PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr VERITY-BCG™

Bacillus Calmette-Guérin (BCG): Strain Russian BCG-I

Freeze-dried powder, 40 mg [contains 1-8 x 10^8 Colony Forming Units (CFU)]
For bladder instillation

Antineoplastic and Immunomodulating Agent
ATC CODE: L03AX03

VERITY-BCG, indicated for:

- Adjuvant therapy after transurethral resection (TUR) of a primary or relapsing superficial papillary urothelial cell carcinoma of the bladder stage Ta (grade 2 or 3) or T1 (grade 1, 2, or 3), without concomitant carcinoma in situ. It is only recommended for stage Ta grade 1 papillary tumors, when there is judged to be a high risk (>50%) of tumor recurrence.

VERITY-BCG has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VERITY-BCG please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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Date of Initial Authorization:
December 24, 2020

Date of Revision:
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Submission Control Number: 221579

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

Not Applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VERITY-BCG (Bacillus Calmette-Guérin (BCG): Strain Russian BCG-I) is indicated for:

- Adjuvant therapy after transurethral resection (TUR) of a primary or relapsing superficial papillary urothelial cell carcinoma of the bladder stage Ta (grade 2 or 3) or T1 (grade 1, 2, or 3), without concomitant carcinoma in situ. It is only recommended for stage Ta grade 1 papillary tumors, when there is judged to be a high risk (>50%) of tumor recurrence.

Marketing authorization with conditions was based on recurrence free survival rates in single arm studies in patients with stage T1 disease only (see Part II: CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (< 18 years of age): No studies of VERITY-BCG have been performed in pediatric patients; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

There are limited data for patients aged 65 years and older. (see 4 **Error! Reference source not found.**, 7 **Error! Reference source not found.** and 14 **Error! Reference source not found.**).

2 CONTRAINDICATIONS

- VERITY-BCG is contraindicated in patients who are hypersensitive to Bacillus Calmette-Guérin (BCG), or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, and COMPOSITION AND PACKAGING.
- VERITY-BCG is not indicated for the treatment of invasive bladder cancer.
- VERITY-BCG should not be used in patients with an impaired immune response irrespective of whether this impairment is congenital or caused by disease, drugs or other therapy.
- VERITY-BCG should not be given to patients with positive HIV serology (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).
- VERITY-BCG is contraindicated during pregnancy and lactation (see 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women).
- VERITY-BCG should not be used for patients with active tuberculosis disease. Patients undergoing treatment with antituberculosis drugs for latent or active infection should not receive VERITY-BCG.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• When used as adjuvant therapy after Transurethral Resection (TUR) of a superficial urothelial cell carcinoma of the bladder (See 1 INDICATIONS), treatment with VERITY-BCG should be started 2 to 3 weeks after performing TUR. Treatment should not be started until mucosal lesions have healed (see 7 WARNINGS AND PRECAUTIONS – Genitourinary).

- Traumatic catheterization or other injuries to the urethra or bladder mucosa can promote systemic BCG infection, so treatment must be delayed. (See 7 WARNINGS AND PRECAUTIONS)
- In case of gross hematuria, therapy should be stopped or postponed until the hematuria has been successfully treated or has resolved.
- VERITY-BCG should not be administered to patients with fever without prior evaluation and treatment. (See 8 ADVERSE REACTIONS, 8.1 Adverse Reaction Overview)
- In patients with urinary tract infections, treatment with VERITY-BCG should be withheld until the urine culture becomes negative and antibiotic therapy is stopped.
- Clinical evidence of active tuberculosis disease should be ruled out in individuals who react to the Tuberculin Skin Test (TST) with purified protein derivative (PPD), prior to starting treatment with VERITY-BCG. (See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

VERITY-BCG is an antineoplastic agent for bladder instillation only.

VERITY-BCG must not be administered intravenously, subcutaneously, intradermally or intramuscularly.

Delay treatment in patients who experience traumatic catheterization until mucosal damage has healed.

