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

ANKTIVA 400 micrograms concentrate for intravesical solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial contains 400 micrograms nogapendekin alfa inbakicept in 0.4 mL solution (1 mg/mL).

Nogapendekin alfa inbakicept is an interleukin-15 (IL-15) receptor superagonist. It is a soluble complex consisting of two nogapendekin alfa units (a human IL-15N72D variant) bound to a single inbakicept unit [a dimeric human IL-15Rα sushi domain/human IgG1 Fc fusion protein]. Nogapendekin alfa inbakicept is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for intravesical solution.

Clear to slightly opalescent, colourless to slightly yellow solution, pH 7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ANKTIVA in combination with Bacillus Calmette-Guérin (BCG) is indicated for the treatment of adult patients with 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

For preparation of the BCG ANKTIVA admixture see section 6.6.

Posology

Induction therapy
ANKTIVA is recommended at a dose of 400 micrograms; administered intravesically with BCG once a week for 6 weeks. A second induction course may be administered if complete response is not achieved at month 3.

Maintenance therapy
After BCG and ANKTIVA induction therapy, ANKTIVA is recommended at a dose of 400 micrograms administered intravesically with BCG once a week for 3 weeks at months 4, 7, 10, 13 and 19 (for a total of 15 doses). For patients with an ongoing complete response at month 25 and later, maintenance instillations with BCG may be administered once a week for 3 weeks at months 25, 31, and 37 for a maximum of 9 additional instillations.

The recommended duration of treatment is until disease persistence after second induction, disease recurrence or progression, unacceptable toxicity, or a maximum of 37 months.

Special populations

Elderly
No dose adjustments are necessary in the elderly population.

Of the total number of patients in clinical studies of ANKTIVA for BCG-unresponsive NMIBC, 84% were 65 years of age or older and 40% were 75 years or older. Clinical studies of ANKTIVA did not include sufficient numbers of younger adult patients to determine if patients 65 years of age and older respond differently than younger adult patients.

Paediatric population
The safety and efficacy of ANKTIVA in children have not been established.

Method of administration

For instructions on dilution of the medicinal product before administration, see section 6.6.

Administering the medicinal product
The admixture of ANKTIVA in combination with BCG is instilled into the bladder via a catheter. After instillation is complete, the catheter is removed. The ANKTIVA in combination with BCG admixture is retained in the bladder for 2 hours and then voided. Patients unable to retain the suspension for 2 hours should be allowed to void sooner, if necessary. Do not repeat the dose if the patient voids before 2 hours.

See BCG Summary of Product Characteristics for information on retention in the bladder and patient positioning during bladder instillation.

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

For Intravesical Use Only. Do NOT administer ANKTIVA by subcutaneous or intravenous or intramuscular routes.

Risk of 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 77 evaluable patients with BCG-unresponsive CIS treated with ANKTIVA with BCG in QUILT-3.032, 10% (n = 8) progressed to muscle invasive (T2 or greater) bladder cancer, including 7 during the treatment period. Three patients had progression determined at the time of cystectomy. The median time between determination of persistent or recurrent CIS and progression to muscle-invasive disease was 107 days (range: 0 – 210).

If patients with CIS do not have a complete response to treatment after a second induction course of ANKTIVA with BCG, reconsider cystectomy.

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.

Excipients

This medicinal product contains less than 1 mmol potassium (39 mg) per dose, i.e. essentially "potassium-free".

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

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

The pregnancy status in women of childbearing potential has to be verified prior to initiating treatment with ANKTIVA. Advise females of reproductive potential to use effective contraception during treatment with ANKTIVA and for 1 week after the last dose.

Pregnancy

No effects during pregnancy are anticipated, since systemic exposure to nogapendekin alfa inbakicept following intravesical administration is below the limit of quantitation.

