SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

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1. NAME OF THE MEDICINAL PRODUCT

ANKTIVA 400 microgram solution for intravesical instillation.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nogapendekin alfa inbakicept is a complex consisting of two nogapendekin alfa bound to inbakicept, produced in a Chinese hamster ovary (CHO-K1) cell line by recombinant DNA technology.

For the full list of excipients, see section 6.1.

One vial (0.4 mL) contains 400 micrograms nogapendekin alfa inbakicept.

3. PHARMACEUTICAL FORM

Nogapendekin alfa inbakicept is a clear to slightly opalescent, colourless to slightly yellow solution, pH 7.4.

Solution for intravesical instillation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ANKTIVA in combination with Bacillus Calmette-Guérin (BCG) is indicated for the treatment of adult patients with high-risk BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) of carcinoma in situ (CIS) with or without papillary disease.

4.2 Posology and method of administration

Induction therapy

ANKTIVA is recommended at a dose of 400 micrograms; administered intravesically as a mixture with BCG recommended at a dose of 50 mL once a week for 6 weeks. A second induction course (re-induction) is recommended if complete response is not achieved at the first assessment after induction (at week 12). See section 5.1 for pharmacodynamic properties.

Maintenance therapy

After BCG and ANKTIVA induction therapy, for patients with lack of disease or low-grade Ta, continued treatment is recommended at a dose of 400 micrograms administered intravesically with BCG once a week for 3 consecutive weeks at months 4, 7, 10, 13 and 19 (for a total of 15 doses).

Presence of a low-grade Ta will require a transurethral resection of bladder tumour (TURBT) procedure prior to instillation. Treatment may be delayed by up to 28 days after TURBT procedure if required. For patients with an ongoing complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable] and urine cytology) in NMIBC CIS or the absence of progression in NMIBC papillary, at month 25 and later, maintenance instillations with ANKTIVA and BCG may be administered once a week for 3 consecutive 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 (new CIS and/or any T1 disease or greater), unacceptable toxicity, or a maximum treatment duration of 37 months.

Special populations

Elderly

No dose adjustments are necessary in the elderly population.

Hepatic and/or renal impairment

No dose adjustments are necessary in patients with hepatic and/or renal impairment.

Paediatric population

There is no relevant use of ANKTIVA in the paediatric population in children aged 0 to less than 18 years in the indication BCG-unresponsive NMIBC CIS with or without papillary disease.

Method of administration

For intravesical use.

Do not shake.

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

ANKTIVA is administered intravesically with BCG into the bladder via a catheter. Connect a catheter to the suspension container directly or using a 60-mL syringe connected to an appropriate size needle/connecter, withdraw the 50 mL ANKTIVA with BCG mixture and attach to a urinary catheter. Instil the mixture through the urinary catheter and into the bladder.

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. The dose should not be repeated 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

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 potassium, less than 1 mmol (39 mg) per dose, i.e. essentially ‘potassium-free’.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.4.1 Traceability

For BCG-unresponsive NMIBC, intravesical use only. ANKTIVA should NOT be administered by subcutaneous or intravenous or intramuscular use.

Severe systemic BCG-infections/reactions

The possibility of severe systemic BCG-infections with the necessity of anti-tuberculosis therapy has to be considered before starting the BCG-therapy. See Summary of Product Characteristics for the specific BCG being used.

Risk of muscle invasive and metastatic bladder cancer with delayed cystectomy

Delaying cystectomy in patients with BCG-unresponsive CIS with or without papillary disease after ANKTIVA therapy in combination with BCG could lead to development of muscle invasive or metastatic bladder cancer.

Of the 100 evaluable patients with BCG-unresponsive CIS treated with ANKTIVA with BCG in QUILT-3.032, 10% (n = 10), (0.049, 0.176), progressed to muscle invasive (T2 or greater) bladder cancer, including 2 during the treatment period. Of these 10 patients, 3 had reached CR (treatment period 16.1-108.0 weeks) and 7 had not reached CR before progression (treatment period 5.3-24.1 weeks). Four out of these 7 participants without CR received a second induction. Four 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 224 days (range: 0-854). Among all study participants in QUILT-3.032 and over a total follow-up period of up to 63.5 months, 5% of participants developed metastatic disease by 24 months, with none at 12 months. Five of seventy (5/70) patients not re-inducted progressed to muscle invasive/metastatic disease, whereas 5/30 patients that received a second induction course progressed.