In cases of significant toxicity, the physician may elect to terminate treatment with BCG.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose per instillation of VERITY-BCG is 80 mg (two 4 mL vials each containing 40 mg).

Treatment should be started two to three weeks after performing Trans Urethral Resection (TUR).

Induction treatment: The induction treatment schedule consists of 6 consecutive weekly instillations with VERITY-BCG.

Maintenance treatment: Maintenance may include 3 consecutive weekly instillations at 3, 6 and 12 months if 1-year maintenance planned (15 instillation). If 3-year maintenance is planned, 3 consecutive weekly instillations at 3 and 6 months, and then every 6 months up to 36 months (27 instillations), are given.

The duration and frequency of maintenance treatment should be evaluated on the basis of tumour classification (grade, stage and size) and clinical diagnosis. Risk stratification is recommended to determine length of maintenance therapy, whereby patients with intermediate-risk disease are treated with maintenance until 12 months and patients with high-risk disease, 36 months.

Health Canada has not authorized an indication for pediatric use (See 1 INDICATIONS, Pediatrics).

4.3 Reconstitution

Add 1 mL of sterile isotonic preservative free saline (0.9% NaCl) using a sterile syringe to the contents of one vial of VERITY-BCG and allow to stand for few minutes. Then gently swirl the vial

until a homogenous suspension is obtained (Caution: Avoid forceful agitation). Repeat the above procedure to reconstitute each subsequent vial used. To achieve the recommended dose of 80 mg, two vials (each of 40 mg) should be reconstituted; each reconstituted vial contains Bacillus Calmette-Guerin Russian strain BCG-I (40 mg/mL [between 1-8 X 10^8 Colony Forming Units (CFU)]).

Transfer the reconstituted suspension from the first vial into a 50 mL syringe. Rinse the empty vial with 1 mL sterile isotonic saline. Add the rinse fluid to the reconstituted suspension in the 50 mL syringe. Repeat the above procedure for the second vial. Finally, dilute the contents of the 50 mL syringe (by adding sterile physiological saline solution) up to a total volume of 50 mL. Mix the suspension carefully. The suspension is now ready to use.

Although it is recommended to use VERITY-BCG immediately after reconstitution, the reconstituted solution can be stored for up to 2 hours when refrigerated at 2 to 8° C and protected from light. Any unused portion should be discarded as biohazardous waste (see 11 STORAGE, STABILITY AND DISPOSAL).

Table 1 - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
Each 4 mL vial contains 40 mg of VERITY-BCG	1 mL sterile isotonic preservative free saline (0.9% NaCl)	1 mL	40 mg/mL

4.4 Administration

Insert a catheter by aseptic technique through the urethra into the bladder and drain completely. Attach a 50 mL syringe containing the prepared solution to the catheter and instill into the bladder by gravity flow or gentle pressure, where it should be retained for 2 hours. After instillation, remove the catheter. Patients should not ingest any fluid 4 hours before and 2 hours after instillation and should lie on their stomach for the first 15 minutes after instillation. Patients should be advised to change positions frequently (i.e., every 15 minutes) to distribute the medication properly throughout the bladder. Thereafter, patients should be made to void the instilled contents in a sitting position. See PATIENT MEDICATION INFORMATION for post-procedure precautions.

4.5 Missed Dose

If a patient misses a dose, resumption of therapy is recommended, if benefits outweigh the risks. When possible, a missed dose should be replaced so that the patient receives a total of 15 instillations (for intermediate-risk) or 27 instillations (for high-risk) (see section 4 **Error! Reference source not found.**, RECOMMENDED DOSE AND DOSE ADJUSTMENT).

5 OVERDOSAGE

In case of overdose, patients should be monitored closely for signs of systemic BCG infection and treated with anti-tuberculosis medications if clinically warranted.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

VERITY-BCG is supplied as 40 mg freeze-dried powder containing Bacillus Calmette-Guérin with 1-8 X 10^8 Colony Forming Units (CFU) in amber colored glass vials.

