ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ADSTILADRIN 3×10^{11} viral particles/mL intravesical suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Nadofaragene firadenovec is a gene therapy medicinal product that embeds the gene for expression of the human interferon-α2b (IFNα2b) protein in bladder cells. It is a non-replicating recombinant type 5 adenovirus vector containing the cDNA of the IFNα2b transgene under the control of the cytomegalovirus immediate-early promoter.

Nadofaragene firadenovec is produced in human embryonic kidney cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each vial contains 20 mL suspension of nadofaragene firadenovec with a concentration of 3×10^{11} viral particles (vp)/mL.

Excipients with known effect

Each vial contains 9.6 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intravesical suspension.

Opalescent, colourless suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADSTILADRIN is indicated as monotherapy for the treatment of adult patients with Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.

4.2 Posology and method of administration

Treatment should be initiated and administered in clinical centres and supervised by a physician experienced in the management of patients with NMIBC.

Posology

The recommended dose of ADSTILADRIN is 75 mL at a concentration of
3×10^{11} viral particles (vp)/mL administered by intravesical instillation every three (3) months.

The maximum duration of treatment should be determined based on the individual patient's clinical response and tolerability. Response should be reassessed prior to each instillation, and the medicinal product discontinued in case of high-grade (HG) recurrence or unacceptable toxicity.

Anticholinergic pretreatment

Premedication with a single dose of an anticholinergic medicinal product before each instillation is recommended (see section 4.4).

Special populations

Elderly
No dose adjustment is recommended in patients aged 65 years or older.

Hepatic or renal impairment
The safety and efficacy of ADSTILADRIN have not been established in patients with hepatic or renal impairment. No dose adjustment is recommended in these patients.

Paediatric population
There is no relevant use of ADSTILADRIN in the paediatric population for the indication of treatment of BCG-unresponsive NMIBC with CIS with or without papillary tumours.

Method of administration

ADSTILADRIN is for intravesical instillation only.

Precautions to be taken before handling or administering the medicinal product
ADSTILADRIN must be thawed and prepared for intravesical instillation prior to administration. For instructions on preparation and administration, see section 6.6.

Intravesical instillation
- Insert a straight or intermittent urinary catheter with a proximal funnel opening that will accommodate the Luer lock adaptor into the bladder under aseptic conditions. Use only catheters made of vinyl/PVC (uncoated or coated with hydrogel), red rubber latex or silicone to instil ADSTILADRIN. Do not use catheters coated or embedded with silver or antibiotics.
- Use the catheter to completely empty the bladder before instillation. Do not remove the catheter, it should be left in place for instillation of the product.
- Attach the Luer lock end of the catheter adaptor to the syringe containing ADSTILADRIN and insert the tapered end of the catheter adaptor into the funnel opening of the catheter.
- Instil 75 mL of ADSTILADRIN slowly into the bladder through the catheter, ensuring that the complete volume is administered.
- Remove the catheter after instillation.
- Retain ADSTILADRIN in the bladder for 1 hour. During the 1-hour dwell time, reposition the patient from left to right, back and abdomen to maximise bladder surface exposure. Reposition the patient approximately every 15 minutes. If, during the dwell time, the patient exhibits bladder cramping or premature voiding, turning of the patient may be adjusted or discontinued.
- Evacuate ADSTILADRIN from the bladder via urinary catheter, or the patient may void and completely empty the bladder after 1 hour has elapsed.
- Disinfect voided urine for 15 minutes with 2 cups of virucidal agent (e.g. household bleach) before flushing the toilet. Instruct the patient to do this after every voiding for the first 2 days after each treatment (see also section 4.4.).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Risk of muscle invasive and metastatic bladder cancer with delayed cystectomy

Delaying cystectomy in patients with BCG-unresponsive CIS with or without papillary tumours could lead to development of muscle invasive or metastatic bladder cancer.

Of the 107 patients with CIS treated with ADSTILADRIN in Study CS-003, 7.5% (n = 8) progressed to muscle invasive (pT2 or greater) and/or lymph node metastatic (pN+) bladder cancer. Four patients had progression during treatment at time of first recurrence with a median time from first dose to progression of 686 days (range: 76-1178). The remaining four patients were upstaged at the time of cystectomy with a median time from persistence or recurrence of CIS to cystectomy of 235 days (range: 64-335).

If patients with CIS who are eligible for cystectomy do not have a complete response to treatment after 3 months or if CIS recurs, cystectomy should be considered. The risk of developing muscle-invasive or metastatic bladder cancer increases the longer cystectomy is delayed in the presence of persisting CIS.

Urinary tract infection

Urinary tract infection should be excluded before each bladder instillation (bladder mucous membrane inflammation may increase the risk of haematological dissemination of ADSTILADRIN). If a urinary tract infection is diagnosed during therapy, the therapy should be interrupted until the patient is asymptomatic and treatment with antibiotics is completed.

Immunocompromised, immune-deficient and pregnant healthcare professionals

Healthcare professionals who are immunocompromised, immune-deficient, or pregnant should not prepare, administer, or come in contact with ADSTILADRIN due to the theoretical risk of adenoviral infection (see section 6.6).

