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 microgram concentrate for intravesical suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for intravesical suspension.

Nogapendekin alfa inbakicept is a 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

Posology

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) may be administered in case of residual CIS +/- High grade Ta at the first assessment after induction (at week 12) (see section 4.4. concerning the re-consideration of cystectomy in patients with residual disease). 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 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. Assessment of tumour status should be performed every 3 months for up to 24 months. Assessment for ongoing response beyond month 24 is per local community standards.

The recommended duration of treatment is until disease persistence after the last induction cycle (initial, or if administered, 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 tumours.

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 50-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

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.

For 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 should be considered before initiating the BCG-therapy. See Summary of product Characteristics for the specific BCG being used.

Risk of progression to muscle invasive and metastatic bladder cancer with delayed cystectomy

Delaying cystectomy in patients with BCG-unresponsive NMIBC with CIS, with or without papillary tumours, treated with 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 in combination with BCG in QUILT-3.032, 10% (n = 10; 95% CI 4.9-17.6%), progressed to muscle-invasive (T2 or greater) bladder cancer, including 2 cases occuring during the treatment period. Among these 10 patients, 3 achieved a complete response (CR) before progression (treatment period 16.1-108.0 weeks), while 7 had not reached CR (treatment period 5.3-24.1 weeks). Four out of these 7 subjects without CR received a second induction (re-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 with up to 63.5 months of follow up, 5% of participants developed metastatic disease by 24 months (none at 12 months). Progression to muscle invasive or metastatic disease occurred in five of seventy (5/70) patients who were not re-inducted, and in five of thirty (5/30) patients that received a second induction course (re-induction).
In patients who received re-induction (n=30, 30%) the CR rate was 50% (95% CI: 31.3, 68.7) and the duration of complete response (DoR) was 12.0 months (95% CI: 3.9, 21.5). In the subgroup of patients who did not need re-induction (n=70), the CR rate was 80% (95% CI: 68.7, 88.6) and the DoR was 28.7 months (95% CI: 20.7, not reached).

If patients with CIS that are medically eligible for cystectomy have not achieved a CR (absence of disease or low-grade Ta) to treatment after an induction course of ANKTIVA in combination with BCG at the 12-weeks assessment, cystectomy should be reconsidered as an alternative to re-induction (see section 4.2.). The risk of developing muscle-invasive or metastatic bladder cancer increases the longer cystectomy is delayed in the presence of persisting CIS.

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’.

4.5 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

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

Summary of the safety profile

The most common adverse drug reactions from QUILT-3.032 were: dysuria (35%), haematuria (35%), pollakiuria (32%), urinary tract infection (24%), micturition urgency (22%), fatigue (20%), chills (13%), musculoskeletal pain (11%), and pyrexia (10%). Adverse drug reaction frequencies presented may not be fully attributable to the drug alone but may contain contributions from the underlying disease or from other drugs used in a combination.

More than one patient experienced the following grade ≥ 3 adverse reactions: urinary tract infection (4 patients, 2%), bacteraemia (2 patients, 1%), sepsis (2 patients, 1%), haematuria (5 patients, 3%), musculoskeletal pain (2 patients, 1%), and myalgia (2 patients, 1%).

More than one patient experienced the following serious adverse reactions: urinary tract infection (3 patients, 2%), bacteraemia (2 patients, 1%), haematuria (5 patients, 3%).

Tabulated list of adverse reactions

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).

Adverse reaction frequency was determined according to the following criteria: 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 are listed by MedDRA System Organ Class (SOC) and by frequency.

Table 1: Adverse reactions with ANKTIVA in combination with BCG

System organ class	Frequency category	Adverse reaction
Infections and infestations	Very common	Urinary tract infection
	Common	Cystitis, Bacteriuria[a], Bacteraemia, Sepsis
Blood and lymphatic system disorders	Common	Anaemia[b], Leukocytosis, Lymphadenopathy
Metabolism and nutrition disorders	Common	Decreased appetite, Dehydration
Nervous system disorders	Common	Dizziness, Headache
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Diarrhoea, Nausea, Abdominal pain[c], Constipation, Vomiting
Skin and subcutaneous tissue disorders	Common	Night sweats, Pruritus, Rash
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[d]
	Common	Myalgia[e], Arthralgia, Muscular weakness
	Uncommon	Arthritis
Renal and urinary disorders	Very Common	Haematuria[f], Dysuria, Pollakiuria, Micturition urgency
	Common	Bladder spasm, Cystitis noninfective, Nocturia, Urinary incontinence, Urinary tract pain[g], Urinary retention, Bladder pain[h], Urge incontinence, Lower urinary tract symptoms, Urinary hesitation, Urine flow decreased, Leukocyturia[i]
	Uncommon	Urine abnormality, Polyuria, Glomerular filtration rate decreased, Blood urea increased
Reproductive system and breast disorders	Common	Genital pain[j], Prostatitis, Benign prostatic hyperplasia
	Uncommon	Penile discharge