Systemic exposure of nogapendekin alfa inbakicept (ANKTIVA) following intravesical administration of the approved dosage of ANKTIVA was below the limit of quantitation (see section 5.2). Based on its mechanism of action, ANKTIVA may cause fetal harm when administered to a pregnant woman if systemic exposure occurs (see section 5.1). There are no available data on ANKTIVA use in pregnant women to inform a drug-associated risk. Animal reproductive and developmental toxicity studies have not been conducted with nogapendekin alfa inbakicept.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure (see section 5.2) of the breast-feeding woman to nogapendekin alfa inbakicept (ANKTIVA) following intravesical administration is negligible (below the limit of quantitation). There are no data on the presence of nogapendekin alfa inbakicept (ANKTIVA) in human milk, or the effects on the breastfed child, or on milk production. ANKTIVA can be used during breast-feeding.

Fertility

Systemic exposure of nogapendekin alfa inbakicept (ANKTIVA) following intravesical administration of the approved dosage of ANKTIVA was below the limit of quantitation (see section 5.2). No clinical data are available on the possible effects of ANKTIVA on fertility. There were no notable effects in the male and female reproductive organs in rats and monkeys administered ANKTIVA subcutaneously and intravenously based on the 13-week and the 1-month repeat-dose toxicity studies, respectively (see section 5.3).

4.7 Effects on ability to drive and use machines

ANKTIVA has no or negligible influence on the ability to drive and use machines since systemic absorbption is below the limit of quantification.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were those related to bladder instillation: dysuria, haematuria, pollakiuria, and micturition urgency. Also common was fatigue.

The safety profile presented below is based on data obtained from clinical trial QUILT-3.032 where ANKTIVA in combination with BCG was administered to subjects (aged 50 to 91 years) (Table 1).

The safety profile of ANKTIVA plus BCG was comparable to that of BCG monotherapy.

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency: 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). Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 summarises the incidence of treatment related adverse events, from trial QUILT-3.032, which represents the total subjects treated with ANKTIVA and BCG.

Table 1: Adverse reactions reported in clinical trials with ANKTIVA in combination with BCG

System organ class	Frequency category	Adverse reaction
Infections and infestations	Common	Urinary tract infection, Cystitis
Metabolism and nutrition disorders	Common	Decreased appetite, Dehydration
Nervous system disorders	Common	Headache
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Diarrhoea, Nausea, Abdominal pain lower, Vomiting
Skin and subcutaneous tissue disorders	Common	Night sweats, Pruritus, Rash
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Muscular weakness, Myalgia, Arthritis, Flank pain, Pain in extremity
Renal and urinary disorders	Very common	Dysuria, Pollakiuria, Haematuria, Micturition urgency

System organ class	Frequency category	Adverse reaction
	Common	Bladder spasm, Cystitis noninfective, Nocturia, Urinary tract pain, Incontinence, Urinary incontinence, Urinary retention, Urinary tract discomfort, Bladder irritation, Lower urinary tract symptoms, Polyuria, Urge incontinence, Urinary hesitation, Urine abnormality
Reproductive system and breast disorders	Common	Prostatitis, Benign prostatic hyperplasia, Penile discharge, Penile pain, Vulvovaginal burning sensation
General disorders and administration site conditions	Very common	Fatigue
	Common	Chills, Pyrexia, Influenza like illness, Pain, Suprapubic pain
Investigations	Common	Bacterial test positive, Blood urine present, Blood creatinine increased, Cells in urine, Blood urea increased, Glomerular filtration rate decreased

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:

Yellow Card Scheme
Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There are no data indicating that an overdose may lead to any other symptoms than the described undesirable effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interleukins, ATC code: L03AC03

Mechanism of action

Nogapendekin alfa inbakicept is an IL-15 receptor superagonist. IL-15 signals through a heterotrimeric receptor that is composed of the common gamma chain (γc) subunit, the beta chain (βc) subunit, and the IL-15-specific alpha subunit, IL-15 receptor α. IL-15 is trans-presented by the IL-15 receptor α to the shared IL-2/IL-15 receptor (βc and γc) on the surface of $CD4^+$ and $CD8^+$ T cells and NK cells.