Immunocompromised patients

Immunocompromised patients, including those receiving immunosuppressant therapy, should not come into contact with ADSTILADRIN due to the theoretical risk of adenoviral infection

Vector shedding

Patients should be instructed to add two cups of virucidal agent (e.g. household bleach such as 5 % sodium hypochlorite) to the toilet bowl prior to voiding and wait 15 minutes before flushing the toilet. This should be done for the first 2 days after each treatment. Patients should be instructed to wash their hands after toilet use.

Urinary tract injury and contamination

Because of the intravesical route of administration, care should be taken not to traumatise the urinary tract or to introduce contaminants into the urinary system.

Contraceptive measures in males and females

Male patients with female partners of childbearing potential should use a barrier protection contraceptive method during treatment, and for 3 months following the last dose to avoid exposing sexual partners to virus (see section 4.6).

Women of childbearing potential should use an effective (double) contraceptive method during treatment, and for a period of 6 months following the last dose to avoid the theoretical risk of exposing foetal cells to virus (see section 4.6).

Blood, organ, tissue and cell donation

Patients treated with ADSTILADRIN should not donate blood, organs, tissues and cells for transplantation.

Anticholinergic pretreatment

Premedication with a single dose of an anticholinergic medicinal product before each instillation is recommended (unless contraindicated) to reduce potential bladder irritation and to prevent premature voiding of the bladder.

Excipient with known effect

ADSTILADRIN contains polysorbate 80, which can cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

Pregnancy status in women of childbearing potential should be verified prior to initiating ADSTILADRIN.

Women of childbearing potential should use an effective (double) contraception method during treatment, and for 6 months following the last dose.

Male patients with female partners of childbearing potential should use a barrier protection contraception method during treatment, and for 3 months following the last dose.

Pregnancy

There are no or limited amount of data from the use of nadofaragene firadenovec in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). ADSTILADRIN should not be used during pregnancy and in women of childbearing potential not using contraception unless the clinical condition of the woman requires treatment with nadofaragene firadenovec.

Breast-feeding

It is unknown whether nadofaragene firadenovec is excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ADSTILADRIN therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data are available on the possible effects of nadofaragene firadenovec on fertility, and nonclinical studies have not been conducted (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions were lower urinary tract signs and symptoms related to the intravesical instillation procedure, instillation site discharge (33.1 %), bladder spasm (19.7 %), micturition urgency (18.5 %), haematuria (16.6 %), dysuria (15.9 %), urinary tract infection (14.6 %), lower urinary tract pain (10.8 %), and pollakiuria (9.6 %). In addition, other adverse reactions such as fatigue (23.6 %), pyrexia (15.9 %), chills (15.3 %), headache (15.3 %), and diarrhoea (10.8 %) were also commonly reported.

The most common severe adverse reactions (NCI CTCAE Grade ≥3) were micturition urgency (1.3 %), syncope (0.6 %), hypertension (0.6 %), bladder spasm (0.6 %), and urinary incontinence (0.6 %).

The most common serious adverse reaction was syncope (0.6 %).

The frequency of treatment discontinuation due to adverse reactions was 1.3 %. The most common adverse reactions leading to treatment discontinuation were instillation site discharge (0.6 %) and bladder spasm (0.6 %).

The frequency of dose interruption due to adverse reactions was 34.4 %. The most common adverse reactions leading to dose interruption were instillation site discharge (24.2 %), micturition urgency (8.3 %), bladder spasm (8.3 %), and urinary incontinence (2.5 %).

Tabulated list of adverse reactions

In the pivotal, single-arm study CS-003, 157 patients were exposed to ADSTILADRIN. Table 1 lists the adverse reactions identified in patients with BCG-unresponsive NMIBC. Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies identified in 157 patients exposed to nadofaragene firadenovec during a median treatment duration of 3.4 months in clinical study CS-003. The adverse reaction frequencies in clinical study CS-003 are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than the drug, such as the disease, the instillation procedure, other medication or unrelated causes.

Adverse reactions are ranked according to the MedDRA system organ class and frequency grouping. Frequencies are defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1 Tabulated list of adverse reactions

System organ class	Frequency	Adverse reactions
Infections and infestations	Very common	Urinary tract infection
Blood and lymphatic system disorders	Common	Thrombocytopenia, Neutropenia
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Common	Restlessness
Nervous system disorders	Very common	Headache
	Common	Syncope, Dizziness, Paraesthesia
Vascular disorders	Common	Hypertension, Hot flush
Gastrointestinal disorders	Very common	Diarrhoea, Abdominal pain[1]
	Common	Nausea, Vomiting, Defaecation urgency, Gastrointestinal pain
Skin and subcutaneous tissue disorders	Common	Night sweats, Hyperhidrosis, Dermatitis allergic
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia, Pain in extremity, Muscular weakness, Musculoskeletal stiffness
Renal and urinary disorders	Very common	Bladder spasm, Micturition urgency, Haematuria[2], Dysuria, Lower urinary tract pain[3], Pollakiuria
	Common	Urinary incontinence[4], Nocturia, Urinary retention, Haemorrhage urinary tract, Urine odour abnormal, Cystitis noninfective
Reproductive system and breast disorders	Common	Vulvovaginal discomfort
General disorders and administration site conditions	Very common	Instillation site discharge, Fatigue[5], Pyrexia, Chills
	Common	Pain, Influenza like illness, Malaise, Drug intolerance
Investigations	Common	Urine output increased