Presentation: Pack of two monocartons (one carton containing two monocartons). Each monocarton contains one 40 mg vial of freeze-dried Bacillus Calmette-Guérin with 1-8 X 10^8 Colony Forming Units (CFU).

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
For intravesical (bladder) instillation only	40 mg Freeze-dried powder BCG 1-8 x 10^8 CFU	Monosodium glutamate

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

VERITY-BCG is for intravesical instillation only. Do not inject subcutaneously, intradermally, or intravenously.

VERITY-BCG is not for oral or intradermal use.

VERITY-BCG is not a vaccine for the prevention of cancer, or for the prevention of tuberculosis.

Physicians that use this product should be familiar with the literature on the prevention and treatment of BCG related complications and should be prepared in such emergencies to contact, when appropriate, infectious disease specialists with experience in treating the infectious complications of intravesical BCG. The treatment of infectious complications of BCG requires long term, multiple-drug antibiotic therapy.

Patients should be monitored for the presence of symptoms of systemic BCG infection and for signs of toxicity after each intravesical treatment as death has been reported as a result of systemic BCG infections and sepsis.

Contamination

VERITY-BCG contains live, potentially pathogenic bacteria. Reconstitution, preparation of the VERITY-BCG suspension for instillation and administration should be performed under aseptic conditions. Unused VERITY-BCG and all equipment, supplies, and receptacles in contact with

VERITY-BCG should be handled and disposed of as biohazardous. Urine voided for 6 hours after instillation also needs to be properly disinfected (see 4.3 RECONSTITUTION, 4.4 ADMINISTRATION and 12 SPECIAL HANDLING INSTRUCTIONS).

Genitourinary

Traumatic catheterization or other injuries to the urethra or bladder mucosa can promote systemic BCG infection. VERITY-BCG administration should be delayed until mucosal damage has healed.

Monitoring and Laboratory Tests

Before the first intravesical instillation of VERITY-BCG, a Tuberculin Skin test with PPD should be performed. In the event that this test is positive, the intravesical instillation of VERITY-BCG is contraindicated only if there is clinical evidence of active tuberculosis disease.

In patients with known risk factors for HIV infection, it is recommended to perform adequate HIV assays prior to therapy.

Peri-Operative Considerations-Transurethral Resection (TUR)

When used as adjuvant therapy after TUR of a superficial urothelial cell carcinoma of the bladder (see 1 INDICATIONS), treatment with VERITY-BCG should be started 2 to 3 weeks after performing TUR. Treatment should not be started until mucosal lesions have healed.

Reproductive Health: Female and Male Potential

To protect their partners, patients should be advised to either refrain from sexual intercourse for one week after VERITY-BCG instillation, or to use a condom with intercourse throughout the treatment period and for one week after VERITY-BCG instillation. Women should be advised not to become pregnant while on therapy (see 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women).

Sensitivity/Resistance

The use of VERITY-BCG may sensitize patients to tuberculin skin testing and result in a positive reaction to PPD, therefore determination of tuberculin reactivity by PPD skin testing should be performed before starting the treatment with VERITY-BCG.

The stopper of the vial for this product is latex free.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with VERITY-BCG. It is also not known whether VERITY-BCG can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. As safety of VERITY-BCG in pregnant women has not been evaluated, it should not be given to a pregnant woman.

7.1.2 Breast-feeding

Safety of VERITY-BCG in nursing women has not been evaluated. It is not known whether VERITY-BCG is excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions from VERITY-BCG in

nursing infants, it is advisable to discontinue breastfeeding if the mother's condition requires treatment with VERITY-BCG.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorised an indication for pediatric use.

7.1.4 Geriatrics

There are limited data for patients aged 65 years and older (see 4 DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and CLINICAL TRIALS]

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse reactions are often localized to the bladder but may be accompanied by systemic manifestations.