Binding of nogapendekin alfa inbakicept to its receptor, as a lymphocyte stimulating agent, results in proliferation and activation of NK, $CD8^+$, and memory T cells without proliferation of immuno-suppressive Treg cells. In vivo, intravesicular nogapendekin alfa inbakicept alone or in combination with BCG showed anti-tumour activity when compared to BCG alone, in a carcinogen-induced model of bladder cancer in immunocompetent rats.

Pharmacodynamic effects

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of nogapendekin alfa inbakicept have not been fully characterised.

Immunogenicity

There is insufficient information to characterize the anti-drug antibody response to ANKTIVA and the effects of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of nogapendekin alfa inbakicept (ANKTIVA) products.

Clinical efficacy and safety

The efficacy of ANKTIVA was evaluated in QUILT-3.032 (NCT03022825), a single-arm, multicentre trial in 77 adults with BCG-unresponsive, high-risk, NMIBC with CIS with or without Ta/T1 papillary disease following transurethral resection.

BCG unresponsive high-risk NMIBC CIS was defined as persistent or recurrent CIS alone or with Ta/T1 disease within 12 months of completion of adequate BCG therapy. Adequate BCG therapy was defined as administration of at least 5 of 6 doses of an initial induction course plus either of at least 2 of 3 doses of maintenance therapy or at least 2 of 6 doses of a second induction course. Prior to treatment, all patients with Ta or T1 disease had undergone transurethral resection of bladder tumour (TURBT) to remove all resectable disease. Residual CIS not amenable to complete resection, fulguration, or cauterization was permitted. The trial excluded patients with history of or evidence of muscle invasive (i.e., T2, T3, T4), locally advanced, metastatic, and/or extra-vesical (i.e., urethra, ureter, or renal pelvis) bladder cancer.

Patients received 400 micrograms ANKTIVA with BCG weekly for 6 consecutive weeks during the induction treatment period and then once a week every 3 weeks at 4, 7, 10, 13, and 19 months for patients with no or low-grade disease. Patients with persistent CIS or high-grade Ta disease at 3 months were eligible to receive a second induction course. Patients with ongoing CR at 25 months were eligible to receive additional instillations once a week every 3 weeks at months 25, 31, and 37. Assessment of tumour status was performed every 3 months for up to two years. Assessment for ongoing response beyond month 24 was per local community standards. Random or cystoscopy directed biopsies were required within the first 6 months after treatment initiation. 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.

The median age of patients was 73 years (range, 50 – 91 years); 86% were male; race was White (90%), Black (6%), Asian (1%), American Indian or Alaska Native (1%), or Unknown (1%); and patients had baseline ECOG performance status of 0 (83%) or 1 (17%).

Tumour characteristics at study entry were CIS without Ta/T1 papillary disease (69%), CIS with Ta papillary disease (21%) or CIS with T1 +/- Ta papillary disease (10%). Baseline high-risk NMIBC disease status was 43% refractory and 57% relapsed. The median number of prior BCG doses received was 12 doses (range: 8 – 45 doses); 13% received partial-dose prior BCG. Baseline cystoscopy imaging modality was white light (57%), blue light or narrow band imaging (40%), and unknown (3%).

Efficacy results are summarised in Table 2. Thirty-one percent (n = 24) of patients received a second induction course.

Table 2: Efficacy results in QUILT-3.032

	ANKTIVA with BCG (n = 77)
Complete Response Rate (95% CI)	62% (51, 73)
Duration of Response[a]	
Range in months	0.0, 47.0+
% (n) with duration ≥ 12 months	58% (28)
% (n) with duration ≥ 24 months	40% (19)

+ Denotes ongoing response.

[a] Based on 48 patients that achieved a complete response at any time; reflects period from the time complete response was achieved.

Paediatric population

The licensing authority has waived the obligation to submit the results of studies with nogapendekin alfa inbakicept in all subsets of the paediatric population in the treatment of malignant bladder neoplasms (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Systemic exposure of nogapendekin alfa inbakicept (ANKTIVA) was less than 100 pg/mL following the approved recommended dosage in all patients. This was below the lower limit of quantitation in all patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of toxicity since the systemic exposure to nogapendekin alfa inbakicept (ANKTIVA) following intravesical administration is negligible.