1 Includes Abdominal pain, Abdominal pain upper, Abdominal pain lower, and Abdominal discomfort
2 Includes Haematuria and Blood urine present

3 Includes Bladder pain, Urethral pain, Bladder discomfort, and Bladder irritation
4 Includes Urinary incontinence and Urge incontinence
5 Includes Fatigue and Asthenia

Description of selected adverse reactions

Syncope (0.6 %) was reported as an adverse reaction with an onset of 4 days from treatment. A fall resulting from the loss of consciousness led to injuries requiring urgent medical care. The syncope resolved 3 days after the onset and did not recur with subsequent treatments.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There has been no experience with overdose of ADSTILADRIN in clinical studies. In the event of a suspected overdose, the patient should be closely monitored for signs or symptoms of adverse reactions, treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents. Antineoplastic cell and gene therapy. ATC code: L01XL10.

Mechanism of action

ADSTILADRIN is a non-replicating recombinant type 5 adenovirus vector-based gene therapy containing the human IFNα2b transgene. Intravesical administration of ADSTILADRIN results in the entry of viral particles into the tumour cells and the urothelium that make up the luminal surface of the bladder, leading to the expression of IFNα2b protein by those cells. In the transduced cells, the viral DNA does not integrate into the genome. Treatment with nadofaragene firadenovec has shown anti-tumour effects in mice with bladder (cancer cell) xenografts.

Pharmacodynamic effects

The pharmacodynamic marker IFNα2b was present in urine from all patients in the phase 1 and 2 studies except for two patients at the lowest dose level in the phase 1 study (3×10^9 vp/mL). Urine IFNα2b protein was detected up to Day 12 post-dose.

Quantifiable levels of IFNα2b protein in serum were detected in a subset of patients (4 out of 17) in the phase 1 study. The extent of exposure was low and transient with a maximum of a 96-hour duration of exposure post-dose. In the phase 2 study, 12 out of 40 patients had measurable serum IFNα2b protein at month 1 day 2 and 2 out of 40 patients by day 12.

Clinical efficacy and safety

The efficacy and safety of ADSTILADRIN was evaluated in Study CS-003 (NCT02773849), an open-label, single arm, multicentre, pivotal study in 157 patients with high-grade (HG) BCG-unresponsive NMIBC. The study included 107 patients with Carcinoma in situ (CIS) with or without concomitant HG Ta or T1 tumours (CIS ± Ta/T1), and 103 of those patients were evaluated for efficacy.

BCG-unresponsive high-risk NMIBC was defined as persistent disease following adequate BCG therapy, disease recurrence after an initial tumour-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG therapy 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 tumour (TURBT) to remove all resectable disease (Ta and T1 components). Residual CIS (Tis components) not amenable to complete resection was allowed. The study excluded patients with extra-vesical (i.e., urethra, ureter, or renal pelvis), muscle invasive (T2-T4), or metastatic urothelial carcinoma.

The primary objective was to evaluate complete response (CR) rate (as defined by negative results for cystoscopy, with TURBT/biopsies as applicable, and urine cytology). Secondary objective was to evaluate durability of CR.

Disease status was assessed every 3 months by cystoscopy, cytology and biopsies when clinically indicated. Mandatory bladder biopsies were conducted in patients remaining in response at Month 12.

Patients received ADSTILADRIN (75 mL intravesical instillation with 3×10^{11} viral particles/mL, see section 4.2) treatment every three months for 12 months in absence of HG-recurrence. All patients were offered continued ADSTILADRIN treatment in the absence of HG recurrence and followed for safety irrespective of continued treatment for up to 5 years from the first dose.

The efficacy CIS study population (n=103) characteristics were median age of 71 years (ranging from 44 to 89 years), with 76.7 % of the patients being above 65 years of age. 88.3 % of the patients were male and 11.7 % female. Tumour pattern at study entry was CIS with T1 (4.9 %), CIS with high-grade Ta (18.4 %), and CIS only (76.7 %). The median number of prior BCG instillations was 12 (range 8 to 18).

ADSTILADRIN met the primary endpoint of complete response at month 3 in patients with CIS ± Ta/T1.

The efficacy results are summarised in Table 2.

Table 2 Efficacy results from Study CS-003

Efficacy outcome measure	**ADSTILADRIN (n=103)**
Complete response[a] rate at month 3, % (n)	53.4% (55)
(95% CI)	(43.3, 63.3)
Duration of response[b]	-
Median in months[c] (range)	9.7 (3, 61)
% (n) with duration ≥ 12 months[d]	45.5% (25)

[a] CR was achieved when urine cytology was negative and no lesions were visualised by cystoscopy, and/or biopsies of the bladder (if performed) were negative
[b] Based on 55 patients that achieved a complete response.
[c] Reflects period from the time complete response was achieved.
[d] Nominal value for the efficacy assessment visit from time of first ADSTILADRIN instillation.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ADSTILADRIN in all subsets of the paediatric population for the treatment of malignant bladder neoplasms (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency

will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

There was no detectable systemic exposure of vector-derived DNA in patients in the phase 1 and 2 studies, except for in 1 out of 40 patients in the phase 2 study.