General disorders and administration site conditions	Very common	Fatigue, Chills, Pyrexia
	Common	Influenza like illness, Chest pain
	Uncommon	Installation site pain
Investigations	Common	Blood creatinine increased, Cancer cells urine present
[a] includes bacteriuria, asymptomatic bacteriuria and bacterial test positive [b] includes anaemia and anaemia macrocytic [c] includes abdominal pain, abdominal pain lower and suprapubic pain [d] includes musculoskeletal pain, back pain, flank pain and pain in extremity [e] includes myalgia and pain [f] includes haematuria, cystitis haemorrhagic and blood urine present [g] includes urinary tract pain and urinary tract discomfort [h] includes bladder pain, bladder discomfort and bladder irritation [i] includes leukocyturia and white blood cells in urine [j] includes penile pain, penile burning sensation, vulvovaginal burning sensation		

Immune-related adverse events

Given the immune-activating mechanism of nogapendekin alfa inabakicept, immune-related toxicities cannot be excluded, although systemic exposure following intravesical administration is below the limit of quantitation.

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 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 subjects had treatment-emergent anti-drug antibodies. In QUILT-3.032, 3% of subjects 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

The efficacy of treatment was evaluated in QUILT-3.032, a single-arm, open-label, multicentre trial in 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).

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 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. 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.

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 2. Thirty percent (n = 30) of patients received a second induction course.

Table 2: Efficacy results in QUILT-3.032

	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.

The European Medicines Agency has waived the obligation to submit the results of studies with ANKTIVA in all subsets of the paediatric population in the treatment of bladder cancer. 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

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 signaling 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.

Chemical 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.

ANKTIVA has only been studied with OncoTICE and BCG-medac.

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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Do not freeze.
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 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. Only OncoTICE and BCG-medac should be 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 Ireland Limited
6th Floor, 2 Grand Canal Square
Dublin 2, Ireland, D02 A342

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2002/001

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 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

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 of the biological active substance

AGC Biologics, Inc.
2210 220th Street SE (Building 2)
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
The 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 Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation 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 nogapendekin alfa inbakicept in combination with Bacillus Calmette-Guérin (BCG) 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, the MAH shall submit the results of the ongoing open-label randomized QUILT-2.005 Phase 2b study to evaluate the efficacy and safety of intravesical BCG in combination with nogapendekin alfa inbakicept versus BCG alone in patients with BCG-naïve NMIBC.	30 June 2027
In order to confirm the efficacy and safety of nogapendekin alfa inbakicept in combination with Bacillus Calmette-Guérin (BCG) 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, the MAH shall submit the final results including the 5-years follow up period for patients of the ongoing open-label single-arm phase II/III QUILT-3.032 study.	31 December 2029

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 microgram concentrate for intravesical suspension
nogapendekin alfa inbakicept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial (0.4 mL) contains 400 micrograms 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

Concentrate for intravesical suspension
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. EXPIRY DATE

EXP

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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
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. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2002/001

13. BATCH NUMBER

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

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 suspension
nogapendekin alfa inbakicept
For intravesical use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

ANKTIVA 400 microgram concentrate for intravesical suspension
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 substance nogapendekin alfa inbakicept.

ANKTIVA is used in adults to treat a type of bladder cancer that has not spread outside the bladder. It is used in adults who have not responded to treatment with Bacillus Calmette-Guérin (BCG). ANKTIVA is used together with BCG and both are given through the urethra into the bladder. For more information on BCG, read the package leaflet for the BCG medicine you will be given.

How ANKTIVA works
The active substance in ANKTIVA, nogapendekin alfa inbakicept, works by binding to a protein in the immune system known as the interleukin-15 (IL-15) receptor. This activates cells in the immune system that target and destroy cancer 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
Risk of your cancer getting worse if surgery to remove all or part of the bladder is delayed following treatment with this medicine

Children and adolescents
The safety and efficacy of ANKTIVA in children have not been established. You should not be given this medicine if you are under 18 years old.

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 contraception

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Treatment with ANKTIVA is not recommended during pregnancy. This is because it is not known if the medicine may harm the foetus.

Breast-feeding
ANKTIVA can be used during breast-feeding.

Contraception
If you are a woman who can become pregnant, you must use effective contraception (birth control) during treatment with ANKTIVA and for one week after you receive the last dose. Your doctor will give you advice on appropriate contraception methods.

Driving and using machines
Treatment with ANKTIVA has no or minimal impact on your ability to drive or use machines.

ANKTIVA contains potassium and sodium
This medicine contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially 'potassium-free'.

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How ANKTIVA is given

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

The recommended dose of ANKTIVA is 400 micrograms. This medicine is given together with BCG.

Administration
Before administration, do not drink any liquid the 4 hours before treatment is given to you. ANKTIVA is given with BCG as an intravesical instillation, which is a liquid medicine delivered directly into the bladder through a thin, flexible tube (catheter) inserted into the urethra (the tube through which urine leaves the body from the bladder). After ANKTIVA and BCG are delivered to the bladder, the catheter is removed from your urethra.

You should wait 2 hours after you are given this medicine before you empty your bladder (i.e. urinate). If you are unable to hold the mixture for two hours, you will be allowed to empty your bladder sooner, without having to repeat the dose.