In the re-inducted patients (n=30) the CR rate was 50% (31.3, 68.7) and the DoR was 12.0 months (3.9, 21.5). In the subgroup of patients who did not need re-induction (n=70), the CR was 80% (68.7, 88.6) and the DoR was 28.7 months (20.7, not reached).

Of the 80 evaluable patients with BCG-unresponsive papillary NMIBC treated with ANKTIVA in QUILT-3.032, 10% (n=8) progressed to muscle invasive (T2 or greater) bladder cancer. The median time to progression to muscle-invasive disease was 16.2 months (range: 2.5-46.5).

If patients with NMIBC CIS with or without papillary are medically eligible for cystectomy do not have a complete response (absence of disease or low-grade Ta) to treatment after an induction course of ANKTIVA with BCG at the 12 weeks assessment, re-induction is indicated or reconsider cystectomy. The risk of developing muscle invasive or metastatic bladder cancer increases the longer cystectomy is delayed in the presence of persisting CIS.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed for NMIBC.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential / contraception

Women of childbearing potential have to use effective contraception during treatment and for 1 week after the last dose.

Pregnancy

There are no data on the use of treatment in pregnant women. Animal reproduction studies have not been conducted with ANKTIVA; however, in murine models of pregnancy, IL-15 pathway increases uterine natural killer cells, whereby producing interferon-gamma (IFN-γ). This disrupts maternal tolerance to the foetus and results in an increase in embryofoetal loss (see section 5.3). These results indicate a potential risk. Treatment is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

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. Treatment can be used during breast-feeding.

Fertility

There are no clinical data on the effects of treatment on fertility. No effects on fertility are expected since systemic exposure to nogapendekin alfa inbakicept following intravesical administration is below the limit of quantitation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

4.8.1: Adverse Reactions

Tabulated list of adverse reactions

Adverse reaction frequency was determined according to the following criteria: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000). Adverse drug reactions (ADRs) organised by MedDRA System Organ Class (SOC) and by frequency are presented in Table 1.

The most common treatment related adverse drug reactions from QUILT-3.032 (for both NMIBC CIS and NMIBC papillary disease) were: dysuria (27%), pollakiuria (26%), haematuria (21%), micturition urgency (16%), and fatigue (17%).

More than one patient experienced the following grade ≥ 3 treatment related adverse reaction: myalgia (2 patients, 1%).

Two patients experienced the following treatment related serious adverse reactions: cystitis noninfective and haematuria (1%, each).

Table 1 lists adverse reactions in a clinical study (n=180) where ANKTIVA in combination with BCG was administered to subjects (aged 46 to 93 years).

Table 1: Treatment related adverse reactions with ANKTIVA in combination with BCG

System organ class	Frequency category	Adverse reaction
Infections and infestations	Common	Urinary tract infections Cystitis
Metabolism and nutrition disorders	Common	Decreased appetite
Nervous system disorders	Common	Dizziness
Gastrointestinal disorders	Common	Diarrhea, Nausea, Abdominal pain, Abdominal pain lower
Skin and subcutaneous tissue disorders	Common	Night sweats,
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia, Flank pain, Muscular weakness
Renal and urinary disorders	Very Common	Haematuria, Dysuria, Pollakiuria, Micturition urgency
	Common	Bladder spasm, Cystitis noninfective, Nocturia, Urinary incontinence, Urinary tract pain, Urinary retention, Bladder irritation Bladder pain, Urge incontinence, Lower urinary tract discomfort,
Reproductive system and breast disorders	Common	Penile burning sensation, Penile pain, Prostatitis
General disorders and administration site conditions	Very common	Fatigue
	Common	Chills, Pyrexia, Influenza like illness, Pain
Investigations	Common	Blood creatinine increased, Bacterial test positive, Blood in urine present, Cancer cells urine present

Report any side effects to:

To report SUSPECTED ADVERSE REACTIONS, contact ImmunityBio +966-539455825 or +966-12-6148000

- The National Pharmacovigilance Centre (NPC):

  - SFDA Call Center: 19999
  - E-mail: npc.drug@sfda.gov.sa
  - Website: http://ade.sfda.gov.sa/

4.9 Overdose

There are no data indicating that an overdose may lead to any other symptoms than the described undesirable effects. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interleukins, ATC code: L03AC03

Mechanism of action

Nogapendekin alfa inbakicept is an IL-15 receptor agonist. 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 results in proliferation and activation of NK, CD4+, CD8+, and memory T cells without proliferation of immuno-suppressive Treg cells.