Vector-specific DNA was present in the urine of most of the patients in the phase 1 study and all patients in the phase 2 study. Presence was correlated to the dose level. The vector-specific DNA persisted for at least 14 days in the phase 1 study and at least 12 days in the phase 2 study. 3 out of 23 (13 %) patients in the phase 2 study were positive for vector-specific DNA prior to the second dose.

The excipient Syn3NODA enhances an efficient entry of the adenovirus into the urothelial cells. Systemic exposure of Syn3NODA was assessed in the phase 1 study and was found to be transient with a mean elimination t½ of 8.4 hours with no evidence of retention.

5.3 Preclinical safety data

In a repeat-dose toxicity study in monkeys, intravesical nadofaragene firadenovec caused mild to moderate urinary tract inflammation, including chronic inflammation in the tunica muscularis, ulceration, and tissue changes (urothelial hyperplasia and cytoplasmic vacuolation) after the first and second doses. Following a 2-month recovery period after the second dose, partial resolution was observed, with minimal urothelial inflammation and fibrosis in the lamina propria of the bladder remaining in a few animals.

Carcinogenicity studies have not been conducted with nadofaragene firadenovec.

Reproductive toxicity studies have not been conducted with nadofaragene firadenovec. The excipient Syn3NODA distributed to the ovary and uterus in female rats and to the testes and prostate in male rabbits after intravesical dosing. Nadofaragene firadenovec distributed to ovary in female monkeys and testes in male monkeys after intravesical dosing. In repeat-dose toxicity studies with Syn3NODA, there were no treatment-related macroscopic or histopathologic findings in reproductive tissues of rats (IV study, Syn3NODA only) or cynomolgus monkeys (intravesical study) at exposures up to 143-fold and 124-fold, 47-fold and 57-fold the clinical systemic AUC in female and male monkeys, female rats and male rats, respectively. In a repeat-dose toxicity study with nadofaragene firadenovec, there were no treatment-related macroscopic or histopathologic findings in reproductive tissues of cynomolgus monkeys at exposures up to 11-fold the clinical systemic dose.

Syn3NODA has been demonstrated to be non-genotoxic both in in vitro assays (bacterial mutagenicity and chromosome aberration in human lymphocytes) and in an in vivo rat micronucleus study.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Syn3NODA ([N-(3-cholamidopropyl)-N-(3-lactobionamidopropyl)]-cholamide)
Citric acid monohydrate (for pH adjustment) (E 330)
Sodium citrate (for pH adjustment) (E 331)
Polysorbate 80 (E 433)
Hydroxypropylbetadex (E 459)
Sodium dihydrogen phosphate dihydrate (for pH adjustment) (E 339)
Trometamol (for pH adjustment)
Sucrose
Magnesium chloride hexahydrate (E 511)
Glycerol (E 422)
Water for injections

6.2 Incompatibilities

Do not use catheters coated or embedded with silver or antibiotics. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years

Temporary storage conditions for unopen vials

The product can be stored at -20 ± 5°C for a maximum period of three months without exceeding the original expiry date printed on the vial and carton.

When stored at -20 ± 5°C the date of placement at -20 ± 5°C should be noted. In addition, the date for when the medicinal product should be discarded if not used, must be written on the carton. These dates should be three months apart but should not pass the original expiry date. This discard date supersedes the original expiry date.

Once the vial thawing procedure is initiated ADSTILADRIN can be stored:

- refrigerated at 2-8°C for a total of seven days and
- at room temperature for a maximum of 24 hours, all including thawing time.
- do not refreeze vials once thawing has been initiated.

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

In use stability after withdrawal from the vial

If unable to administer the suspension shortly after withdrawal, the solution may be stored in syringes for up to 6 hours at room temperature (20-25°C), protected from light.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below -60°C.

Protect the vials from light. Keep vials in outer carton.

For storage conditions of unopened vials and after withdrawal from the vial, see section 6.3

6.5 Nature and contents of container

20 mL of intravesical suspension in a single-dose clear Type 1 glass vial with a bromobutyl rubber stopper sealed with a tamper-evident aluminium crimp.

Each carton contains four vials.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified organisms (GMOs).

- Any ADSTILADRIN spills should be treated with a virucidal agent (such as 5 % sodium hypochlorite or hydrogen peroxide disinfectant) for 30 minutes. Disinfectant should be present in the preparation area and patient room in case of spill.
- Personal protective equipment (including gloves, safety glasses, apron or protective clothing) should be worn while handling or administering ADSTILADRIN.
- Healthcare professionals who are immunocompromised, immune deficient, or pregnant should not prepare, administer, or come into contact with ADSTILADRIN.

Thawing and thawing time

When thawing at room temperature:
Frozen vials will thaw in approximately 3-5 hours outside the cardboard nest when placed at room temperature (20-25°C) (8-10 hours inside the nest). Protect the vials from light, even if thawed outside the cardboard nest.

When thawing in refrigerator:
Frozen ADSTILADRIN vials will thaw in approximately 4-5 hours outside the cardboard nest when placed in the refrigerator (up to 8°C) (11-13 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.

All four vials should be inspected 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.

