1. NAME OF THE MEDICINAL PRODUCT

ADSTILADRIN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial has a nominal concentration of 3×10^{11} viral particles (vp)/mL of nadofaragene firadenovec (vp)/mL.

Each vial of ADSTILADRIN contains an extractable volume of not less than 20 mL. For a full list of excipients, see section 7.

ADSTILADRIN is provided in a carton containing four (4) vials

3. PHARMACEUTICAL FORM

ADSTILADRIN is a sterile, clear to opalescent suspension for intravesical instillation

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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.

4.2. Dosage and administration

Important Administration Instructions

ADSTILADRIN is for intravesical instillation only.

ADSTILADRIN is <u>not</u> for intravenous use, topical use, or oral administration.

4.2.1. Dose

The recommended dose of ADSTILADRIN is 75 mL at a concentration of 3×10^{11} viral particles of nadofaragene firadenovec (vp)/mL instilled once every three (3) months into the bladder via a urinary catheter [*see Dosage and Administration (4.2)*].

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

4.2.2. Preparation and Handling

ADSTILADRIN is a non-replicating adenoviral vector-based gene therapy. Follow local 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 (4.4)*].

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) prior to use.

WHEN THAWING AT ROOM TEMPERATURE

Frozen ADSTILADRIN vials will thaw in approximately 3 to 5 hours outside the cardboard nest (protective carton in the package) when placed at room temperature (up to 25°C) (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) (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 should be clear to opalescent 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 local 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) 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.

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

4.2.3. 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 (4.2)*].
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 Preparation and Handling (4.2.2.)*].

4.3. Contraindications

Hypersensitivity to the active substance, interferon alfa or to any of the excipients listed in section 7.

4.4. Warnings and Precautions

4.4.1. 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.

4.4.2. 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.

4.4.3. Effects on ability to drive and use machines

ADSTILADRIN has no or negligible influence on the ability to drive and use machines.

5. Adverse Reactions

5.1. 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 (10)*] 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 (3×10^{11} vp/mL) ADSTILADRIN administered intravesically once every 3 months for up to 12 months [*see Clinical Studies (10)*]. 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 %**
General disorders and administration site conditions	-	-
Instillation site discharge	33	0
Fatigue	24	0
Pyrexia	16	0
Chills	15	0
Renal and urinary disorders	-	-
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[1] (All Grades, %)**	**ADSTILADRIN[1] (Grade 3 or 4, %)**
Chemistry	-	-
Glucose increased	38	6
Triglycerides increased	30	1.9
Creatinine increased	17	0
Phosphate decreased	16	1.4
Hematology	-	-
Hemoglobin decreased	16	0.6

[1] 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form *https://sideeffects.health.gov.il/*

6. USE IN SPECIFIC POPULATIONS

6.1. 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.

6.2. 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.

6.3. 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.

6.4. Pediatric Use

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

6.5. 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.

6.6. Gender-specific Use

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

7. DESCRIPTION

ADSTILADRIN (nadofaragene firadenovec) 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 (IFNα2b).

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

A single-use vial of ADSTILADRIN contains an extractable volume of 20 mL and the following excipients:.Glycerol, sucrose, hydroxypropyl-beta-cyclodextrin, trometamol, Sodium dihydrogen phosphate dihydrate, Syn3NODA, Polysorbate 80, Magnesium chloride hexahydrate, Sodium citrate, Citric acid monohydrate, Water for Injection.

Excipient with known effect

ADSTILADRIN contains Polysorbate 80, which can cause allergic reactions.

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

8. CLINICAL PHARMACOLOGY

8.1. 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 (IFNα2b) to the bladder urothelium. Intravesical instillation of ADSTILADRIN results in cell transduction and transient local expression of the IFNα2b protein that is anticipated to have anti-tumor effects.

8.2. 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 (3×10^9 vp/mL, 1×10^{10} vp/mL, 3×10^{10} vp/mL, 1×10^{11} vp/mL, and 3×10^{11} vp/mL; all in a dose volume of 75 mL) of ADSTILADRIN were tested and quantifiable concentrations of the pharmacodynamic marker IFNα2b protein were detected in the urine of all patients, with the exception of two patients at the lowest dose level. Measurable concentrations of urine IFNα2b protein up to Day 10 post-dose suggested expression of IFNα2b in the bladder. In a Phase 2 study, all patients had quantifiable concentrations of IFNα2b protein in the urine at Day 2 after dosing with ADSTILADRIN at two different dose levels (1×10^{11} vp/mL and 3×10^{11} vp/mL). Measurable concentrations of urine IFNα2b protein was detected up to Day 12 post-dose. This was more common in patients at the high dose level.

Generally, higher IFNα2b concentrations and exposure were observed with increasing doses of ADSTILADRIN.

8.3. 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 3×10^{11} vp/mL (2.25×10^{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 3×10^{11} vp/mL (2.25×10^{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.

9. NONCLINICAL TOXICOLOGY

9.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

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

9.2. Animal Toxicology and/or Pharmacology

In cynomolgus monkeys, two repeat intravesical administrations of ADSTILADRIN of either 2.5 x 10^{11} or 1.25 x 10^{13} viral particles (1 x 10^{10} or 5x10^{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.

10. 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 x 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

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

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

11. HOW SUPPLIED/STORAGE AND HANDLING

ADSTILADRIN is shipped frozen at ≤ -60°C Each carton 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 closed with a bromobutyl rubber stopper and sealed with a crimped aluminum cap with flip-of seal.

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

- In a freezer ≤ -60°C until expiry date printed on the carton.
- In a freezer between -25°C to -15°C 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 3×10^{11} viral particles of nadofaragene firadenovec (vp)/mL.

Prior to use, ADSTILADRIN must be brought to room temperature (20°C to 25°C). 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, 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).

- Protect the vials from light. [*see Dosage and Administration (2.2)*].

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).

- ADSTILADRIN is a non-replicating adenoviral vector-based gene therapy. Follow local 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.

12. MANUFACTURER

Ferring Pharmaceuticals AS, Denmark

13. 1MARKETING AUTORIZATION HOLDER

Ferring Pharmaceuticals Ltd., 8 Hashita Street, Industrial Park, Caesarea 3088900 Israel

14. REGISTRATION NUMBER:

180-94-38421-00