Frequent adverse reactions (>10%) include hematuria, dysuria, urinary frequency and urgency. The symptoms usually resolve within 2 days but during maintenance treatment, symptoms may be prolonged.

Fever less than 39°C, malaise and and/or influenza-like symptoms (fever, rigors, malaise and myalgia) are common. These symptoms usually occur 4 hours after instillation and fever usually resolves within 24 to 48 hours with antipyretics and fluids. Fever higher than 39°C for more than 12 hours or any fever lasting more than 24 to 48 hours requires further evaluation for potential systemic BCG infection.

Systemic BCG infection resulting from BCG immunotherapy is a serious complication that may lead to death. Systemic BCG infections may be manifested by pneumonitis, hepatitis, cytopenia, vasculitis, infective aneurysm or sepsis. Contributing factors include traumatic catheterization, perforation of bladder or early BCG instillation after extensive TUR. Localized BCG infection may present as infection in the genitourinary tract (such as granulomatous prostatitis, epididymitis, orchitis or renal granulomatosis) or infection in other sites (such as eye, peritoneum, liver or bone). Presentation of BCG infection may be acute or delayed by months to years.

Treatment with antituberculosis therapies should be considered for severe cystitis, localized BCG infection and systemic BCG infection. Severe cystitis may be treated with single-agent Isoniazid, but systemic infection requires triple drug therapy (isoniazid-rifampicin-ethambutol) with or without cycloserine. Anti-tuberculosis treatment may be prolonged and require discontinuation of VERITY-BCG. Consultation with infectious diseases specialist may be necessary to determine optimal treatment regimen and duration.

Arthritis, renal failure, nephritis, urinary retention, or bladder contraction may occur.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Safety of VERITY-BCG was studied in 259 patients in three post-marketing surveillance studies. Adverse reactions were recorded and evaluated after each instillation. In addition, laboratory investigations (hematological, renal, and hepatic), chest x-rays, USG, and CT/MRI were performed in two of these studies. In these studies, 37/259 patients were lost to follow-up and reasons for dropping out were not available. Adverse reactions were reported as 'mild', but no formal classification of severity was used. No serious adverse reactions were reported in any of the studies.

Table 3 - List of studies on VERITY-BCG to evaluate safety

Study No.	Centre	Evaluation	Dose	Study Duration	Number of patients	Number of instillations of VERITY-BCG
#1	Dr. R. M. L. Hospital, New Delhi	Safety and Efficacy	120 mg	36 months	53	1335
			80 mg		51	1329
#2	Safdarjung Hospital, New Delhi	Safety and Efficacy	80 mg	12 months	50	687
#3	Urology Clinics across India	Safety	120 mg	6 weeks	68	345
			80 mg		37	204
Total					259	3900

Study 01

In the 120 mg cohort, there were 476 episodes of dysuria (36%) and 475 episodes of fever (36%) whereas in the 80 mg cohort, there were 383 episodes of fever (29%) and 297 episodes of dysuria (22%).

Table 4 - Adverse Reactions Observed after Administration of VERITY-BCG in Study 01

Adverse Event	80 mg (N* = 1329)	120 mg (N* = 1355)
	Number of adverse events, (%)	Number of adverse events, (%)
Fever	383 (29)	476 (36)
Dysuria	297 (22)	475 (36)
Hematuria	6 (0.5)	15 (1)
Supra pubic pain	20 (2)	31 (2)
Urinary tract infection	1 (0.1)	0 (0)
Increased frequency	0 (0)	5 (0.4)
Burning micturition	0 (0)	6 (0.5)

*N represents the number of instillations

Study 02

Very common adverse reactions (≥ 10%) were dysuria (23%) and fever (18%). Common adverse reactions (≥ 1% and ≤10%) were urinary frequency (9%) and hematuria (7%).

Study 03

This post-marketing surveillance study was conducted to assess the safety of VERITY-BCG in patients with intermediate and high-risk Ta, T1 Transitional Cell Carcinoma (TCC) of the urinary bladder. VERITY-BCG was administered intravesically in patients 10 to 14 days after transurethral resection (TUR).