Once the thawing procedure is initiated (at 2-8°C and/or at room temperature), the date and time for placing and removing the product from the specified storage condition, should be noted on the carton. When removing the product, the time remaining at the specific storage condition should be noted on the carton.

Items required for instillation

- Four (4) thawed vials of ADSTILADRIN
- Four (4) vented vial adaptors (20 mm) suitable for a 30R 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 adaptors:
  - One (1) straight, or intermittent, urethral catheter with a proximal funnel opening that will accommodate the Luer lock adaptor.
  - Use only catheters made of vinyl/PVC (uncoated or coated with hydrogel), red rubber latex or silicone to instil ADSTILADRIN. Do not use catheters coated or embedded with silver or antibiotics.

Follow universal biohazard precautions for handling. Healthcare professionals who are immunocompromised, immune-deficient, or pregnant should not prepare, administer, or come into contact with ADSTILADRIN.

Preparation

1. Using aseptic technique, remove the cap from an ADSTILADRIN vial and attach a vented vial adaptor according to manufacturer's instructions.
2. Connect the syringe to the vial adaptor 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 the facility's standard operating procedures (see below Precautions to be taken for the disposal of the medicinal product).
4. Use ADSTILADRIN within 6 hours of drawing into syringe.

Bladder instillation of ADSTILADRIN

- Premedication with an anticholinergic agent before each instillation of ADSTILADRIN is recommended.
- ADSTILADRIN must be brought to room temperature before administration.
- Before administering ADSTILADRIN to the patient, insert one straight, or intermittent, urinary catheter with a proximal funnel opening that will accommodate the Luer lock adaptor into the bladder under aseptic conditions.
- Use only catheters made of vinyl/PVC (uncoated or coated with hydrogel), red rubber latex or silicone to instil ADSTILADRIN. Do not use catheters coated or embedded with silver or antibiotics.
- Use the catheter to completely empty the patient's bladder before instillation. Do not remove the catheter.
- Attach the Luer lock end of the catheter adaptor to the syringe containing ADSTILADRIN and insert the tapered end of the catheter adaptor into the funnel opening of the catheter.
- Instil 75 mL of ADSTILADRIN slowly into the bladder through the catheter, ensuring that the complete volume is administered.
- Remove the catheter after instillation.
- Retain ADSTILADRIN in the bladder for 1 hour. During the 1-hour dwell time, reposition the patient approximately every 15 minutes from left to right, back and abdomen to maximize bladder surface exposure. If the patient exhibits bladder cramping or premature voiding during the dwell time, repositioning of the patient may be adjusted or discontinued.
- Evacuate ADSTILADRIN from the bladder via urinary catheter, or the patient may void and completely empty the bladder after 1 hour has elapsed.
- Voided urine should be disinfected for 15 minutes with 2 cups of virucidal agent (e.g. household bleach) before flushing of the toilet. Instruct the patient to do this after every voiding for the first 2 days after each treatment.

Measures to take in case of accidental exposure

Accidental exposure to nadofaragene firadenovec, including contact with skin, eyes and mucous membranes, is to be avoided.

- In case of accidental exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes.
- In case of accidental exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.
- In case of accidental ingestion, immediately rinse the mouth and drink plenty of water.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and disposable materials that have come into contact with ADSTILADRIN should be placed in biohazard containers for destruction. Non-disposable equipment must be decontaminated according to the facility's biohazard standard operating procedures.

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Amager Strandvej 405
2770 Kastrup
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2035/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

FinVector Oy
Microkatu 1s
70210 Kuopio
Finland

Name and address of the manufacturer(s) responsible for batch release

FinVector Oy
Microkatu 1s
70210 Kuopio
Finland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSUR for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and accordingly, the marketing authorization holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of ADSTILADRIN in adult patients with BCG-unresponsive NMIBC with CIS with or without papillary tumours, the MAH shall submit the primary clinical trial report of ABLE-22, an ongoing phase III randomised, multi-centre, open-label trial, including from the nadofaragene firadenovec monotherapy Arm 1: i) the CR rate at month 3 (excluding re-induction) and duration of these responses; and ii) safety data.	31 March 2029

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

ADSTILADRIN 3×10^{11} viral particles/mL intravesical suspension
nadofaragene firadenovec

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 20 mL nadofaragene firadenovec suspension with a concentration of 3×10^{11} viral particles/mL

3. LIST OF EXCIPIENTS

Excipients: Syn3NODA, citric acid monohydrate, sodium citrate, polysorbate 80, hydroxypropylbetadex, sodium dihydrogen phosphate dihydrate, trometamol, sucrose, magnesium chloride hexahydrate, glycerol, and water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Intravesical suspension

20 mL × 4 vials

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For single use only
Intravesical use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Protect from light. Keep vials in carton.

Store below -60°C.

Below the remaining shelf-life period under different storage conditions can be logged.

Date moved to –20 ± 5°C:_ /__ /___
New expiration date (three months after) –20 ± 5°C):_/__/___

After thawing initiation:

Temp.	Start date + time	End date + time	Time remaining

After thawing, the total storage time at each condition should not exceed 7 days at 2-8°C and 24 hours at 20-25°C.

