NMIBC in CS-003**

Adverse Reaction*	ADSTILADRIN (n=157)	
	Grade 1 and 2 %	Grade 3 %
<b>General disorders and administration site conditions</b>	-	-
Instillation site discharge	33	0
Fatigue	24	0
Pyrexia	16	0
Chills	15	0
<b>Renal and urinary disorders</b>	-	-
Bladder spasm	20	1
Micturition urgency	19	1
Hematuria	17	1
Dysuria	16	0

\* Graded per NCI CTCAE v4.03; there were no Grade 4 or 5 reactions.

Clinically relevant adverse reactions in <10% of patients who received ADSTILADRIN included coronary artery disease (1.3%), acute coronary syndrome (1.3%), atrial fibrillation (1.3%), dehydration (1.3%), hypoglycemia (low blood sugar) (1.3%), syncope (fainting) (1.3%), heart failure (0.6%), pericarditis, (0.6%), brain edema (swelling) (0.6%), bile duct stone (0.6%), and sepsis (0.6%).

Table 2 summarizes the laboratory abnormalities in CS-003.

**Table 2: Selected Laboratory Abnormalities (>15.0%) That Worsened from Baseline in Patients with NMIBC in CS-003**

Laboratory Abnormality	ADSTILADRIN <sup>1</sup> (All Grades, %)	ADSTILADRIN <sup>1</sup> (Grade 3 or 4, %)
<b>Chemistry</b>	-	-
Glucose increased	38	6
Triglycerides increased	30	1.9
Creatinine increased	17	0
Phosphate decreased	16	1.4
<b>Hematology</b>	-	-
Hemoglobin decreased	16	0.6

<sup>1</sup> The denominator used to calculate the rate varied from 148 to 156 based on the number of patients with a baseline value and at least one post-treatment value.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Adequate and well-controlled studies with ADSTILADRIN have not been conducted in pregnant women. Animal reproductive and developmental toxicity studies have not been conducted with ADSTILADRIN. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of ADSTILADRIN in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADSTILADRIN and any potential adverse effects on the breastfed infant from ADSTILADRIN or from the underlying maternal condition.

### 8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of ADSTILADRIN on fertility.

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ADSTILADRIN.

## Contraception

### *Females*

Advise females of reproductive potential to use effective contraception during treatment with ADSTILADRIN and for 6 months following the last dose.

### *Males*

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ADSTILADRIN and for 3 months following the last dose.

## **8.4 Pediatric Use**

Safety and effectiveness of ADSTILADRIN in pediatric patients have not been established.

## **8.5 Geriatric Use**

Clinical studies of ADSTILADRIN in BCG-unresponsive high-risk NMIBC with CIS did not include sufficient numbers of patients younger than 65 years of age to determine whether safety and effectiveness differ from older patients.

## **8.6 Gender-specific Use**

In clinical studies with ADSTILADRIN, no overall differences in safety or efficacy were observed between females and males.

## **11 DESCRIPTION**

ADSTILADRIN (nadofaragene firadenovec-vncg) is a non-replicating adenoviral vector-based gene therapy for intravesical instillation.

It is a recombinant adenovirus serotype 5 vector containing a transgene encoding the human interferon alfa-2b (IFN $\alpha$ 2b).

ADSTILADRIN has a nominal concentration of  $3 \times 10^{11}$  vp/mL.

A single-use vial of ADSTILADRIN contains an extractable volume of 20 mL and the following excipients: [N-(3-cholamidopropyl)-N-(3-lactobionamidopropyl)]-cholamide (Syn3) (0.95 mg/mL), citric acid monohydrate (0.01 mg/mL), glycerol (84 mg/mL), hydroxypropyl-beta-cyclodextrin (7.9 mg/mL), magnesium chloride hexahydrate (0.34 mg/mL), polysorbate 80 (Tween 80) (0.48 mg/mL), sodium dihydrogen phosphate dihydrate (1.4 mg/mL), sucrose (17 mg/mL), tri-sodium citrate dihydrate (0.04 mg/mL), tromethamine (1.4 mg/mL) and Water for Injection (q.s. 1 mL).