A total of 549 doses of VERITY-BCG were administered to 105 patients. VERITY-BCG was instilled intravesically at a dose of 80 mg or 120 mg per instillation.

Very common adverse reactions (≥ 10%) reported after the first treatment were hematuria (21%) and dysuria (19%). Common adverse reactions were fever (8%), urgency/frequency (7%), bladder cramps (4%), pain (3%), urinary tract infection (3%), influenza-like symptoms (2%), and cystitis (2%).

8.5 Post-Market Adverse Reactions

The following table summarizes serious and non-serious adverse reactions from post-market surveillance of VERITY-BCG. Other uncommon adverse reactions to BCG have been reported in the literature and are not confined to a particular BCG strain. These include pulmonary infection, hepatitis, ocular disorder (uveitis/conjunctivitis), arthralgia/myalgia, and fatigue.

Table 5 – Post-Marketing Adverse Reactions

Occurrence	MedDRA	Preferred terms
Not known (cannot be estimated from the available data)	General disorders and administration site conditions	Pyrexia
	Infections and infestations	Disseminated Bacillus Calmette-Guérin infection
		Granulomatous lesion
	Renal and urinary disorders	Cystitis
		Cystitis-like symptom
		Dysuria
		Hematuria
		Pollakiuria
		Strangury
	Skin and subcutaneous tissue disorders	Rash

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Immunosuppressants and/or bone marrow depressants and/or radiation may interfere with the development of the immune response and thus with the anti-tumour efficacy and should,

therefore, not be used in combination with VERITY-BCG.]

9.3 Drug-Behavioural Interactions

Although there is evidence that smoking worsens bladder cancer outcomes, there is no direct evidence for the need to quit smoking or vaping while undergoing treatment with Verity-BCG.

9.4 Drug-Drug Interactions

VERITY-BCG is sensitive to most antibiotics and in particular, to the routinely used anti-tuberculous agents, like streptomycin, para-aminosalicylic acid (PAS), isoniazid (INH), rifampicin and ethambutol except for pyrazinamide. Therefore, the anti-tumour activity of VERITY-BCG may be decreased by concomitant therapy with antibiotics. If a patient is being treated with an antibiotic it is recommended to postpone the intravesical instillation until the end of the antibiotic treatment (see also 2 CONTRAINDICATIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

VERITY-BCG has anti-tumor activity, but the exact mechanism of action is not known. Study data suggest that an active nonspecific immune response takes place. BCG invokes a local inflammatory response involving a variety of immune cells, such as macrophages, natural killer cells and T cells.

10.2 Pharmacodynamics

VERITY-BCG is an immunostimulating agent.

10.3 Pharmacokinetics

Studies to evaluate pharmacokinetic properties of VERITY-BCG were not conducted.

11 STORAGE, STABILITY AND DISPOSAL

Vials of VERITY-BCG are stable for up to 24 months when stored at 2 to 8°C and protected from light. The expiry date indicated on the label of the vials only applies if the vials are stored under these conditions.

12 SPECIAL HANDLING INSTRUCTIONS

VERITY-BCG contains live attenuated mycobacteria. Reconstitution, preparation of the VERITY-BCG suspension for instillation and administration should be performed under aseptic conditions in a biohazardous containment cabinet, wearing appropriate personal protective equipment.

Spillage of VERITY-BCG suspension may cause BCG contamination. Any spilled VERITY-BCG suspension should be cleaned by covering the area with paper towels soaked with tuberculocidal disinfectant for at least 10 minutes. Unused VERITY-BCG and all equipment, supplies, and receptacles in contact with VERITY-BCG should be handled and disposed of as bio-hazardous.