Do not refreeze

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically modified organisms.
Unused medicinal product and disposable materials that have come into contact with ADSTILADRIN should be placed in biohazard containers for destruction

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Amager Strandvej 405
2770 Kastrup
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2035/001

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

ADSTILADRIN 3×10^{11} viral particles/mL intravesical suspension
nadofaragene firadenovec

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 20 mL nadofaragene firadenovec suspension with a concentration of 3×10^{11} viral particles/mL.

3. LIST OF EXCIPIENTS

Excipients: Syn3NODA, citric acid monohydrate, sodium citrate, polysorbate 80, hydroxypropylbetadex, sodium dihydrogen phosphate dihydrate, trometamol, sucrose, magnesium chloride hexahydrate, glycerol, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Intravesical suspension

20 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only
Intravesical use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Protect from light. Keep vials in carton.

Store below -60°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically modified organisms.
Unused medicinal product and disposable materials that have come into contact with ADSTILADRIN should be placed in biohazard containers for destruction.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Amager Strandvej 405
2770 Kastrup
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2035/001

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ADSTILADRIN 3 × 10^{11} viral particles/mL intravesical suspension
nadofaragene firadenovec

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADSTILADRIN is and what it is used for

ADSTILADRIN is a gene therapy product that contains the active substance nadofaragene firadenovec.

ADSTILADRIN is used in adults for the treatment of non-muscle invasive bladder cancer. In non-muscle invasive bladder cancer, the cancer cells are found in the tissue lining the inside of the bladder but have not spread to the bladder wall. It is used in adults whose cancer has not responded to or has come back after treatment with Bacillus Calmette-Guérin (BCG, a solution used to stimulate the immune system, the body's natural defences, in the treatment of bladder cancer).

The active substance in ADSTILADRIN, nadofaragene firadenovec, is based on a virus that has been changed so that it cannot spread in the body. The virus delivers a working copy of the gene that provides instructions for making the interferon-α2b (IFNα2b) protein into the cells in the surface of your bladder. This allows the bladder to make the IFNα2b protein which slows down or stops the cancer cells from growing and also helps to stimulate the immune system to attack them.

2. What you need to know before you are given ADSTILADRIN

You must not be given ADSTILADRIN
- if you are allergic to nadofaragene firadenovec or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Risk of your cancer getting worse if surgery to remove all or part of the bladder is delayed following treatment with this medicine.

Talk to your doctor before you are given ADSTILADRIN if:
- you are immunocompromised or immune-deficient (when your immune system's ability to fight infections is reduced). Your doctor will evaluate if you should be given ADSTILADRIN.

- you have a urinary tract infection. Tell your doctor if you have signs of infection or inflammation of your bladder or kidneys before or during treatment with ADSTILADRIN, including:
  - cloudy or bloody urine;
  - pain or burning sensation when passing urine;
  - fever
  - pressure or cramping in the lower belly or back
  - a strong need to urinate often, even right after the bladder has been emptied.

  If you are diagnosed with a urinary tract infection during your treatment with ADSTILADRIN, your doctor will pause the treatment until you have finished treatment with antibiotics and the urinary tract infection is cured.

If any of the above apply to you (or you are not sure), talk to your doctor before having ADSTILADRIN.

After you have been given ADSTILADRIN:
- you should for the first 2 days after you have been given ADSTILADRIN, add two cups of household bleach (e.g. 5 % sodium hypochlorite) to the toilet bowl before passing urine. After passing of urine, wait for 15 minutes before flushing the toilet. Make sure to wash your hands after toilet use. This is due to theoretical risk that the active substance of ADSTILADRIN may be temporarily excreted through your urine,
- you should not donate blood, organs, tissues or cells.

Children and adolescents
The use of ADSTILADRIN in children or adolescents under 18 has not been studied because the disease indicated occurs in adults only.

Other medicines and ADSTILADRIN
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant, breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given ADSTILADRIN.

Pregnancy

ADSTILADRIN is not recommended if you are pregnant or if you are a woman who can become pregnant who is not using effective contraception (birth control). There are no data regarding the use of ADSTILADRIN in pregnant women. It is not known if ADSTILADRIN is safe to use during pregnancy or can cause harm to your unborn baby.

If you are able to become pregnant, you should use effective (double, i.e. two methods of birth control used together, typically a barrier method such as condoms alongside hormonal contraceptives) contraception (birth control) during treatment with ADSTILADRIN, and for 6 months after you have been given the last dose. Your doctor will check if you are pregnant before you are given ADSTILADRIN.

Breast-feeding

It is not known if ADSTILADRIN is passed into breastmilk. Your doctor will decide if you should continue breastfeeding during treatment with ADSTILADRIN.

Men

Use effective barrier contraception during treatment with ADSTILADRIN, and for 3 months after you have been given the last dose. You should also not donate sperm during treatment with ADSTILADRIN and for 3 months after you have been given the last dose.

Partners

Partners must avoid contact with semen during your treatment with ADSTILADRIN, and for 3 months after you have been given the last dose. This is to prevent your partner from coming in contact with the virus.

If your partner is a woman who can become pregnant, they should use effective (double) contraception while you are receiving treatment with ADSTILADRIN, and for 6 months after you have been given the last dose. This is to prevent the theoretical risk of exposing foetal cells to the virus.

Discuss with your doctor which methods of contraception are suitable.