ADSTILADRIN is a sterile, clear to opalescent suspension, and contains no preservative.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

ADSTILADRIN is a non-replicating adenoviral vector-based gene therapy designed to deliver a copy of a gene encoding a human interferon-alfa 2b (IFN $\alpha$ 2b) to the bladder urothelium. Intravesical instillation

of ADSTILADRIN results in cell transduction and transient local expression of the IFN $\alpha$ 2b protein that is anticipated to have anti-tumor effects.

## 12.2 Pharmacodynamics

A Phase 1 first-in-human study was performed to determine the safety, tolerability, and maximum tolerated dose (MTD) of ADSTILADRIN in 17 patients with BCG-unresponsive NMIBC. Five dose levels ( $3 \times 10^9$  vp/mL,  $1 \times 10^{10}$  vp/mL,  $3 \times 10^{10}$  vp/mL,  $1 \times 10^{11}$  vp/mL, and  $3 \times 10^{11}$  vp/mL; all in a dose volume of 75 mL) of ADSTILADRIN were tested and quantifiable concentrations of the pharmacodynamic marker IFN $\alpha$ 2b protein were detected in the urine of all patients, with the exception of two patients at the lowest dose level. Measurable concentrations of urine IFN $\alpha$ 2b protein up to Day 10 post-dose suggested expression of IFN $\alpha$ 2b in the bladder. In a Phase 2 study, all patients had quantifiable concentrations of IFN $\alpha$ 2b protein in the urine at Day 2 after dosing with ADSTILADRIN at two different dose levels ( $1 \times 10^{11}$  vp/mL and  $3 \times 10^{11}$  vp/mL). Measurable concentrations of urine IFN $\alpha$ 2b protein was detected up to Day 12 post-dose. This was more common in patients at the high dose level.

Generally, higher IFN $\alpha$ 2b concentrations and exposure were observed with increasing doses of ADSTILADRIN.

## 12.3 Pharmacokinetics

### *Nonclinical data*

Human IFN protein in urine, and vector-specific DNA in blood and tissue samples, were detectable following ADSTILADRIN dosing in monkeys, with higher levels at higher doses. All monkeys had vector-specific DNA in the bladder tissue at necropsy on Days 8 and 98 (i.e., seven days after the first and second dose, respectively). Vector-specific DNA was also detected in a limited number of monkeys in the liver, kidney and gonad. At Day 148, only one animal showed vector-specific DNA in one tissue (kidney).

### *Clinical data*

ADSTILADRIN biodistribution and shedding were investigated in two clinical studies. Only a single patient receiving a second dose in one study (Phase 2 study) at dose level of  $3 \times 10^{11}$  vp/mL ( $2.25 \times 10^{13}$  vp) had measurable vector DNA in blood; no other patients in either study had measurable vector DNA at one hour post-dosing in blood. In urine, measurable vector DNA was detected in both studies. Generally, a higher frequency of detection of urine samples positive for vector-derived DNA, and persistence of vector-derived DNA, correlated with increasing dose level.

At the dose level of  $3 \times 10^{11}$  vp/mL ( $2.25 \times 10^{13}$  vp), one patient (out of 4 enrolled) had detectable levels of vector DNA at Day 14 in the Phase 1 study and 16 subjects (out of 19 at visit) had detectable levels of vector DNA at Day 12 in the Phase 2 study.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted to evaluate the effects of ADSTILADRIN on carcinogenesis, mutagenesis, or impairment of fertility.

### 13.2 Animal Toxicology and/or Pharmacology

In cynomolgus monkeys, two repeat intravesical administrations of ADSTILADRIN of either  $2.5 \times 10^{11}$  or  $1.25 \times 10^{13}$  viral particles ( $1 \times 10^{10}$  or  $5 \times 10^{11}$  viral particles/mL, 90 days apart) were associated with inflammation, urothelial hyperplasia, cytoplasmic vacuolation, and focal/multifocal ulceration in the urinary bladder and irritation in the ureter and urethra at necropsy 7 days after the first and second doses. Near complete resolution of these findings was observed following the 57-day recovery period after the second administration, with minimal fibrosis in the lamina propria of the bladder in a limited number of monkeys. Both dose level groups developed antibodies to the adenovirus and human interferon protein.