The safety of nogapendekin alfa inbakicept (ANKTIVA) was evaluated by systemic routes of exposure in 1-month repeat-dose toxicity studies in four mouse and one monkey studies and in a 13-week repeat-dose toxicity study in rats. Mice were administered four intravenous or subcutaneous doses of ANKTIVA at dose levels ranging from 0.1 to 4.0 mg/kg. The lowest no observed effect dose level was 0.1 mg/kg. Rats were administered subcutaneous doses (0.1, 0.3, 1.0 mg/kg/day) once every other week for 13 weeks. The no-observed-adverse-effect (NOAEL) level was 1.0 mg/kg. Monkeys were administered intravenous doses of 0.03 and 0.1 mg/kg once a week in the 1-month study, followed by a 2-week treatment-free period. No findings of toxicological significance were observed and the NOAEL was 0.03 mg/kg in monkeys.

Animal fertility studies have not been conducted with nogapendekin alfa inbakicept (ANKTIVA). In pivotal 13-week and 1-month repeat-dose toxicology studies in rats and monkeys, respectively, there were no notable effects in the male and female reproductive organs. However, the monkeys were not sexually mature.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate
Potassium dihydrogen phosphate
Sodium chloride
Water for injections
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

36 months.

If the admixture of ANKTIVA in combination with BCG is not used immediately, store refrigerated at 2°C to 8°C and use within 2 hours.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.4 mL solution in a clear type I glass vial with a chlorobutyl elastomer stopper and an aluminium alloy seal containing a yellow plastic polypropylene flip-off cap.

Pack size: 1 single-dose vial.

6.6 Special precautions for disposal

For single use only.

Do not shake.

Before administration, visually inspect the solution for particulate matter and discolouration prior to administration. Discard the vial if visible particles or discolouration are observed.

Draw 0.4 mL of ANKTIVA into a small syringe and using aseptic technique add to the saline containing the BCG suspension that has been prepared following the instructions provided in the Summary of Product Characteristics for BCG. Mix the suspension gently. Using a 60-mL syringe connected to an appropriate size needle, withdraw the ANKTIVA BCG mixture to a final volume of 50 mL.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ImmunityBio Ireland Limited
6th Floor, 2 Grand Canal Square
Dublin 2, D02 A342
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

PL 61542/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/07/2025

10. DATE OF REVISION OF THE TEXT

26/01/2026

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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

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

Name and address of the manufacturer of the biological active substance

AGC Biologics, Inc.
21511 23rd Dr SE
Bothell, WA 98021
United States of America

Name and address of the manufacturer responsible for batch release

Bilthoven Biologicals
Antonie van Leeuwenhoeklaan 9, 3721 MA
Bilthoven, Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

ANKTIVA 400 micrograms concentrate for intravesical solution

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single-dose vial contains 400 micrograms nogapendekin alfa inbakicept in 0.4 mL solution (1 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: Disodium phosphate, potassium dihydrogen phosphate, sodium chloride, water for injections, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single-dose vial (0.4 mL). Concentrate for intravesical solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravesical use after dilution.
Read the package leaflet before 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

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Do not shake.
Store in the original package in order to protect from light.

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

Discard 2 hours after dilution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ImmunityBio Ireland Limited
6th Floor, 2 Grand Canal Square
Dublin 2, D02 A342
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 61542/0001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ANKTIVA 400 mcg concentrate for intravesical solution

2. METHOD OF ADMINISTRATION

Intravesical use after dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 single-dose vial (0.4 mL)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

ANKTIVA® 400 micrograms concentrate for intravesical solution
Nogapendekin alfa inbakicept

▼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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ANKTIVA is and what it is used for

ANKTIVA contains the active ingredient nogapendekin alfa inbakicept; a modified version of a protein called interleukin-15 (IL-15). ANKTIVA acts as a receptor superagonist.