Driving and using machines
It is unlikely that ADSTILADRIN will affect your ability to drive and use machines.

ADSTILADRIN contains polysorbate 80
ADSTILADRIN contains an excipient called polysorbate 80. Polysorbates can cause allergic reactions.

3. How ADSTILADRIN is given

Treatment with ADSTILADRIN will be supervised by a doctor experienced in the management of patients with non-muscle invasive bladder cancer.
Treatment with ADSTILADRIN is given with a dose of 3×10^{11} viral particles/mL with a volume of 75 mL passed into your bladder. The treatment will be given to you every three months until you do no longer respond to the treatment or if you can no longer tolerate the treatment.

Before you are given ADSTILADRIN
Your doctor may give you another medicine (a so-called anticholinergic agent) before you are given ADSTILADRIN. This medicine is given to reduce possible irritation of the bladder and to stop you from passing urine when ADSTILADRIN is given. Take this medicine as instructed by your doctor.

How you are given ADSTILADRIN
- A urinary catheter (flexible tube) will be inserted into your bladder to empty it of urine.
- ADSTILADRIN will be passed slowly into your bladder through the urinary catheter, which will be removed after all the medicine is given.
- ADSTILADRIN will be left in your bladder for 1 hour and your doctor may ask you to change position from left to right and from your back to your stomach. This is to make sure that ADSTILADRIN reaches the whole surface of your bladder.
- If you get bladder cramping or pass urine during the procedure, your doctor may ask you to change position.
- After 1 hour, your doctor will empty your bladder with a urinary catheter, or you may be asked to pass urine.

If you are given more ADSTILADRIN than you should
As this medicine is given to you by a doctor, it is unlikely that you will be given too much. If it does occur, your doctor will treat the symptoms as necessary.

If you miss an appointment to get ADSTILADRIN
- Call your doctor right away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

If you stop receiving ADSTILADRIN
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with ADSTILADRIN unless you have discussed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may happen with ADSTILADRIN:
In a clinical study, fainting (common, may affect up to 1 in 10 people) has been reported as a serious side effect. Immediately seek medical attention if you experience fainting.

Very common (may affect more than 1 in 10 people)

- Fluid leaking from where the medicine was given (instillation site discharge)
- Feeling tired (fatigue)
- Fever (pyrexia)
- Chills
- Involuntary contraction of the bladder muscle (bladder spasm)
- Sudden urge to pass urine (micturition urgency)
- Blood in the urine (haematuria)
- Painful urination (dysuria)
- Pain in parts of the body that collect and pass out urine (lower urinary tract pain)
- Abnormally frequent urination (pollakiuria)
- Diarrhoea
- Belly (abdominal) pain
- Headache
- Infection of parts of the body that collect and pass out urine (urinary tract infection)

Common (may affect up to 1 in 10 people)

- Pain
- Flu-like illness
- Feeling generally unwell (malaise)
- Drug intolerance
- Lack of control over passing urine (urinary incontinence)
- Need to pass urine at night (nocturia)
- Inability to completely empty the bladder (urinary retention)
- Bleeding in parts of the body that collect and pass out urine (haemorrhage urinary tract)
- Urine odour abnormal
- Inflammation in the bladder which can cause pain and discomfort when passing urine (cystitis noninfective)
- Feeling sick (nausea)
- Vomiting
- Urgent need to empty the bowels (defaecation urgency)
- Stomach and gut (gastrointestinal) pain
- Dizziness
- Fainting (syncope)
- Sensations like numbness, tingling, pins and needles (paraesthesia)
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Pain in the fingers, toes, feet, hands (pain in extremity)
- Muscular weakness
- Muscle, bone and join (musculoskeletal) stiffness
- Night sweats
- Excessive sweating (hyperhidrosis)
- Allergic inflammation of the skin (dermatitis allergic)

- High blood pressure (hypertension)
- Hot flush
- Excessive urine (urine output increased)
- Decreased appetite
- Low levels of blood platelets, components that help the blood to clot(thrombocytopenia)
- Low levels of neutrophils, a type of white blood cell that fights infection (neutropenia)
- Feeling restless
- Vulvovaginal discomfort

Talk to your doctor if you develop any other side effects.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADSTILADRIN

The following information is for healthcare professionals who will prepare and give the medicine.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and on the carton after EXP. The expiry date refers to the last day of that month.

Protect the vials from light. Keep vials in outer carton.

Before vial thawing procedure is initiated

- Store below -60°C.
- Can be stored at -20 ± 5°C for a maximum of three months. When stored at -20 ± 5°C the date of placement at -20 ± 5°C should be noted. In addition, the date for when the medicinal product should be discarded if not used, must be written on the carton. These dates should be three months apart but should not pass the original expiry date. This discard date supersedes the original expiry date.

From vial thawing procedure is initiated

- Keep refrigerated at 2-8°C for a total of 7 days (including thawing time), and/or
- Keep at room temperature for a maximum of 24 hours (including thawing time).

In-use stability after withdrawal from the vial

If unable to administer the suspension shortly after withdrawal, the solution may be stored in syringes for up to 6 hours at room temperature (20-25°C), protected from light.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

For thawing details see the information intended for healthcare professionals at the end of this leaflet.