## 14 CLINICAL STUDIES

The efficacy of ADSTILADRIN was evaluated in CS-003 (NCT02773849), an open-label, multicenter, single-arm trial in 103 adults with BCG-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ (CIS) with or without papillary tumors following transurethral resection, of whom 98 were considered evaluable for response. BCG-unresponsive high-risk NMIBC was defined as persistent disease following adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG was defined as the administration of at least five of six doses of an initial induction course plus either of: at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Prior to treatment, all patients had undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components). Residual CIS (Tis components) not amenable to complete resection was allowed. The trial excluded patients with extra-vesical (i.e., urethra, ureter, or renal pelvis), muscle invasive (T2-T4), or metastatic urothelial carcinoma.

Patients received ADSTILADRIN 75 mL intravesical instillation ( $3 \times 10^{11}$  vp/mL) once every three months for up to 12 months (four doses) or until unacceptable toxicity or recurrent high-grade (HG) NMIBC. Patients without evidence of HG recurrence were allowed to continue ADSTILADRIN treatment every three months.

The major efficacy outcome measures were complete response (CR) at any time (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable] and urine cytology) and duration of response. Low-grade (Ta) papillary disease was not considered a recurrence for the purposes of evaluating CR. CR was assessed at 3, 6, 9, and 12 months by cystoscopy and cytology. Random bladder biopsy of five sites was conducted in patients remaining in CR at Month 12. Assessment of durability of CR subsequent to these evaluations was performed per local standards of care.

The evaluable CIS study population characteristics were median age of 70 (range 44-89) with 32%  $>75$  years of age; 88% male, 92% White. Tumor pattern at study entry was CIS with T1 (5%), CIS with high-grade Ta (19%), and CIS (76%). The median number of instillations of prior BCG was 12 (range 8 to 18).

Efficacy results are summarized in Table 3.

**Table 3: Efficacy Results in Study CS-003**

<b>Efficacy Outcome Measure</b>	<b>ADSTILADRIN (n=98)</b>
<b>Complete Response Rate, %</b>	51%
(95% CI)	(41%, 61%)
<b>Duration of Response*</b>	-
Median in months (range)	9.7 (3, 52+)
% with duration $\geq$ 12 months	46%

\*Based on patients (n=50) that achieved a complete response; reflects period from the time complete response was achieved.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

ADSTILADRIN is shipped frozen at  $\leq$  -60°C ( $\leq$  -76°F) in an insulated shipping box that will maintain the required temperature for a minimum of 72 hours after being sealed. Each carton (NDC 55566-1050-1) contains a removable cardboard nest of four (4) clear glass vials of ADSTILADRIN. Each vial contains a sterile frozen suspension with an extractable volume of 20 mL and is either sealed with a bromobutyl rubber stopper and a tamper-evident aluminum crimp (NDC 55566-1050-0) or with a bromobutyl rubber stopper embedded within a press-fit closure (NDC 55566-1050-2).

Upon receipt, cartons of ADSTILADRIN can be stored as indicated below:

- In a freezer  $\leq$  -60°C ( $\leq$  -76°F) until expiry date printed on the carton.
- In a freezer between -25°C to -15°C (-13°F to 5°F) up to 3 months, without exceeding the original expiry date printed on the vial and outer carton.
  - When stored in freezer, the date of placement in freezer should be noted. In addition, the date for when the carton should be discarded if not used, must be written on the outer carton. These dates should be three months apart but should not past the original expiry date. This discard date supersedes the original expiry date.

When thawed, ADSTILADRIN is a clear to opalescent suspension, with nominal concentration of  $3 \times 10^{11}$  viral particles (vp)/mL.

Prior to use, ADSTILADRIN must be brought to room temperature (20°C to 25°C [68°F to 77°F]). Once it is taken out of the freezer, the vials may be stored for up to 24 hours at room temperature and a total of up to 7 days refrigerated at 2°C to 8°C (36°F to 46°F), including thawing time.