For up to six hours after treatment, once a patient urinates, bleach should be poured into the toilet. The bleach should be allowed to stand for 15 minutes prior to flushing. Clothing that is soiled within six hours of treatment should be laundered and dried separately at a high temperature. Incontinence pads should be soaked in bleach, wrapped separately in a plastic bag and disposed of.

Accidental exposure to VERITY-BCG could occur through self-inoculation, by dermal exposure through an open wound or by ingestion of VERITY-BCG suspension. VERITY-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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Product Characteristics:

VERITY-BCG is prepared from a culture of Bacillus Calmette-Guérin (BCG) Russian strain BCG-I. Product is provided in freeze-dried form, with each 40 mg vial containing 1-8 X 10^8 CFU.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Two post-marketing studies of efficacy and safety were conducted in patients with stage T1 urothelial cell carcinoma of the bladder between 2006 and 2012 to fulfil regulatory requirements in India. Recurrence free survival and progression free survival were evaluated as study endpoints; however, due to the single arm nature of the studies, there are limitations in the interpretation of the study results. Therefore, a confirmatory clinical trial in Canada is a condition of authorization.

Table 6 - Summary of patient demographics for clinical trials in patients with stage 1 urothelial cell carcinoma of the bladder

Study No.	Study Design	Dosage, route of administration and duration	Study Subjects (n)	Mean Age (range)	Sex
01	Single-arm, non-randomized, single centre, phase IV, post-marketing study	120 mg and 80 mg Induction (6 consecutive weekly instillations) followed by 3-year maintenance	53 51	**120 mg** 56.60 (SD 12.11) **80 mg** 58.09 (SD 11.6)	**120 mg** 43 male 10 female **80 mg** 48 male 3 female
02	Single-arm, non-randomized, single centre, phase IV, post-marketing study	80 mg Induction (6 consecutive weekly instillations) followed by 1-year maintenance	50	**58.3** **(27 – 75)** (22 (44%) <60 and 28 (56%) ≥60	45 males 5 females

14.2 Study Results

Study 01

A total of 51 patients were enrolled in the 80 mg dose group. One patient was lost to follow up during the maintenance course of treatment. Out of the remaining 50 patients, 8 (16%) patients had muscle

invasive recurrence during the maintenance therapy. VERITY-BCG instillations were discontinued and these patients underwent cystectomy. At the end of 36 months of treatment with VERITY-BCG 80 mg/instillation, 42 patients did not have any recurrence.

With the 120 mg dose, out of 53 patients who were enrolled in this group, 5 patients were lost to follow up. Out of the 48 remaining patients, 3 patients (6%) had muscle-invasive recurrence. VERITY-BCG instillations were discontinued and these patients underwent cystectomy. Four patients had non-muscle invasive recurrence during the maintenance therapy. At the end of 36 months, 41 patients did not have any recurrence.

Study 02

Fifty (50) patients were enrolled in Study 02. Three (3) patients who had muscle invasive tumors during the study underwent radical surgery and discontinued further VERITY-BCG instillations. Five patients had 7 non-muscle invasive recurrences and after undergoing TUR, continued on BCG immunotherapy. At the last study visit, another patient was diagnosed with non-muscle invasive recurrence. Seven patients were lost to follow-up. In total, 34/43 patients (79%) did not recur or progress during the 12-month study.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

VERITY-BCG

Bacillus Calmette-Guérin (BCG), Freeze-dried Powder

Read this carefully before you start taking **VERITY-BCG** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VERITY-BCG.**