ANKTIVA is used to treat adult patients with non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS), with or without papillary tumours, that have not responded to treatment with BCG (Bacillus Calmette-Guérin). When ANKTIVA is used with BCG it activates the immune system, including immune memory cells, to kill bladder cancer cells. This may help the patient to have a durable complete response.

How ANKTIVA works
Interleukin-15 (IL-15) is a protein that plays an important role in the immune system by affecting the development, maintenance, and function of immune cells. The active substance in ANKTIVA is an IL-15 superagonist complex that works by binding to IL-15 receptors on immune cells. It activates anti-tumour immune cells and limits the activation of immune-suppressing cells.

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

You should not be given ANKTIVA
- if you are allergic to nogapendekin alfa inbakicept or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before receiving ANKTIVA.

Before you get ANKTIVA, tell your doctor:
- if you have a tumour for which removal of the bladder or another systemic therapy (e.g. chemotherapy) is indicated.

- if you have had a history of or evidence of muscle-invasive, locally advanced metastatic bladder cancer.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age.

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

Pregnancy, breast-feeding and fertility
Exposure to ANKTIVA during pregnancy may harm the foetus.

There is no information on the presence of ANKTIVA in breast milk or the effects on the breast-fed child, or on milk production.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Treatment with ANKTIVA and BCG could influence your ability to drive or use machines.

ANKTIVA contains potassium and sodium
This medicine contains less than 1 mmol potassium (39 mg) and less than 1 mmol sodium (23 mg) per vial (0.4 mL), that is to say essentially “potassium- and sodium-free”.

3. How ANKTIVA is given

ANKTIVA will be given to you by a trained health care professional.

Dosage
The recommended dose is 400 micrograms. The content of one vial is required for one bladder instillation. This medicine is used together with BCG.

Administration
ANKTIVA must not be used for administration under the skin, into the muscle or vein.

ANKTIVA is prepared and administered by trained healthcare personnel only. ANKTIVA is given with BCG as an intravesical instillation, which is a liquid medicine delivered into the bladder through a tube (catheter) from the urethra.

You should wait 2 hours before you empty your bladder. If you are unable to hold the mixture for two hours, you may be allowed to empty it sooner, without having to repeat the dose.

Duration of the treatment

Induction therapy
- You will receive one dose of ANKTIVA with BCG once a week for 6 weeks.
- If you do not completely respond to the treatment after 3 months, you may receive a second induction course.

Maintenance therapy
- After induction therapy with ANKTIVA and BCG, you will receive one dose of ANKTIVA with BCG once a week for 3 weeks at months 4, 7, 10, 13 and 19 (for a total of 15 doses).

- In case of an ongoing complete response at month 25 and later, you may receive maintenance instillations with BCG once a week for 3 weeks at months 25, 31 and 37 (for a maximum of 9 additional instillations).
- Your doctor may recommend to stop maintenance therapy with ANKTIVA and BCG if the disease remains after a second induction course, if the disease reappears or worsens, if you experience unacceptable toxicity or if you have been on the treatment for over 3 years.

If you stop receiving ANKTIVA
Do not stop treatment with ANKTIVA without talking to your doctor.

If you have any further questions about your treatment, ask your doctor.

4. Possible side effects

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

Irritable bladder symptoms may occur during instillation, and retention of ANKTIVA, and following voiding. For the first 24 hours following administration, red-tinged urine may occur. These symptoms are generally mild and temporary, occurring at a similar frequency as with BCG therapy alone. **Tell your doctor or nurse immediately if you experience severe or prolonged symptoms.**

The following side effects were seen in patients who received ANKTIVA together with BCG. Tell your doctor if you have any of the following:

Serious side effects
No serious side effects were reported as related to ANKTIVA in the 88 patients with BCG-resistant NMIBC CIS who had received ANKTIVA with BCG.