After withdrawing the suspension into syringes, the syringes may be stored for up to 6 hours at room temperature (20°C to 25°C [68°F to 77°F]).

- Protect the vials from light. [see *Dosage and Administration* (2.2)].
- DO NOT REFREEZE

- ADSTILADRIN is a non-replicating adenoviral vector-based gene therapy. Follow universal biosafety precautions for handling [*see Dosage and Administration (2.2)*].
- Dispose of unused product and disposable materials that may have come in contact with ADSTILADRIN in accordance with local biosafety guidelines applicable for handling and disposal of the biohazard waste.

## **17 PATIENT COUNSELING INFORMATION**

### Risk of Metastatic Bladder Cancer with Delayed Cystectomy

- Inform patients that delaying cystectomy in patients with BCG-unresponsive CIS could lead to development of muscle-invasive or metastatic bladder cancer. Discuss the risk of muscle-invasive or metastatic bladder cancer and that the risk increases the longer cystectomy is delayed in the presence of persisting CIS [*see Warnings and Precautions (5.1)*].

### Risk of Disseminated Adenovirus Infection

- Inform patients and their caregivers that treatment or contact with ADSTILADRIN in those who are immunocompromised, including those receiving immunosuppressive therapy, may increase the risk for disseminated adenovirus infection [*see Warnings and Precautions (5.2)*].

### Shedding of ADSTILADRIN

Inform patients and their caregivers that transient and low-level shedding of ADSTILADRIN may occur in urine. Instruct patients and their caregivers that for 2 days following treatment, voided urine should be disinfected for 15 minutes with an equal volume of bleach before flushing [*see Dosage and Administration (2.2)*].

Manufactured for:

Ferring Pharmaceuticals  
2770 Kastrup, Denmark

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PATIENT INFORMATION  
ADSTILADRIN® (add-STILL-a-drin)  
(nadofaragene firadenovec-vnccg)  
Suspension for Intravesical Use

Read this Patient Information before you have each ADSTILADRIN treatment. This information is not comprehensive and there may be new information.

How to get more information:

- Talk to your health care provider
- Call 1-888-337-7464

What is the most important information I should know about ADSTILADRIN?

- Individuals who are immunosuppressed or immune-deficient should not prepare, administer, receive or come into contact with ADSTILADRIN.

What is ADSTILADRIN used for?

- ADSTILADRIN is a prescription medicine for the treatment of a certain type of bladder cancer.

What is ADSTILADRIN?

- ADSTILADRIN is a therapy that contains a copy of the gene for human interferon alfa-2b.
- When administered into the bladder, the treatment delivers this gene, which is non-replicating, to cells in your bladder wall.
- Interferon alfa-2b has anti-tumor effects.
- The purpose of this gene therapy is to increase the level and length of time your bladder wall is exposed to interferon alfa-2b protein.

You should not receive ADSTILADRIN if:

- You have a sensitivity to interferon alfa or any of its components.

What should I tell my healthcare provider?

- Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

## What are the possible side effects of ADSTILADRIN?

The most common side effects of ADSTILADRIN include:

- Urinary discharge
- Fatigue
- Bladder spasm
- Urgency to urinate
- Blood in your urine

These common side effects (above) are not all the possible side effects of ADSTILADRIN. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Ferring Pharmaceuticals at 1-888-337-7464.

## How is ADSTILADRIN used?

- Once every 3 months your healthcare provider will administer 75 mL (about 2 and a half ounces) of ADSTILADRIN into your bladder through a urinary catheter and leave it there for 1 hour. During this time your healthcare provider may move you about every 15 minutes.

## What other information should I know about using ADSTILADRIN?

Take these steps to prepare your toilet bowl after each treatment:

- Add about half a cup of bleach to the toilet bowl before you urinate.
- After urinating, wait 15 minutes before flushing the toilet.
- Repeat these steps every time you urinate for the first 2 days after treatment.

For more information, call 1-888-337-7464 or talk with your health care provider.

This Patient Information has been approved by the U.S. Food and Drug Administration.  
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Rx Only

Manufactured for:  
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