Pharmacodynamic effects

Immunogenicity

In QUILT-2.005 Phase 2b, 5% of participants had treatment-emergent anti-drug antibodies. In QUILT-3.032, 3% of participants had treatment-emergent anti-drug antibodies.

No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. However, data are limited.

Clinical efficacy and safety

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 a total of 15 doses) for patients with no or low-grade Ta disease. Presence of low-grade Ta disease required a TURBT procedure prior to instillation. Treatment delay was permitted for up to 28 days after TURBT/biopsy if required. Patients with persistent CIS or high-grade Ta disease at 3 months were eligible to receive a second induction course. Patients with ongoing CR, as defined by negative results for cystoscopy (with TURBT/biopsies as applicable) and urine cytology at 25 months were eligible to receive additional instillations once a week every 3 consecutive weeks at months 25, 31, and 37 for a maximum of 9 additional instillations. 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 to confirm CR.

The efficacy of treatment was evaluated in QUILT-3.032, a single-arm, open-label, multicentre trial. Cohort A included 100 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 and immunocompromised patients with ongoing chronic systemic steroid therapy (> 10 mg oral prednisone daily or equivalent). 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.

The major efficacy outcome measure was complete response (CR) at any time by local pathological review and duration of response. CR was defined as:

a. Negative cystoscopy and negative (including atypical) urine cytology; or
b. Positive cystoscopy with biopsy-proven benign or low-grade Ta NMIBC and negative cytology; or
c. Negative cystoscopy with malignant urine cytology if both of the following criteria are met: i) cancer is found in the upper tract or prostatic urethra, and ii) random bladder biopsies are negative.
d. A visit where a negative cystoscopy with one or more consecutive missing, suspicious, or malignant urine cytologies, and the subsequent urine cytology is negative or atypical and normal cystoscopy (or negative biopsy if cystoscopy is suspicious or abnormal) is considered a complete response.

The median age of patients was 73 years (range, 50-91 years); 87% were male; race was White (90%), Black (7%), Asian (1%), American Indian or Alaska Native (1%), or Unknown (1%); and patients had baseline ECOG performance status of 0 (83%) or 1 (17%). Smoking status was not collected in QUILT-3.032.

Tumour characteristics at study entry were CIS without Ta/T1 papillary disease (74%), CIS with Ta papillary disease (17%) or CIS with T1 +/- Ta papillary disease (9%). Baseline high-risk NMIBC disease status was 44% refractory and 56% relapsed. The median number of prior BCG doses received was 12 doses (range: 5-48 doses); 13% received partial-dose prior BCG. Baseline cystoscopy imaging modality was white light only (63%), white and blue light (28%), narrow band (6%), and unknown (3%).

The median duration of follow-up was 25.68 months. Efficacy results are summarised in Table 3. Thirty percent (n = 30) of patients received a second induction course.

Table 2: Efficacy results in QUILT-3.032: NMIBC CIS (Cohort A)

	ANKTIVA with BCG (n=100)
Complete response rate (95% CI)	71% (61, 80)
Median duration of complete response (DoR) (n=71)	26.6 months (13.0, 49.9)
Range in months[a]	0.0, 54+ months
CR rate of responders at 12 and 24 months	
% (n) with CR at 12 months	66% (47/71)

% (n) with CR at 24 months	42% (30/71)

+Denotes ongoing response

[a] Based on 71 patients that achieved a complete response at any time; reflects period from the time complete response was achieved.

5.2 Pharmacokinetic properties

Systemic exposure of nogapendekin alfa inbakicept (ANKTIVA) was less than 100 pg/mL following the approved recommended dose 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 using intravenous or subcutaneous administration since the clinical systemic exposure to nogapendekin alfa inbakicept (ANKTIVA) following intravesical administration is negligible.