Do not throw away any medicines via wastewater or household waste. 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. These measures will help protect the environment.

6. Contents of the pack and other information

What ADSTILADRIN contains

- The active substance is nadofaragene firadenovec. Each vial contains 20 mL suspension with a concentration of 3×10^{11} viral particles/mL.
- The other excipients are Syn3NODA, citric acid monohydrate (for pH adjustment) (E 330), sodium citrate (for pH adjustment) (E 331), polysorbate 80 (E 433) (see section 2 "ADSTILADRIN contains polysorbate 80"), hydroxypropylbetadex (E 459), sodium dihydrogen phosphate dihydrate (for pH adjustment) (E 339), trometamol (for pH adjustment), sucrose, magnesium chloride hexahydrate (E 511), glycerol (E 422), and water for injections.

What ADSTILADRIN looks like and contents of the pack
ADSTILADRIN is an intravesical suspension. When thawed, ADSTILADRIN is an opalescent colourless suspension.

The vials are single-use transparent Type 1 glass vials with a bromobutyl rubber stopper sealed with a tamper-evident crimp.

ADSTILADRIN is supplied in a carton containing four (4) 20 mL single-use vials.

Marketing Authorisation Holder
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2770 Kastrup
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Manufacturer
FinVector Oy
Microkatu 1s
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This leaflet was last revised in.

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics (SmPC) before using.

Immunocompromised, immune-deficient and pregnant healthcare professionals

Healthcare professionals who are immunocompromised, immune-deficient, or pregnant should not prepare, administer, or come in contact with ADSTILADRIN due to the theoretical risk of adenoviral infection.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified organisms (GMOs).

- Any ADSTILADRIN spills should be treated with a virucidal agent (such as 5 % sodium hypochlorite or hydrogen peroxide disinfectant) for 30 minutes. Disinfectant should be present in the preparation area and patient room in case of spill.
- Personal protective equipment (including gloves, safety glasses, apron or protective clothing) should be worn while handling or administering ADSTILADRIN.

Thawing and thawing time

When thawing at room temperature:
Frozen ADSTILADRIN vials will thaw in approximately 3-5 hours outside the cardboard nest when placed at room temperature (20-25°C) (8-10 hours inside the nest). Protect the vials from light, even if thawed outside the cardboard nest.

When thawing in refrigerator:
Frozen ADSTILADRIN vials will thaw in approximately 4-5 hours outside the cardboard nest when placed in the refrigerator (2-8°C) (11-13 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.

All four vials should be inspected 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.

Once the thawing procedure is initiated (at 2-8°C and/or at room temperature), the date and time for placing and removing the product from the specified storage condition, should be noted on the carton. When removing the product, the time remaining at the specific storage condition should be noted on the carton.

Items required for instillation

- Four (4) thawed vials of ADSTILADRIN
- Four (4) vented vial adaptors (20 mm) suitable for a 30R 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 adaptors:
  - One (1) straight, or intermittent, urethral catheter with a proximal funnel opening that will accommodate the Luer lock adaptor.
  - Use only catheters made of vinyl/PVC (uncoated or coated with hydrogel), red rubber latex or silicone to instil ADSTILADRIN. Do not use catheters coated or embedded with silver or antibiotics.

Preparation

1. Using aseptic technique, remove the cap from an ADSTILADRIN vial and attach a vented vial adaptor according to manufacturer's instructions.
2. Connect the syringe to the vial adaptor 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.
4. Use ADSTILADRIN within 6 hours of drawing into syringe.

Bladder instillation of ADSTILADRIN

- Premedication with an anticholinergic before each instillation of ADSTILADRIN is recommended.
- ADSTILADRIN must be brought to room temperature before administration.
- Before administering ADSTILADRIN to the patient, insert one straight, or intermittent, urinary catheter with a proximal funnel opening that will accommodate the Luer lock adaptor.
- Use only catheters made of vinyl/PVC (uncoated or coated with hydrogel), red rubber latex or silicone to instil ADSTILADRIN. Do not use catheters coated or embedded with silver or antibiotics.
- Use the catheter to completely empty the patient's bladder before instillation of ADSTILADRIN. Do not remove the catheter.
- Attach the Luer lock end of the catheter adaptor to the syringe containing ADSTILADRIN and insert the tapered end of the catheter adaptor into the funnel opening of the catheter.
- Slowly instil 75 mL of ADSTILADRIN into the bladder through the catheter, ensuring that the complete volume is administered.
- After instillation the catheter should be removed.
- 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 the patient exhibits bladder cramping or premature voiding during the dwell time, repositioning of the patient may be adjusted or discontinued.
- 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.

- Voided urine should be disinfected for 15 minutes with two cups of virucidal agent before flushing of the toilet; this should be done for the first 2 days after each treatment.

Measures to take in case of accidental exposure

Accidental exposure to nadofaragene firadenovec, including contact with skin, eyes and mucous membranes, is to be avoided.

- In case of accidental exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes.
- In case of accidental exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.
- In case of accidental ingestion, immediately rise the mouth and drink plenty of water.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and disposable materials that have come into contact with ADSTILADRIN should be placed in biohazard containers for destruction. Non-disposable equipment must be decontaminated according to the facility's biohazard standard operating procedures.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION AND PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.