Serious Warnings and Precautions

- After the surgery to remove the cancer in your bladder you must wait two or three weeks, to give time for the bladder to heal, before treatment with VERITY-BCG can be started.
- If the bladder is injured when the tube in the urethra (catheter) is inserted on the day of treatment, then the treatment must be postponed until the bladder heals. Treatment with VERITY-BCG when the bladder is injured could cause a serious infection.
- If you have blood in your urine, you must have it evaluated and treated before VERITY-BCG can be given.
- If you have a fever, you must have it evaluated and treated before VERITY-BCG can be given.
- If you have a urinary tract infection or if you suffer from cystitis (inflammation of the bladder), you must have antibiotics before treatment with VERITY-BCG starts. Treatment with antibiotics needs to be finished before VERITY-BCG can be given.
- Before you start VERITY-BCG, your doctor will do a tuberculin skin test (also called a 'Mantoux' test) to see if you have ever been exposed to tuberculosis (TB). A small amount of TB protein is injected into the top layer of the skin in your lower arm. If you have ever been exposed to TB, your skin will react with a firm red bump in 2 or 3 days. If your skin does react, then you will need a medical evaluation and chest x-ray to make sure you do not have active TB disease. VERITY-BCG treatment cannot be given to you, if you have active TB disease.

What is VERITY-BCG used for?

VERITY-BCG contains something called 'BCG' ('Bacillus Calmette-Guérin'). This bacteria has been weakened, so that it can be used as a safe medicine.

VERITY-BCG is used to treat early bladder cancer that has not invaded the muscle wall of the bladder. It is used after bladder surgery – to prevent or delay bladder cancers from growing back or spreading into the deeper layers of the bladder.

For the following indication(s) VERITY-BCG has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- Adjuvant therapy after transurethral resection (TUR) of a primary or relapsing superficial papillary urothelial cell carcinoma of the bladder stage Ta (grade 2 or 3) or T1 (grade 1, 2, or 3), without concomitant carcinoma in situ. It is only recommended for stage Ta grade 1 papillary tumors, when there is judged to be a high risk (>50%) of tumor recurrence.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does VERITY-BCG work?

VERITY-BCG belongs to the group of medicines called immunostimulants. These medicines stimulate your immune system to fight the cancer in the bladder.

What are the ingredients in VERITY-BCG?

Medicinal ingredients: Bacillus Calmette-Guérin (BCG): Strain Russian BCG-I.

Non-medicinal ingredients: Monosodium glutamate.

VERITY-BCG comes in the following dosage forms:

Each vial contains 40 mg ($1 – 8 \times 10^8$ CFU) of VERITY-BCG in freeze-dried powder form.
Each instillation in the bladder contains 80 mg of VERITY-BCG (2 vials) which is diluted in 50 mL of saline.

Do not use VERITY-BCG if:

- If you are hypersensitive (allergic) to Bacillus Calmette-Guérin (BCG) or any of the other ingredients of VERITY-BCG.
- If you have invasive bladder cancer.
- If you have any disease that impairs your immune system (and reduces your immunity against infectious diseases).
- If you take medicines that make your immune system weak.
- If you have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS).
- If you are pregnant or breastfeeding.
- If you have active tuberculosis.
- If you are being treated with anti-tuberculosis drugs.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VERITY-BCG. Talk about any health conditions or problems you may have, including if you:

- If your bladder wall or ureter is damaged, treatment will need to be postponed until the lesion has healed.

Other warnings you should know about:

- Treatment with VERITY-BCG may cause a positive reaction to the Tuberculin Skin Test.
- Your doctor might ask about activities that can put you at risk for HIV, such as having unsafe sex or

sharing needles or syringes, if you use drugs. It may be necessary to take a blood test for HIV before starting treatment with VERITY-BCG. You cannot be treated with VERITY-BCG if you have HIV infection.

- You might pass on the BCG bacteria to your partner when you have sex during the first week after treatment. It is recommended that you avoid having sex during this time but if you do, then use a condom with intercourse throughout the entire treatment period and during the first week after treatment.
- If you are pregnant, VERITY-BCG should not be given.
- If you are breastfeeding, VERITY-BCG should not be given.
- There is no warning that your ability to drive or operate machines will be affected.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VERITY-BCG:

- Antibiotics
- Medicines for tuberculosis
- Medicines which suppress the immune system (immune suppressants)
- Medicines which suppress the production of bone marrow cells (bone marrow suppressants)
- Radiation therapy
- If you are using any of these medicines or are undergoing one of these therapies, your doctor will probably postpone the treatment until you have stopped this treatment.