Animal reproduction studies have not been conducted with ANKTIVA. The IL-15 pathway is thought to be involved in maintaining tolerance to the foetus during pregnancy. A secondary signalling mechanism of IL-15 has been shown in murine models of pregnancy to increase uterine natural killer cells. This produces interferon-gamma (IFN-γ), which disrupts maternal tolerance to the foetus and has been shown to result in an increase in embryofoetal loss.

Animal fertility studies have not been conducted with nogapendekin alfa inbakicept (ANKTIVA). In a 13-week and 1-month repeat-dose toxicology study 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

3 years.

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

< hemical and physical in-use stability of the admixture of ANKTIVA with:

- OncoTICE has been demonstrated for up to 2 hours at 2 °C to 8 °C, protected from light.
- BCG-medac has been demonstrated for up to 24 hours at 2 °C to 8 °C, protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Do not freeze. Do not shake.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.4 mL solution in a glass vial with a serum stopper (chlorobutyl elastomer with a Flurotec B2-40 coating) and an aluminium alloy seal containing a yellow matte plastic polypropylene flip-off cap.

Pack size: 1 single-dose vial.

6.6 Special precautions for disposal and other handling

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if visible particles are observed.

Prepare a suspension of BCG according to the instructions provided in the manufacturer's Summary of Product Characteristics for the specific BCG being used.

Obtain a vial of ANKTIVA (do not shake), remove the flip-off cap and disinfect the stopper. Withdraw 0.4 mL of ANKTIVA using a sterile needle and syringe (1-3 mL). Using clean technique, promptly add ANKTIVA to the sodium chloride solution containing the BCG suspension utilizing appropriate connectors and/or septum (as needed), depending on the saline container used for the BCG suspension. Mix the suspension gently.

Any spilled ANKTIVA BCG mixture should be cleaned by covering the area with paper towels soaked with tuberculocidal disinfectant for at least 10 minutes. Unused ANKTIVA with BCG and all equipment, supplies, and receptacles in contact with it should be handled and disposed of as biohazardous.

Accidental exposure to ANKTIVA BCG mixture could occur through self-inoculation, by dermal exposure through an open wound or by ingestion of ANKTIVA with BCG. Exposure should not produce significant adverse health outcomes in healthy individuals. However, in case of suspected, accidental self-inoculation, PPD skin testing is advised at the time of the accident and six weeks later to detect skin test conversion.

Precautions to be taken before handling or administering the medicinal product

Standard precautions of personal protective equipment are the same as BCG. No precautions are needed for ANKTIVA in addition to the BCG precautions.

7. MARKETING AUTHORISATION HOLDER

ImmunityBio

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 January 2026

9. DATE OF REVISION OF THE TEXT

LABELLING

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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

ANKTIVA
nogapendekin alfa inbakicept
0.4 mg per 0.4 mL
solution for intravesical instillation

2. STATEMENT OF ACTIVE SUBSTANCE

One vial (0.4 mL) contains 0.4 milligrams nogapendekin alfa inbakicept.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for intravesical instillation
1 single-dose vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.
For 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. MANUFACTURING AND EXPIRY DATE

MFG
EXP
Read the leaflet for the shelf life of the reconstituted medicine.

9. SPECIAL STORAGE CONDITIONS

Store refrigerated at 2-8°C.
Do not freeze.
Keep the vial in the outer carton 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

11. MANUFACTURER NAME

Manufacturer:
PCI San Diego, Inc.
San Diego, CA USA

Packaged by:
Millmount Healthcare Ltd.
Stamullen, Ireland

12. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ImmunityBio
Akaria 2, Floor 5 Office 511
Olaya Street
Riyadh 12244, Saudi Arabia
MA# 2901269043

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

N/A

15. DATAMATRIX

16. GLOBAL TRADE ITEM NUMBER

GTIN: 00381481000025

17. SERIAL NUMBER

S/N

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MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

ANKTIVA
nogapendekin alfa inbakicept
0.4 mg per 0.4 mL
solution for intravesical instillation
For intravesical use.

2. METHOD OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.

3. MANUFACTURING AND EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 mL

6. SPECIAL STORAGE CONDITIONS

N/A

7. OTHER

N/A

8. DATAMATRIX

N/A

9. GLOBAL TRADE ITEM NUMBER

N/A

10. SERIAL NUMBER

N/A

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