Duration of treatment
Induction therapy
- You will receive one dose of ANKTIVA with BCG once a week for 6 weeks. This is known as induction therapy.

If the first round of induction therapy does not fully work after 3 months, you may receive a second course (called re-induction) of ANKTIVA with BCG once a week for 6 more weeks.

Maintenance therapy
- If induction therapy was successful, you will receive one dose of ANKTIVA with BCG once a week for 3 weeks at months 4, 7, 10, 13, and 19. This adds up to 15 maintenance doses.

- If there are no signs of cancer at month 25 or later, you may receive ANKTIVA with BCG once a week for 3 weeks at months 25, 31, and 37. A maximum of 9 additional doses may be given. Your tumour's response to treatment will be evaluated at least every 3 months for up to 24 months.
- Your doctor may recommend stopping ANKTIVA with BCG in these situations:
    - if the disease remains after re-induction therapy,
    - if the disease comes back or worsens,
    - if you experience serious side effects, or
    - if you have been on the treatment for 37 months.

If you stop receiving ANKTIVA
Do not stop treatment with this medicine without talking to 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 were seen in patients who received ANKTIVA together with BCG.

Bladder irritation (such as burning or discomfort) may occur during treatment, while the medicine is in your bladder, or after you urinate. You may also notice blood in the urine for up to 24 hours after treatment. These symptoms are usually mild and temporary. **Tell your doctor or nurse right away if your symptoms are severe or last a long time.**

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) and bladder inflammation with bleeding (cystitis haemorrhagic)
- A sudden strong need to urinate (micturition urgency)
- Tiredness (fatigue)
- Urinary tract infection
- Chills
- Fever (pyrexia)
- Musculoskeletal pain, back pain, flank pain, and pain in arm or leg

Common side effects (may affect up to 1 in 10 people)
- Sudden squeeze of the bladder (bladder spasm), difficulty in emptying the bladder (urinary retention), urinary hesitation, excessive urination at night (nocturia), lower urinary tract symptoms, urine flow decreased (poor urinary stream), inability to control urination (urinary incontinence), bladder inflammation (cystitis), bladder inflammation not caused by infection (cystitis noninfective), urinary tract pain, urinary tract discomfort, bladder pain, bladder discomfort, bladder irritation, urgent and uncontrolled need to pee (urge incontinence), white blood cells in the urine (leukocyturia), cancer cells in urine
- Shortness of breath or difficulty breathing (dyspnoea), chest pain
- Swollen lymph nodes (lymphadenopathy)
- Nausea
- Night sweats
- Diarrhoea
- Headache
- Decreased appetite
- Itchy skin (pruritus)
- Rash
- Muscular weakness

- Penile pain, penile burning sensation, inflammation of the prostate gland (prostatitis), enlargement of the prostate gland that is not cancerous (benign prostatic hyperplasia), vulvovaginal burning sensation
- Dehydration
- Vomiting
- Influenza like illness
- Bacteria in urine with no symptoms (asymptomatic bacteriuria), and bacterial test positive in urine (bacteriuria),
- Low red blood cells (anaemia), low red blood cells caused by unusually large red blood cells (macrocytic anaemia), increase in creatinine seen in blood test, increased white blood cells in the blood (leukocytosis), bacteria in the blood (bacteraemia)
- Dizziness
- Constipation
- Muscle pain/soreness and pain (myalgia), abdominal pain, lower abdominal pain, and pain just above the pubic bone (suprapubic pain)
- Joint pain (arthralgia)
- Body-wide infection (Sepsis)

Uncommon side effects (may affect up to 1 in 100 people)
- Reduced kidney filtering (glomerular filtration rate decreased)
- Urine abnormality
- Increase in blood waste levels (blood urea increased)
- Frequent urination (polyuria)
- Unusual liquid from the penis (penile discharge)
- Joint pain (arthritis)
- Soreness at the treatment site (installation site pain)

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 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 ANKTIVA

ANKTIVA will be stored at the hospital or clinic. Store in a refrigerator (2 °C-8 °C).
Do not freeze. Keep the vial in the outer carton in order to protect from light

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. See section 2 "ANKTIVA contains potassium and sodium".

What ANKTIVA looks like and contents of the pack
This medicine is a clear to slightly opalescent and colourless to slightly yellow solution.

The medicine is available in a carton containing 1 single-dose vial.

Marketing Authorisation Holder
ImmunityBio Ireland Limited

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

Manufacturer
Bilthoven Biologicals
Antonie van Leeuwenhoeklaan 9
3721 MA Bilthoven
The Netherlands

This leaflet was last revised in

Other sources of information

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

The following information is intended for healthcare professionals only:

Administering the medicinal product

ANKTIVA is recommended at a dose of 400 micrograms; administered intravesically as a mixture with BCG recommended at a dose of 50 mL 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.

In-use stability

Chemical 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.

ANKTIVA has only been studied with OncoTICE and BCG-medac.

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.

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. Only OncoTICE and BCG-medac should be 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 for BCG. No precautions are needed for ANKTIVA in addition to the BCG precautions.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION 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.