How to take VERITY-BCG:

- VERITY-BCG will always be given by a healthcare professional in a healthcare setting.

Usual dose:

The recommended dose per instillation is 80 mg (2 vials) of VERITY-BCG.

VERITY-BCG is usually given once a week for 6 weeks followed by additional doses of VERITY-BCG as part of your 'maintenance treatment'. Maintenance treatments will be given every few months for as long as one or three years, depending on the chances of your cancer coming back. Your doctor will talk to you about this.

<u>Before it is given</u>

- Do not drink any liquid the 4 hours before VERITY-BCG is given to you.
- You will be asked to pass urine immediately before VERITY-BCG is given to you.

<u>Being given your medicine</u>

- Your genital area will be cleaned with a sterile solution.

- A nurse will then pass a small flexible tube into your bladder. This will remove any urine that is still in your bladder.
- Next, the doctor or nurse will attach a container of VERITY-BCG solution to the tube. VERITY-BCG will then run into your bladder through this tube. This will only take a few minutes.
- The tube will then be removed.

<u>After it has been given</u>

- VERITY-BCG will be left in your bladder for 2 hours.
- Do not drink any liquid for 2 hours after you have been given VERITY-BCG.
- You will be asked to change positions every 15 minutes during the 2 hours VERITY-BCG is in your bladder. This will make sure that VERITY-BCG comes into contact with your bladder wall during treatment.
- After 2 hours, you will be asked to pass urine, to empty your bladder. You should do this while sitting down to avoid splashing your urine around the toilet.

<u>During the next 6 hours</u>

- If you need to pass urine again, also do this while sitting down.
- Every time you pass urine, add two cups of household bleach to the toilet.
- Leave the bleach and urine to stand in the toilet for 15 minutes before flushing. If clothing has been soiled, it should be laundered and dried separately at a high temperature. Incontinence pads should be soaked in bleach, wrapped separately in a plastic bag and thrown in the garbage.

Overdose:

VERITY-BCG is made up from a standard bottle by your doctor, pharmacist, or nurse. It is unlikely that you will receive too much VERITY-BCG.

If you think you, or a person you are caring for, have taken too much VERITY-BCG, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is very important to go to all your appointments for treatment. If you miss an appointment, call your doctor to make another one as soon as you can. If doses are missed, they may be replaced later. Your doctor will talk to you about this.

What are possible side effects from using VERITY-BCG?

These are not all the possible side effects you may have when taking VERITY-BCG. If you experience any side effects not listed here, tell your healthcare professional.

- You may feel unwell and have fever, chills, muscle aches or tiredness.
- You may have burning or pain when you urinate.

- You may urinate more often than usual.
- You may have sudden urges to urinate immediately.
- You may have blood in your urine.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Blood in the Urine		✓	
Painful or difficult urination	✓		
Fever less than 39°C	✓		
Flu-like symptoms, fatigue	✓		
COMMON			
Urinary Frequency or Urgency	✓		
Fever greater than 39°C		✓	
Any Fever Lasting longer than 24-48 hours		✓	
Allergic reactions		✓	
RARE			
Burning during urination	✓		
Skin rash		✓	
Joint pain		✓	
Cough	✓		
Eye pain or irritation/redness	✓		
Nausea or vomiting	✓		
Jaundice		✓	
BCG infection in the blood (sepsis)		✓	
Abnormal arterial dilation due to bacterial infection (infective aneurysm)		✓	
Inability to urinate			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

VERITY-BCG will be stored in the hospital. Vials of VERITY-BCG are stable for up to 24 months when stored at 2 to 8°C and protected from light.

Do not use VERITY-BCG after the expiry date which is stated on the carton and label.

Keep out of reach and sight of children.

If you want more information about VERITY-BCG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.veritypharma.com, or by calling 1-800-977-9778.

This leaflet was prepared by Verity Pharmaceuticals.

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