Other side effects

Very common side effects (may affect more than 1 in 10 people)
- Painful or uncomfortable urination (dysuria)
- Frequent, small amounts of urination (pollakiuria)
- Blood in the urine (haematuria)
- A sudden strong need to urinate (micturition urgency)
- Fatigue

Common side effects (may affect up to 1 in 10 people)
- Sudden squeeze of the bladder (bladder spasm)
- Chills
- Fever (pyrexia)
- Urinary tract infection
- Bladder inflammation not caused by infection (cystitis noninfective)
- Excessive urination at night (nocturia)
- Nausea
- Joint pain (arthralgia)
- Night sweats
- Urinary tract pain
- Inability to control urination (urinary incontinence)
- Increase in creatinine in the blood
- Abnormal presence of cells in the urine
- Diarrhoea
- Muscle pain (myalgia)
- Inflammation of the prostate gland (prostatitis)
- Incontinence
- Difficulty in emptying the bladder (urinary retention)

- Urinary tract discomfort
- Bladder irritation
- Lower urinary tract symptoms, e.g. poor urinary stream, prolonged urination, dribbling of urine, or incomplete bladder emptying
- Excessive or abnormally large production or passage of urine (polyuria)
- Urge incontinence
- Urinary hesitation
- Urine abnormality
- Bladder inflammation (cystitis)
- Headache
- Pain in the lower abdomen
- Decreased appetite
- Difficulty breathing (dyspnoea)
- Itchy skin (pruritus)
- Rash
- Muscular weakness
- Flank pain (pain on the side between the lower ribs and the hip)
- Penile pain
- Pain
- Detection of bacteria in urine test
- Excessive loss of body water (dehydration)
- Vomiting
- Influenza like illness
- Inflammation of the joints (arthritis)
- Pain in extremity
- Decreased filtration activity of the kidneys (glomerular filtration rate decreased)
- Increased the levels of urea (a waste product that needs to be removed from the body) in the blood
- Enlargement of the prostate gland that is not cancerous (benign prostatic hyperplasia)
- Penile discharge
- Vulvovaginal burning sensation
- Pain above the pubic bone (suprapubic pain)
- Urine test shows blood is present

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects, you can help provide more information on the safety of this medicine.

Yellow Card Scheme
Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

5. How to store ANKTIVA

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 label and carton after EXP. The expiry date refers to the last day of that month.
Store in a refrigerator (2 °C to 8 °C). Do not freeze.
Store in original carton in order to protect from light.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ANKTIVA contains

The active substance is nogapendekin alfa inbakicept.

One vial of 0.4 mL contains 400 micrograms nogapendekin alfa inbakicept.

The other ingredients are disodium phosphate, potassium dihydrogen phosphate, sodium chloride, water for injections, hydrochloric acid and sodium hydroxide.

What ANKTIVA looks like and contents of the pack
ANKTIVA is a clear to slightly opalescent and colourless to slightly yellow concentrate for intravesical solution.

ANKTIVA is available in a carton containing 1 single-dose clear type I glass vial of 400 micrograms concentrate for intravesical solution with a chlorobutyl elastomer stopper and an aluminium alloy seal containing a yellow plastic polypropylene flip-off cap.

Marketing Authorisation Holder
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Manufacturer
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The following information is intended for healthcare professionals only:

For information on posology, see section 4.2 of the Summary of Product Characteristics.

Administering the medicinal product

The admixture of ANKTIVA in combination with BCG is instilled into the bladder via a catheter. After instillation is complete, the catheter is removed. The ANKTIVA in combination with BCG admixture is retained in the bladder for 2 hours and then voided. Patients unable to retain the suspension for 2 hours should be allowed to void sooner, if necessary. Do not repeat the dose if the patient voids before 2 hours.

See BCG Summary of Product Characteristics for information on retention in the bladder and patient positioning during bladder instillation.

Special precautions for disposal and other handling

For single use only.

Do not shake.

Before administration, visually inspect the solution for particulate matter and discolouration prior to administration. Discard the vial if visible particles or discolouration are observed.

Draw 0.4 mL of ANKTIVA into a small syringe and using aseptic technique add to the saline containing the BCG suspension that has been prepared following the instructions provided in the Summary of Product Characteristics for BCG. Mix the suspension gently. Using a 60-mL syringe connected to an appropriate size needle, withdraw the ANKTIVA BCG mixture to a final volume of 50 mL.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.